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A double blind study comparing the effect of intravenous rabeprazole and pantoprazole on gastric pH and volume in laparoscopic surgery under general anaeshesia

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Abstract

Background and Aims: Major thrust in reducing potential for acid aspiration is increase the pH by various methods and pharmacological agents. The aim of the study is to compare the effectiveness of intravenous rabeprazole and pantoprazole on gastric volume and pH in patients undergoing elective laparoscopic surgery under general anesthesia.

Materials and Methods: Sixty patients of either sex, aged 18-55 yr, ASA physical status I or II, undergoing elective laparoscopic surgery were randomly assigned in to Group R and Group P to receive intravenous 20mg rabeprazole and 40 mg pantoprazole 15 min before induction of anaesthesia. The post-intubation and pre-extubation gastric aspiration volume and pH was measured with pH meter.

Results: The mean post-intubation volume was 20.52±4.46ml and 22.48±4.33 in group R and group P respectively. The mean pre-extubation volume in group P and group R was 15.14±3.66 and 11.10±2.84 respectively. The mean pH of post-intubation gastric aspiration contents in group P was 6.41±0.69 and in group R was 7.37±0.56. All values were statistically significant ($p<0.05$).

Conclusion: Intravenous rabeprazole is more effective than pantoprazole in reducing the gastric volume and increasing the gastric pH.

Keywords: Rabeprazole, Pantoprazole, Gastric volume, pH

Introduction

Laparoscopic surgery become popular although patients who are undergoing laparoscopic surgery are at a higher risk of aspiration, because of the increase in intra-abdominal pressure and the head-down position. Patients undergoing laparoscopic cholecystectomy will be at an even higher risk, because secretion of gastric acid is increased and because these patients may regurgitate or vomit bile-stained fluid. However various mechanisms prevent regurgitation during surgery.[1,2] Inspite of this, there have been several reports of pulmonary aspiration in patients undergoing laparoscopic cholecystectomy.[3] Measures and maneuvers to prevent aspiration of acid gastric contents during general anesthesia include preoperative fasting, non- particulate antacids, H2 receptor blockers, gastro kinetic drugs like metaclopramide, rapid-sequence induction with cricoid pressure and awake extubation during emergence from general anesthesia.[4] Many published reports are available about intravenous use of H2 receptor antagonist and prokinetics, However reports about use of proton pump inhibitors(PPI'S) in prevention of acid aspiration in patients undergoing laproscopic surgery are scarce.

Aim of our study

Compare the efficacy of rabeprazole and pantaprazole on gastric volume and pH in patients undergoing elective laparscopic surgery under general anaesthesia.

Pantoprazole and rabeprazole both are substituted benzimidazole derivative and irreversibly proton pump inhibitor which have been shown to effectively reduce gastric acid secretion.[5,6,7] However Rabeprazole has been shown in vitro to be more readily converted to its active form than omeprazole, pantoprazole or lansoprazole.[7] Furthermore no trials to date have evaluated the effect of specific proton pump inhibitors on gastric volume and pH. Therefore we postulated that a single dose of intravenous rabeprazole 20mg, would yield greater acid output inhibition and a greater pH when compared to a single dose of intravenous pantoprazole 40mg in patients undergoing laparoscopic surgery under general anaesthesia.

Methodology

This study was undertaken after obtaining institutional ethical committee approval and patient's written informed consent from each patient scheduled for the study. Sixty adult patients of either sex, aged 18-55 yr, ASA physical status I or II, undergoing elective laparoscopic cholecystectomy and appendicectomy were included in this randomized, double-blind, controlled clinical trial. Complete preanesthetic evaluation was performed in each patient including detailed history taking, thorough physical examination and routine preoperative investigations. Obese (>20% of ideal body weight), diabetic patients, those with a history of any gastrointestinal disorder, who were receiving any medication known to interfere

with gastrointestinal function and affect gastric fluid composition or gastric emptying were excluded. The patients were allocated according to a computer-generated randomization method to one of two groups (n= 30 each). Fifteen minutes before the induction of anesthesia, 5mL was given intravenously (IV) in the form of either Pantoprazole 40 mg (Group P) and Rabeprazole 20 mg(Group R) by an anesthesia assistant who did not know the contents of the IV injection. All patients were kept nil orally previous night. Anesthetic monitoring as regard five leads electrocardiography (ECG), non-invasive blood pressure (BP), pulse oximetry (SPO_2), capnography ($ETCO_2$), and temperature was applied to all patients. Anesthetic induction was performed with propofol 2mg/ kg, and tracheal intubation was facilitated with atracurium 0.5mg/ kg. The lungs were ventilated, taking care to avoid inflation of the stomach. Anesthesia was maintained with nitrous oxide in oxygen and isoflurane. Muscle relaxation was maintained with 0.3mg/kg atracurium IV guided. After tracheal intubation and before start of surgery, an anesthesiologist who did not know which drug was given to the patient, inserted a 16 G multiorifice nasogastric tube (NGT) into the stomach. Its placement within the stomach was verified by auscultation over the epigastrium during the introduction of 10ml of air. Gastric fluid samples were obtained by gentle aspiration with a 50ml syringe by an investigator who was unaware of the patient's pre-anesthetic medication. Aspirations were attempted with the patient held in supine, reverse Trendlenburg, and lateral positions to maximize gastric emptying. At any position, pressure was applied over the epigastrium, and gastric contents were aspirated intermittently during removal of NGT. The volume of gastric contents was measured with a syringe. Another NGT was inserted till end of the procedure. Great care was taken to avoid epistaxis, vomiting, oxygen desaturation or any other serious complications during insertion of NGT. The pH of the gastric fluid was determined immediately using a pHep pH meter (Range 0.0 to 14.0 pH, resolution 0.1 pH, accuracy ±0.1 pH).

The time interval between study drug injection to post intubation aspiration estimated. Haemodynamic parameter monitored throughout including SPO_2 at regular interval of 5 min till the end of surgery. Aspiration repeated before extubation and its volume and pH measured as previously. The time interval between study drug injection to pre-extubation aspiration estimated. We observed following findings to rule out aspiration: 1) the presence of foreign material in the mouth or posterior pharynx; 2) sudden coughing or laryngospasm; 3) dyspnea, tachypnea, hyperpnoea or apnea; 4) bronchospasm, wheezing or rales; 5) chest retraction or obvious airway obstruction; 6) cyanosis, particularly if not relieved by oxygen; 7) tachycardia and signs of shock; 8) development of pink frothy exudate.

Patient reversed with Neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. Patient extubated when reflexes are active. All patients were observed in the recovery room and then in the postoperative ward for 24 hours to rule out any complication due to acid aspiration and also side effects of drug injected. Times of administration of study drug and aspiration at post intubation (PI) and pre extubation (PE) were noted. The particulate and non-particulate nature of aspirate was also noted. A pH of ≤3.5 and volume of >25 ml were regarded as clinically significant and a combination of two was regarded as placing the patient at risk of acid aspiration.

A power analysis was performed to determine sufficient sample sizes required for establishing significant differences in the gastric variables based on the results of the preliminary study using an alpha value of 0.05 and power of 0.9, a sample of 20 patients in each group was require. Taking in to considerations the drop outs, we chose a sample size of 30. The data analysed using, percentages, mean value, standard deviation, standard error and 't' test, proportion test also used where ever necessary. The values computed was compared with table values, at 0.05 and 0.01 levels of significance for the corresponding degrees of freedom. P <0.05 or 0.01 was considered as significant and vice-versa.

Results

The demographic data of patients in both the groups is presented in Table 1. The mean value of age distribution, mean NPO status, the mean duration of surgery, the mean duration of anaesthesia, the mean interval between drug injection to post-intubation aspiration, the mean interval between drug injection to pre-extubation aspiration, the mean interval between post-intubation and pre-extubation aspiration all were statistically not significant. The mean post-intubation volume was 20.52±4.46ml in group R and 22.48±4.33 in group P which was statistically significant. The mean pre-extubation volume in group P was 15.14±3.66 and 11.10±2.84 in group R which was statistically significant. The minimum and maximum post intubation and pre-extubation volumes are summarized in Table 2. The pH of gastric aspiration content in both groups is summarized in Table 3. The mean pH of post-intubation gastric aspiration contents in group P was 6.41±0.69 and in group R was 7.37±0.56 which was statistically significant with respect to pH ($p<0.05$). The mean value of pre-extubation aspiration pH in group P was 6.98±0.611 and in group R was 8.14±0.537 which was statistically significant ($p<0.05$). There was no statistically significant difference in time duration between two samples ($p>0.05$). There was no statistically significant changes with respect to pulse rate, blood pressure including mean arterial pressure at various intervals in both the groups ($p>0.05$).

In both the groups with respect to post-intubation aspiration it was observed that no patients met the at risk criteria for acid aspiration. At risk criteria means the volume of gastric aspiration is >25 ml and pH <3.5 or both in any sample of post-intubation or pre-extubation.

Table 1: Demographic data

	Group I	Group II	P value
Age	34.34±3.77	36.06±4.44	NS
Weight	45.12±7.56	47.51±3.09	NS
Sex(M/F)	12/18	14/16	NS
ASA grade I/II	10/20	18/12	NS
Duration of surgery	58.44±14.63	61.46±13.93	NS

Table 2: Post-intubation and pre-extubation volume

Volume	Group P			Group R			P value
	Mean (ml±SD)	Max	Min	Mean	Max	Min	
Post-intubation volume(ml)	20.52±4.46	25	12	22.48±4.33	25	15	0.023*
Pre-extubation volume(ml)	15.14±3.66	32	10	11.10±2.84	5	18	0.000*

P – Pantaprazole; R- Rabeprazole; * - significant($p<0.05$); max- maximum; min-minimum

Table 3: Post-intubation and pre-extubation gastric aspiration pH

pH	Group P			Group R			P value
	Mean	Max	Min	Mean	Max	Min	
Post-intubation	6.412±0.69	7.9	4.6	7.376±0.56	8.6	6	0.000*
Pre-extubation	6.98±0.611	7.9	5.7	8.14±0.537	9.3	6.4	0.000*

P – Pantaprazole; R- Rabeprazole; * - significant($p<0.01$); max- maximum; min-minimum

Discussion

Various measures have been described prevent aspiration.[8] The condition of aspiration pneumonitis and its dreaded sequelae are well known to the anesthesiologists. Although it is not absolutely preventable, but by adopting some precautions or preventive measures, the chance of aspiration or if it occurs, its sequelae can be brought down to an absolute minimum. Approximately in about 1% of the total population, gastric content reaches airway by regurgitation and aspiration, is likely to occur during induction.[9] Patients especially undergoing upper abdominal surgery present a greater risk during induction and recovery.[10] Therefore in our study we have taken in to consideration post intubation and pre-extubation aspiration volume and pH for analysis.

Recently proton pump inhibitors are shown to have better efficacy in preventing acid aspiration(omeprazole, rabeprazole, lansoprazole, pantoprazole, esomeprazole). PPI'S after activation, concentrate in the secretory canaliculus of the parietal cell. The protonated molecules undergo a conversion to an active sulfenamide compound and, in this state, form covalent inhibiting disulfide bonds with surface-exposed cysteine's of the active parietal cell H+/K+-ATPase.

However, the five available PPIs differ in terms of acid stability. Due to the modified functional substituents on the rabeprazole, it can be activated at higher pH levels much faster than other PPIs. At acidic pH rabeprazole is activated faster compared to pantaprazole and other PPI'S. At pH 5.1 (the pH during fasting), the activation half-life was again the shortest one for rabeprazole. In addition, rabeprazole is known to have a faster onset of action in patients with heartburn leading some to suggest that rabeprazole may have efficacy as an on-demand or abortive therapeutic agent.[11] In an isolated hog vesicle model, rabeprazole confirmed its potent and fast onset of action but pantoprazole could only inhibit the 50% of the pump by the end of the 50 minute test.[12] Therefore, rabeprazole sodium produces a dose-related sustained inhibition of both basal and peptone meal-stimulated gastric acid secretion.[13,14]

In our study The mean post-intubation volume and pre-extubation volume in pantaprazole was 20.52±4.46ml and 15.14±3.66 respectively which was in consistent with previous studies who concluded that intravenous 40 mg pantoprazole is effective in reducing gastric volume and pH.[41,42,43] In rabeprazole group the mean post-intubation and pre-extubation volume was 22.48±4.33 and 11.10±2.84 respectively which was statistically significant. Similarly the mean value of post-intubation and pre-extubation aspiration pH was higher in group R compared to group P (8.14 versus 6.98) which was statistically significant. In a recent

study by Padmaja et al,[15] compared the effectiveness of intravenous rabeprazole 20mg and intravenous ranitidine 50mg on gastric fluid properties in patients undergoing elective surgery under general anaesthesia. Their results were consistent with the results of current study in the effectiveness of rabeprazole in reducing the gastric aspiration volume and ph but differ in methodology as they compared the pre intubation, post-intubation and pre-extubation volume and gastric ph. Whereas in our study we have taken in to consideration only post-intubation and pre-extubation gastric volume and ph. Similarly observation was reported by another study.[16] In other comparative trials rabeprazole has shown to be more potent acid inhibitor compared to pantaprazole.[17,18] Similarly in patients with acid peptic ulcer disease rabeprazole 10 mg compared to pantoprazole 40 mg decreased the incidence of nocturnal acid break through(NAB), decreased persisting time of NAB and increased mean pH of NAB.[19] In another cross over study using 5 different PPI'S, the intragastric pH was measured following PPI treatment for 5 consecutive days. On day 5 assessment rabeprazole maintained pH>4 for greater percentage of time compared to pantoprazole and other PPI'S except esomeprazole.

Rabeprazole, in less acidic environments, given its rapid activation over a wide pH range, actually targets a greater population of parietal cells to give a more rapid and pronounced degree of acid inhibition.[20] Its metabolism is largely non-enzymatic and therefore less dependent on CYP2C19, giving a greater consistency of pharmacokinetics across all patients, regardless of CYP2C19 genotype.[21]

A limitation of the study may be directed toward the fact that the gastric volumes in this study are not representative of the total volume of gastric contents, because emptying the stomach with a nasogastric tube has not been shown to ensure complete emptying of gastric contents. The alternate methods include gastric aspiration by using a visually guided gastroscope and dye-dilution technique. Estimated gastric volume by the dye-dilution technique has been shown to be similar to aspirated volume by blind aspiration.[22]

In conclusion prophylactic intravenous administration of rabeprazole 20 mg is more effective than pantaprazole 40mg for reducing gastric volume and improving gastric pH. Therefore, this can reduce the proportion of patients at risk of aspiration pneumonitis who undergo laparoscopic procedures.

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