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Effect of single oral dose of Nizatidine 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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Abstract

Objectives: To evaluate the effect of preanaesthetic administration of oral Nizatidine on pH and volume of gastric contents excluding samples contaminated with duodenogastric reflux. **Design:** Prospective, triple blind, randomized and placebo controlled clinical trial. **Methods:** The patients in Group C (Control) received Placebo while Group N (Nizatidine 300 mg) orally at 9.00 p.m., 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 esophagus after tracheal intubation and analyzed for the presence of bile salts, pH and volume. **Results:** Thirty five samples (29.66 %) out of 118 were contaminated with duodenal contents. One sample was contaminated with blood while one patient has no gastric contents. Duodenogastric reflux significantly affected pH and volume. Nizatidine, after excluding those samples contaminated either with duodenal fluid or blood, did not decrease significantly pH (p 0.0554), volume (p 0.5202) and the proportion of the patients (28.57% versus 24.39%) considered” at risk” compared with Placebo (p 0.8044) according to the criteria defined (pH \leq 2.5 and volume \geq 25 ml). **Conclusion:** Nizatidine 300 mg given orally, a night before surgery did not afford adequate prophylaxis for the acid aspiration syndrome excluding those samples contaminated with duodenogastric reflux.

Introduction

Pulmonary aspiration of gastric contents is the inhalation of gastric contents into the larynx and lower respiratory tract. General anesthesia itself is a potential major risk factor that predisposes the patient to aspirate due to the loss of protective airway reflexes.

Nizatidine, a H₂ – receptor antagonist, is used in peptic ulcers and other acid dyspeptic disorders of upper gastrointestinal tract in a dose of 300 mg orally once daily¹.

Our aim was to study the effect of single oral dose of Nizatidine 300 mg, administered a night before surgery, on intragastric pH and volume in adult patients undergoing elective surgery excluding those cases contaminated with duodenogastric refluxate. To our knowledge, the impact of duodenogastric refluxate on gastric pH and volume has not been reported.

Patients and Methods

This study was approved by the College of Medicine Research Committee. Written informed consent was obtained from all the patients.

Patients and Group Assignment

We examined the effect of single oral dose of Nizatidine 300mg, administered at 9.00 p.m., 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 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 VI and /or mouth opening less than 4 centimeters and /or thyromental distance less than 6.5 centimeters and/or history of difficult intubation, parturients and Diabetes Mellitus were excluded from the study. Patients who were premedicated and their gastric aspirates contained duodenal fluid or in whom gastric contents were mixed with blood in the gastric tube were not included in the final statistical analysis while analyzing pH and volume of gastric contents because these samples were not true gastric contents rather alkaline duodenal fluid mixed with acidic gastric contents or blood.

We repacked the Placebo and Nizatidine tablets in 120 envelopes of the same size, shape and color and their names were changed as either Drug One or Drug Four by a person who was not taking part in the study to keep the patients and investigators blind 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 Four after the statistical analysis. On the pre-operative anesthesia visit 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 N (Nizatidine) randomly by sealed envelope method. Age, sex, weight, height, BMI, ASA physical status, and the drug given were recorded for each patient. These drugs were given orally with 20 ml of drinking water at 9.00 p.m., a night before. 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, 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, 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 tube² (Jamjoom Medical Industries, Jeddah, Saudi Arabia) sized 18 F was passed through this esophageally placed endotracheal tube³. Placement of this tube within the stomach was verified by auscultation over the epigastrium during insufflation of 10-15 ml of air. Gastric contents were gently aspirated manually with 60 ml of syringe by an investigator who was blinded of the group assignment. Applying manual pressure over the epigastrium while the patient was in supine and then left and right lateral positions, gastric tube was then manipulated to ensure maximum emptying of gastric contents. The stomach tube was removed followed by esophageally placed endotracheal tube. Any problem encountered during inserting or removing the oro-esophageally placed endotracheal tube or gastric tube was also recorded. The volume of gastric contents was measured with graduated syringe and pH with pH meter (Model 215 version 3.4, Denver Instrument Company, 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 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 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 ° C or below) liquid. If bile salts are present Sulphur sinks down, sooner or later, in accordance with their percentage.

If bile salts are present in from 1:5000 (0.02 % or 200µg/ml) to 1:10,000(0.01 % or 100µg/ml) Sulphur at once begins to sink and all precipitated in two or three minutes; even in a dilution of 1:120,000 (0.0008 % or 8.33 µg/ml) precipitation occurs⁴. 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 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(contaminated with duodenogastric refluxate) and Group C-2 (non-contaminated with duodenogastric refluxate) and Group N into Group N-1(contaminated with duodenogastric refluxate) and Group N-2 (non-contaminated 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 \pm standard deviation (SD).

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

Results

One hundred and twenty (120) adult inpatients undergoing elective General (n=70), Orthopedic (n=27), Gynecological (n=8), Urology (n=8), and Thoracic (n=7) 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 C& N regarding age, sex, ASA physical status, weight, height, BMI, time since premedication and time since NPO.

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

We obtained gastric contents of 119 patients. One patient has no gastric contents in group C while one sample was mixed with blood in group N. Hay's test was performed on 118 samples and was positive in 35 patients (29.66 %) 17 in group C and 18 in N.

Duodenogastric refluxate significantly affected both the pH and volume of gastric contents in both Groups C-1 & N-1 as shown in Table 2. There was no statistically significant difference between the two Groups C-2 and N-2 (non- contaminated samples with duodenogastric refluxate) regarding

pH (p 0.0554) and volume (p 0.5202) of gastric contents.

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

Note:

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

Group C-2 and Group N-2 represent non-contaminated samples.

Comparison of pH and volume between Group C-1 and C-2 (p value 0.0006 and 0.0444)

Comparison of pH and volume between Group N-1 and N-2 (p value 0.0025 and 0.0377).

Comparison of pH and volume between Group C-2 and N-2 (p value 0.0554 and 0.5202).

The proportion of the patients considered "at risk" of significant lung injury is shown in the Table 3 after excluding contaminated samples with duodenogastric refluxate.

Table 3. Patients at risk according to defined criteria. Values are expressed as numbers (percentage).

Note: Samples mixed either with duodenal contents (35) or blood (1) or having no contents (1) are not included.

There was no statistically significant difference between the two Groups C-2 and N-2 (p 0.8044). One patient in Group C had severe bronchospasm at induction. 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. While attention has usually focused on aspiration as the major consequence of regurgitation and vomiting, other sequelae 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. During the last 16 years we could find only two studies for the use of Nizatidine as premedication drug for the prophylaxis of acid aspiration syndrome. Popat et al⁵ compared the effects of oral Nizatidine and ranitidine on gastric volume and pH in patients undergoing gynaecological laparoscopy. The mean (range) pH and volume of gastric contents in Nizatidine group (150 mg given orally at least 45 minutes before induction of

anaesthesia) were 6.35 (2.0-7.0) and 0 (0-16) ml. According to their criteria defined pH <2.5 and volume >25 ml for patients at risk, there were none (0 %) at risk in group N. Mikawa et al⁶ reported when Nizatidine was given orally 6 mg/ kg at 21.00 hours and placebo at 06.30 hours the mean pH and volume in this group were 2.5 and 5.2 ml/kg. Ten children (38%) were at risk for aspiration pneumonitis as defined by gastric fluid pH <2.5 and volume 0.4 ml/kg. In our study mean±SD pH (2.33 ±1.36) and volume are (17.95±13.17). According to our criteria defined pH <2.5 and volume >25 ml for risk of aspiration, 10 (24.39%) patients were at risk. Our results particularly pH values are less than reported in the above mentioned studied but more accurate because we excluded all the contaminated samples with duodenogastric refluxate.

Duodenogastric reflux, the trans-pyloric retrograde flow of duodenal contents into the stomach, is well known, well established clinical entity 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 Keet⁷ and Huges et al⁸, 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 al⁹ 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. 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 understood¹⁰. Our reported incidence 29.66 % is comparable to previously reported above mentioned studies.

When duodenal contents flow in retrograde fashion, then they mix with acid and Pepsin 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 al¹¹. 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.

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 old², but no body has utilized it for sampling gastric contents in any previous study. In this study two samples were found to be mixed with blood due to gastric mucosal entrapment. Gastric mucosal entrapment occurs particularly when air and fluid has been aspirated and stomach is collapsed. Gastric mucosa is caught into the side holes of stomach 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 ¹² However, any sample containing any amount of visible blood mixed with gastric contents was not considered for pH and volume analysis.

The Bilitec TM 2000 ambulatory bile reflux recorder is currently the only commercially available device that is proven effective in measuring bile reflux ¹³ . 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 depends on the principal that bile salts have the property of reducing the surface tension of fluids in which they are contained ¹⁴ , was devised in 1886 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. 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. This method is simple, inexpensive, and easy to perform and has been widely used.

Conclusion

Duodenogastric reflux significantly affected both the pH and volume of gastric contents. Oral Nizatidine 300 mg administered a night before elective surgery did not afford adequate prophylaxis for acid aspiration syndrome.

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