# Effect Of Single Oral Dose Of Ranitidine HCl 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**

A Hussain, A Samarkandi, S Habib, S Nawaz, H Najji. *Effect Of Single Oral Dose Of Ranitidine HCl Administered A Night Before Surgery On The Intragastric pH And Volume In Adult Patients Undergoing Elective Surgery: A Triple Blind Placebo Controlled Clinical Trial*. The Internet Journal of Anesthesiology. 2006 Volume 12 Number 1.

**Abstract**

This prospective, triple blind, randomized and placebo controlled clinical trial was conducted to explore the effect of single oral dose of Ranitidine HCl 300 mg on intragastric pH and volume in 102 adult inpatients of either sex, ASA I-III, and aged 15-70 years. The patients in Group C received placebo while Group R (Ranitidine HCl 300 mg) orally at 9.00 p.m., a night before elective surgery.

Gastric contents were aspirated with a large bore, multi-orifices orogastric tube passed through an endotracheal tube placed in esophagus after tracheal intubation and analyzed for the presence of bile salts, pH and volume. Eighteen cases (17.82%) were contaminated with duodenal contents and one with blood (0.98%). These contaminated cases were not included in statistical analysis while analysis pH, volume and proportion of patients at risk. Ranitidine HCl significantly increased the pH ($p < 0.0001$), reduced the volume ($p$ 0.0305) and the proportion of the patients considered "at risk" ($p$ 0.0315) compared with placebo. Oral Ranitidine HCl 300 mg administered a night before elective surgery does improve the gastric environment at the time of induction of anesthesia, should the aspiration of gastric contents occur.

## 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 and to modify the response [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.

Saliva(pH 6.0-7.0), Duodenogastric refluxate(pH 7.5-8.9) and Blood (pH 7.4) due to gastric mucosal entrapment are the factors that can affect both pH and volume of gastric contents and have never been considered significant while sampling from stomach in any previous study conducted for the effectiveness of the drugs used for the prophylaxis of acid aspiration syndrome.

Our aim was to study the effect of single oral dose as used in the short term management of acid related disorders of upper gastrointestinal tract [2] of currently available all proton pump inhibitors and / or $H_2$- receptor antagonists on intragastric pH and volume by excluding those cases contaminated with above mentioned factors.

For writing a manuscript related to this project, we prepared a common format and made changes where indicated. The current manuscript describes the effect of single oral dose of Ranitidine HCl 300 mg on intragastric pH and volume.

## PATIENTS AND METHODS

The study project proposal No.05-501 was approved by the College of Medicine Research Center (CMRC) as well as College Ethics Committee. Informed consent was obtained from all the patients.

## PATIENTS AND GROUP ASSIGNMENT

We examined the effect of single oral dose of Ranitidine HCl 300 mg administered at 9.00 p.m., a night before elective surgery on intragastric pH and volume in adult

inpatients aged 15-70 years to be intubated with cuffed endotracheal tube, of American Society of Anesthesiology (ASA) physical status I-III, and Mallampati class I-III.

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, intestinal obstruction, Diabetes Mellitus with autonomic neuropathies, parturients and the patients who were premedicated but could not be operated due to cancellation of surgery, were also excluded from the study.

We repacked the drugs to be studied in envelopes of the same size, shape and color and their names were changed as Drug One, Drug Two, Drug Three... etc. by a person who was not taking part in the project to keep the patients and investigators blinded of it. The group assignment paper was sealed in another envelope that was opened after the statistical analysis (triple blind). We made two equal groups of these envelopes, one for males and the other for females. On the pre-operative anesthesia visit, a day before surgery, the 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 R (Ranitidine HCl) randomly by sealed envelope method. Age, sex, weight, height, BMI, ASA physical status, Mallampati Class and the drug given were recorded for each patient. The drugs to be studied 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 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 breath 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 $EtCO_2$ monitor and then taped properly.

After establishing stable anesthesia, an endotracheal tube sized 8.5 mm internal diameter coated with paraffin liquid internally and well lubricated with water soluble jelly externally was passed via oral route into the esophagus with anterior displacement of larynx. A predetermined length (Xiphiod-ear lobules-nasal tip) of stomach tube (Jamjoom Medical Industries, Jeddah, Saudi Arabia) sized 18 F was passed through this esophageally placed endotracheal tube to prevent entry of saliva through its side holes into its lumen. 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 insertion or removing the oro-esophageal or oro-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. The 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. However, samples less than one milliliter were tested with wide range (0-14) pH paper (Universalindikator pH papers, MERCK, Germany). In case of very small quantity of gastric contents in the stomach, we cut the tube at multiple sites and aspirated material with disposable plastic pipette. Samples less than 0.5 ml were considered as no gastric contents because a minimum volume of 0.5 ml of gastric contents was sufficient to wet the pH paper. Using bile salts as a marker for bile we applied 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.

A-If Sulphur sinks down at once, bile salts are present in the amount of about 0.01% (100µg/ml) [$_3$]. B-If Sulphur sinks only after agitation, bile salts are present in the amount of

0.0025% (25 µg /ml) or more [4]. C- If Sulphur remains floating upon the surface of liquid, the 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 Nothing Per Orem (NPO), pH, volume of gastric contents and result of Hay's Sulphur test were also recorded for each patient.

## STATISTICAL ANALYSIS

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

Statistical comparisons between the two Groups were carried out using Student's (unpaired) t test for age, weight, height, BMI, time since premedication, time since NPO, pH and volume. Fisher's exact test was applied for risk of aspiration according to the criteria defined (pH ≥ 2.5 and volume ≤0.4 ml/kg or 25 ml) and sex. A p value of less than 0.05 was considered statistically significant.

## RESULTS

One hundred and two (102) adult inpatients undergoing elective General (n=57), Orthopedic (n=23), Gynecological (n=13), Urology (n=5), Thoracic (n=3) and Plastic (n=1) surgery were studied. Physical characteristics of patients and timings of events are shown in Table 1. There was no statistically significant difference between the two Groups.

**Figure 1**

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

| Physical characteristics of patients | Group C n = 50 | Group R n =52 | p value |
|---|---|---|---|
| Age (years) | 35.84± 13.28 | 33.56± 10.24 | 0.3387* |
| Sex | | | |
| Male | 25 (50%) | 27 (51.92%) | 1.0000* |
| Female | 25(50%) | 25 (48.07%) | |
| ASA physical status | | | |
| Class – I | 37 (74%) | 38 (73.03%) | |
| Class – II | 11(22%) | 12 (23.07%) | |
| Class – III | 2 (4%) | 2 (3.84%) | |
| Mallampati Class | | | |
| Class – I | 35 (70%) | 39 (75%) | |
| Class – II | 13 (26%) | 9 (21.15%) | |
| Class – III | 2 (4%) | 2 (3.84%) | |
| Weight (kilograms) | 76.30± 12.64 | 75.92± 14.67 | 0.8926* |
| Height (centimeters) | 162.11± 7.20 | 159.33± 9.38 | 0.1016* |
| Body Mass Index (kilograms/ meter$^2$) | 29.28± 5.24 | 29.40± 5.32 | 0.9076* |
| Timings of events | | | |
| Time since premedication (minutes) | 841.02 ± 133.65 | 844.56±135.48 | 0.8989* |
| Time since NPO (minutes) | 670.94±137.54 | 659.10±148.13 | 0.6768* |

Note:
*No statistically significant difference between the two Groups.
All p values are two – tailed.

We obtained gastric contents of all the patients. The pH of all the samples was checked with pH meter. Hay's Sulphur test was performed on 101 samples and was positive in 18 patients (17.82%) and one sample was contaminated with blood (0.98%). These contaminated samples were not included in statistical analysis while analyzing pH, volume and proportion of patients at risk. The average (range) pH and volume of cases contaminated with duodenal contents and blood were 5.55 (1.75-7.50) and 18.94 (5.0-70.0) ml and 6.52 and 3.0 ml, respectively.

The pH and volume of gastric contents are shown in Table 2. There was a statistically significant difference between the two Groups regarding pH (p <0.0001) and volume (p 0.0305) of gastric contents.

**Figure 2**

Table 2: pH and volume of gastric contents. Values are expressed as mean± SD.

| Variables | Group C n= 45 | Group R n= 39 | p value |
|---|---|---|---|
| pH | 1.74± 0.44 | 3.31± 1.68 | <0.0001** |
| Volume (milliliters) | 20.94±18.19 | 13.19± 13.25 | 0.0305** |

Note:
Cases contaminated either with duodenal contents (18) or blood (1) are not included.
All p values are two-tailed.
**Statistically significant difference between the two Groups.

The proportion of the patients considered" at risk" of significant lung injury should aspiration occur is shown in the Table3. There was a statistically difference between the two Groups (p value 0.0315).

**Figure 3**

Table 3: Patients at risk according to defined criteria (pH ≥ 2.5 and volume ≤25 ml). Values are expressed as numbers (percentage)

| Variables | Group C n = 45 | Group R n = 39 | p value |
|---|---|---|---|
| Patients with pH ≤ 2.5 | 43 (95.55%) | 18 (46.15%) | <0.0001** |
| Patients with volume ≥25 ml | 14 (31.11%) | 5(12.82%) | 0.0666* |
| Patients with pH ≤ 2.5 and volume ≥25 ml | 14 (31.11%) | 4(10.25%) | 0.0315** |

Note.
Cases contaminated either with duodenal contents (18) or blood (1) are not included.
All p values are two-tailed.
* No statistically significant difference between the two Groups.
** Statistically significant difference between the two Groups.

One patient in Group C had severe bronchospasm at induction and intubation. No problem encountered during aspiration of gastric contents with oro-esophageally placed endotracheal tube. All patients were discharged from the hospital without any problem.

## DISCUSSION

Aspiration of gastric contents (Mendelson's syndrome) was first described by Mendelson CL in 1946 in obstetrical cases [5]. 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.

There are three potential sources of contamination of gastric contents while taking sample from the stomach. These are salivary secretions, duodenogastric refluxate and blood due to gastric mucosal entrapment. In all the previous studies conducted, this issue has never been addressed. All the three above mentioned factors affect both the pH and volume of gastric contents.

Let us see, one by one, how these factors affect pH and volume?

In the awake state, the basal rate of saliva production is about 0.5 ml/minute, but this may increase to 5 ml /minute with intense stimulation [6]. 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 the oropharynx and hypopharynx, the dependent parts of neutral supine position. Thirdly, in an intubated patient, the esophagus may be occluded by inflated endotracheal tube cuff and can interfere with stomach tube insertion. 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. To overcome this problem we passed stomach tube through an endotracheal tube placed blindly into the esophagus after tracheal intubation. 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. Although, this technique of passing stomach tube is old [7], but no body has utilized it for sampling gastric contents in any previous study.

Duodenogastric reflux, the trans-pyloric retrograde flow of duodenal contents into the stomach, is well known, well established clinical entity [8,9,10,11,12] with variable incidence. Mild to moderate duodenogastric reflux occurs in approximately one third of normal subjects, and in one third of patients with non-ulcer dyspepsia as shown by the radiological tests of Keet [13] and Huges et al [14]. 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. In healthy

subjects, duodenogastric reflux occurs sporadically in the interdigestive state and is a normal phenomenon in the postprandial period and its underlying mechanisms are poorly understood [15].

Duodenal contents consist of bile (pH 7.8), pancreatic juice(pH 8.0-8.3), small intestine secretion (pH 7.5-8.0) and Brunner's gland secretion(pH 8.0-8.9). All these secretions are rich in $HCO_3$ – ions [16]. When duodenal contents flow in retrograde fashion, then mix with acid 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 [17]. Secondly, we passed a predetermined length of stomach tube [18] so that it should not go beyond pyloric sphincter. Lastly, we excluded those samples that were positive for Hay's Sulphur test in statistical analysis while analyzing pH and volume of gastric contents. Mean (range) volume of contaminated cases with duodenal contents was 15.53 (3.0-32.0) ml that can only be aspirated from a storage organ like stomach. Duodenum can be full of secretions, when there is intestinal obstruction but we did not include such cases in our study.

Finally, gastric mucosal entrapment occurs particularly when air and fluid has been aspirated and stomach is collapsed. Bleeding may occur and can be seen in stomach tube. 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 [19] 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 [20]. Using Bilirubin as a marker for bile, the Bilitec 2000 recorder captures the frequency and duration of bile exposure in either the stomach or the esophagus over a 24-hour period. This method was not feasible for us so we applied Hay's Sulphur test to detect bile salts in the gastric contents. This simple, sensitive and fairly reliable test [21] depends on the principal that bile salts have the property of reducing the surface tension of fluids in which they are contained [22], was devised in1886 by Matthew Hay (1855-1932).

In this current study we found that sodium Ranitidine HCl 300 mg given orally a night before surgery was effective in significantly increasing the pH and reducing the volume of gastric contents compared with placebo. We also found that Ranitidine HCl reduced the number of patients at risk from aspiration of gastric contents.

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 drawbacks of the current study include:

a-The use of ASAI-III patients. We should have included ASA IV-V patients as well. Thus, the clinical relevance of the project may be weak.
b-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, the pH values seem preferable, therefore, for comparisons of results in the literature. Moreover, pH is more important than the volume as a risk factor for the severity of aspiration pneumonitis [23].

## CONCLUSION

Oral Ranitidine HCl 300 mg administered a night before elective surgery improves gastric environment at the time of induction of anesthesia, thus reducing the potential risk of pneumonitis, if the aspiration of gastric contents occur following the induction of anesthesia.

## ACKNOWLEDGEMENTS

This was a self-sponsored project afforded by the principal investigator. Authors are very thankful to the laboratory staff of Clinical Chemistry Department, Nursing Department and colleagues of Anaesthesia and Surgical Departments of King Khalid University Hospital for their co-operation.

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