Effect of single oral dose of sodium rabeprazole on the intragastric pH & volume in patients undergoing elective surgery

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Background & objectives: While evaluating the effectiveness of drugs used for the prophylaxis of acid aspiration of gastric contents, the impact of duodeno-gastric reflux on gastric contents has not been studied earlier. This study was carried out to evaluate the effect of preanaesthetic oral administration of sodium rabeprazole on pH and volume of gastric contents in adult patients undergoing elective surgery by excluding cases contaminated with duodeno-gastric refluxate.

Methods: The patients in group C (control) in the triple blind placebo controlled trial received placebo while group S sodium rabeprazole 20 mg orally at 2100 h, 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. The pH and volume of gastric contents were the primary and duodeno-gastric reflux secondary outcome measures of the study.

Results: The pH and volume of group S-2 were 3.97±1.78 and 9.48±8.39 ml respectively compared with 1.90±0.47 and 19.60±18.56 ml of group C-2. Sodium rabeprazole, after excluding contaminated cases with duodeno-gastric refluxate, significantly increased the pH (P<0.001), decreased the volume of gastric contents (P<0.005) and the proportion of the patients (30.76 vs 2.63%) considered at risk compared with placebo (P<0.001) according to the criteria defined (pH < 2.5 and volume > 25 ml). Thirty nine samples (33.33%) out of 117 were contaminated with duodenal contents. Duodeno-gastric reflux significantly (P<0.001) affected pH and volume of gastric in both groups C-1 vs C-2 and S-1 vs S-2.

Interpretation & conclusions: Sodium rabeprazole 20 mg given orally a night before surgery provided adequate prophylaxis for acid aspiration syndrome at the time of induction of anaesthesia and duodeno-gastric reflux significantly affected both the pH and volume of gastric contents.

Key words Aspiration - duodeno - gastric pH & volume - gastric refluxate - sodium rabeprazole
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. 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.

Sodium rabeprazole, a proton pump inhibitor, is used in peptic ulcers and other acid dyspeptic disorders of upper gastrointestinal tract. The recommended oral dose of sodium rabeprazole is 20 mg once a day. In contrast to omeprazole, lansoprazole, pantoprazole and esomeprazole, rabeprazole forms a partially reversible bond with the proton pump and is activated at a broader range of gastric pH. Therefore, it may have a more sustained acid-suppressing effect than other proton pump inhibitors. While evaluating the usefulness of sodium rabeprazole as prophylaxis for acid aspiration syndrome, the impact of duodenogastric reflux on gastric pH and volume has not been reported in previous studies. The aim of the present study was to determine whether a single oral dose of sodium rabeprazole (20 mg) administered a night before surgery, was 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.

**Material & Methods**

The study protocol was approved by the College of Medicine Research Center (CMRC) and College Ethics Committee. Written informed consent was obtained from all the patients.

The effect of single oral dose of sodium rabeprazole 20 mg, administered at 21:00 h, was examined on intragastric pH and volume in 120 adult consecutive inpatients of American Society of Anesthesiologists (ASA) physical status I (a normal healthy patient) and class-II (a patient with mild systemic disease and no functional limitations) to be intubated with cuffed endotracheal tube in the Operating Rooms of King Khalid University Hospital, Al-Riyadh, Saudi Arabia, from August 2006 to November 2006.

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 whose gastric aspirates contained either duodenal fluid due to duodenogastric reflux (DGR) or mixed with blood were not included in the final statistical analysis while analyzing pH and volume of gastric contents because these samples were not true gastric contents but rather were alkaline duodenal fluid mixed with acidic gastric contents.

**Randomization of patients:** We repacked the placebo and rabeprazole tablets in 120 envelopes of the same size, shape and colour and their names were changed as either Drug One or Drug Two by a person who was not taking part in the study to keep the patients and investigators blinded of it (double blind). The group assignment paper was sealed in another envelope that was opened to know which drug corresponds to either Drug One or Drug Two after the statistical analysis (triple blind, statistician blinded of group assignment also). On the pre-operative anaesthesia visit, a day before surgery, the nature and purpose of the study was explained to each patient. Each patient was asked to pick up only one envelope from the envelopes (randomization). Thus, the patients were allocated either to group C (control) or group S (sodium rabeprazole) 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 2100 h, 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 for any unusual feelings (side effects) after taking the study drug.

**Collection and analysis of gastric contents:** After pre-oxygenation with 100 per cent 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 (Datex-Engstrom Division, Instrumentarium Corp. Helsinki, Finland) 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 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 tube7 (Jamjoom Medical Industries, Jeddah, Saudi Arabia) sized 18 F was passed through this oesophageally 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 contents9. The stomach tube was removed followed by oesophageally placed endotracheal tube. Any problem encountered during inserting or removing the oro-oesophageally 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, USA). 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 1 ml volume of gastric contents was sufficient for pH determination. In case of very little amount of gastric contents, the stomach tube was cut and gastric material aspirated with disposable plastic pipette. Samples <1 ml were considered as no gastric contents. Using bile salts as a marker for bile, qualitative Hay’s sulphur test10 was applied for the presence of bile contents. Samples <1 ml were considered as no gastric contents. 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. A minimum of 1 ml volume of gastric contents was sufficient to perform Hay’s sulphur test. A minimum volume of 1 ml of gastric contents was adequate to perform Hay’s sulphur test.

Anaesthesia was continued and 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 rocuronium4. 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, group C was further divided into group C-1 (including samples contaminated with duodenogastric refluxate) and group C-2 (not contaminated with duodenogastric refluxate) and group S into group S-1 (including samples contaminated with duodenogastric refluxate) and group S-2 (not 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. 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). P<0.05 was considered statistically significant.

Power analysis revealed that the sample size (n=30 in each group) was sufficient to detect a difference of 0.7 between groups in gastric pH and volume at a significance level of 0.05 (= a) with a power of 0.8511.

Results

One hundred and twenty (120) adult inpatients undergoing elective general (n=58), orthopaedic (n=30), gynaecological (n=18), urology (n=4), and thoracic (n=4), plastic (n= 4) and Neuro (n = 2) surgery were studied. 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 (Table I).

Gastric contents were obtained from 118 patients.

| Table I. Baseline physical characteristics of patients and timings of events |
|-------------------------------------------------|-----------------|-----------------|
| Physical characteristics of patients | Group C | Group S |
| Age (yr) | 34.32 ± 13.65 | 34.08 ± 10.25 |
| Sex | | |
| Male | 30 (50) | 30 (50) |
| Female | 30 (50) | 30 (50) |
| ASA physical status | | |
| Class - I | 44 (75) | 45 (75.00) |
| Class - II | 16 (25 ) | 15 (25.00) |
| Weight (kg) | 73.68 ± 15.28 | 78.47 ± 13.92 |
| Height (cm) | 161.31 ± 7.84 | 163.14 ±10.69 |
| Body mass index (kg/m2) | 28.40 ± 5.80 | 29.58 ± 5.43 |
| Timings of events | | |
| Time since premedication (min) | 832.25 ±136.51 | 812.50±132.68 |
| Time since NPO (min) | 661.85±138.03 | 636.33±131.27 |

Values are expressed either as mean ± SD or numbers (percentage) NPO, nil per os
Two patients in group S had no gastric contents while one sample in group C was contaminated with blood. Hay’s test was performed on 117 samples and was positive in 39 patients (33.33%). Sixteen samples from group C and 15 from group S were mixed with duodenal contents.

The average (range) pH and volume of contaminated cases with duodenal contents were 5.85 (1.63-6.98) and 73.87 (9.0-118.0) ml and blood 7.13 and 4.0 ml. These cases were considered as contaminated and not included in statistical analysis.

Duodenogastric reflux significantly affected both the pH and volume of gastric contents in both groups. There was a statistically significant difference between the two groups C-2 and S-2 (non-contaminated samples with duodenogastric refluxate) regarding pH (P<0.0001) and volume (P<0.0027) of gastric contents (Table II).

The proportion of the patients considered at risk according to defined criteria (pH<2.5 and volume >25 ml) of significant lung injury should aspiration occur was 12 (30%) in Group C-2 compared with 1 (2.63%) in Group S-2 after excluding contaminated samples with duodenogastric refluxate as shown in Table III. There was a statistically significant difference between the two groups (P<0.0015).

One patient in group C had severe bronchospasm at induction. No side effect of study drugs was noted. 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 per cent of a large collection of incidents that arose during general Anaesthesia. While attention has usually focused on aspiration as the major consequences 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.

Aspiration of gastric contents (Mendelson’s syndrome) was first described by Mendelson in 1946 in obstetrical cases. In all earlier studies conducted, importance of duodeno-gastric 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 a well established clinical entity 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 Keel and Hughes et al, 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. Wolverton et al studied the incidence of duodenogastric reflux in peptic ulcer disease using...

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**Table II. pH and volume of gastric contents**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group C-1 (n= 59)</th>
<th>Group C-2 (n= 39)</th>
<th>Group S-1 (n= 58)</th>
<th>Group S-2 (n= 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>3.06 ± 1.91</td>
<td>1.90 ± 0.47*</td>
<td>4.75 ± 1.86</td>
<td>3.97 ± 1.78††</td>
</tr>
<tr>
<td></td>
<td>(2.56 to 3.55)</td>
<td>(1.74 to 2.05)</td>
<td>(4.26 to 5.23)</td>
<td>(3.39 to 4.54)</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>38.72 ± 33.52</td>
<td>19.60 ± 18.56*</td>
<td>29.77 ± 32.98</td>
<td>9.48 ± 8.30††</td>
</tr>
<tr>
<td></td>
<td>(29.98 to 47.35)</td>
<td>(13.58 to 25.61)</td>
<td>(21.09 to 38.44)</td>
<td>(6.76 to 12.19)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD [95% of confidence interval (CI) of the mean]

* P<0.001 compared to C-1
** P<0.005; †† <0.001 compared to C-2

**Table III. Patients at risk of lung injury according to defined criteria**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group C-2 (n= 39)</th>
<th>Group S-2 (n= 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with pH &lt; 2.5</td>
<td>37 (94.87)</td>
<td>11 (28.20)*</td>
</tr>
<tr>
<td>Patients with volume &gt;25 ml</td>
<td>12 (30.76)</td>
<td>1 (2.63)**</td>
</tr>
<tr>
<td>Patients with pH &lt; 2.5 and volume &gt;25 ml</td>
<td>12 (30.76)</td>
<td>1 (2.63)**</td>
</tr>
</tbody>
</table>

Samples mixed either with duodenal contents (39) or blood (1) or having no contents (2) were not included

P *<0.05 **<0.001 compared to C-2
99mTe 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 per cent dextrose meal. Fifty three per cent patients with duodenal ulceration 46 per cent controls were reflex positive; similarly 53 per cent patients with gastric ulceration and an equal percentage of control subjects were reflex positive21. The mechanisms underlying duodenogastric reflex are poorly understood22.

Duodenal contents consist of bile (volume 1000 ml/day: pH 9.0-8.3), small intestine secretion (volume 1800 ml/day: pH 7.8-8.0) 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^- ions23. When duodenal contents flow in retrograde fashion, then 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 al. 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 was 73.87 (9.0-118.0) ml that can only be aspirated from storage organ like stomach.

Many 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 fluid24. Nishina et al.24, reported pH and volume (ml/kg) of gastric contents 3.8±2.2 (0.8-7.6) and 0.22±0.20 (0-0.95) of the group in whom patients received oral sodium rabeprazole 20 mg the night prior to surgery and placebo on the morning of surgery. We obtained many 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 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/min, but this may increase to 5 ml/min with intense stimulation26.

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 overnight in surgical ICU. Follow up spiral CT chest showed bronchioectatic changes in the right middle lobe, the possible cause of bronchospasm.

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 tube thus giving evidence of aspiration of gastric contents. This patient was considered for surgery.

In this study we passed gastric tube through an endotracheal tube passed blindly in the oesophagus. Although, this technique of passing stomach tube is old9, but nobody has utilized it for sampling gastric contents. We obtained many 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 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/min, but this may increase to 5 ml/min with intense stimulation26.
The limitation of the current study was the use of ASA class-I and class-II. We should have included ASA class-III (a patient with moderate to severe systemic disease that results in some functional limitations) and class-IV (a patient with severe systemic disease that is constant threat to life and functional incapacitating) as well. Thus, the clinical relevance of the study may be weak.

In conclusion, duodeno-gastric reflux significantly affected both the pH and volume of gastric contents. Oral rabeprazole 20 mg administered a night before elective surgery, provided adequate prophylaxis for the acid aspiration syndrome at the time of induction of anaesthesia excluding samples contaminated with duodeno-gastric reflux.

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References


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