

Comparison of the effect of oral esomeprazole with pantoprazole on gastric pH and gastric volume: “A randomised double blind placebo controlled study”

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Abstract

Aim: This study aims to evaluate the effects of prophylactic use of oral esomeprazole, pantoprazole and Placebo on Gastric pH and Gastric volume at the time of induction (post-induction) and at recovery (pre-extubation), in fasting patients undergoing surgical procedure under general anaesthesia. Material and methods: This prospective, randomized, double blind, placebo controlled study was done in sixty patients of ASA physical status I or II, aged between 18 – 65 years, of either sex, scheduled for elective surgery under general anaesthesia, were enrolled for the study.

Results: There was no statistically significant difference between the groups with respect to age and weight and also between the groups when compared to premedication to intubation time, premedication to extubation time and duration of surgery. When compared with placebo, the reduction in gastric volume was statistically ($P < 0.01$) and clinically significant in both pantoprazole and esomeprazole group during post induction (V1) and pre extubation (V2) time. However, when comparing with esomeprazole and pantoprazole there was no significant difference between the two groups. In V1 (post- induction) the maximum volume obtained in placebo, pantoprazole and esomeprazole groups were 25ml, 15ml, and 15ml, respectively whereas in V2 (pre-extubation) the maximum volume for placebo, pantoprazole and esomeprazole were 20ml, 15ml and 10 ml respectively. In fact we failed to obtain any gastric aspirate in one patient in each group. Both post-induction (pH1) and pre-extubation (pH2) pH in esomeprazole group, the increase in gastric pH was statistically ($P < 0.001$) and clinically significant when compared with placebo. In pantoprazole group also, the increase in gastric pH was statistically and clinically very highly significant when compared with placebo. Also when comparing esomeprazole and pantoprazole, esomeprazole was more effective in increasing gastric pH which was statistically significant ($P < 0.01$).

Conclusion: Both esomeprazole and pantoprazole when administered orally are effective in reducing gastric volume and increasing pH as compared to placebo. Tablet esomeprazole and pantoprazole are comparable with respect to reduction in gastric volume but esomeprazole increase the gastric pH more effectively than pantoprazole.

Keywords: Pantoprazole, Esmoprazole, Gastric pH, Gastric volume, General anaesthesia

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Introduction

Aspiration of acidic gastric contents is still a major cause of anaesthetic morbidity and mortality especially during emergency cases. It was Mendelson who described aspiration syndrome as the cause of increase in obstetric death.^(1,2) In 1974, Roberts and Shirley described those patients with a pH less than 2.5 and volume more than 25 ml (0.4ml/kg) were at a risk of developing Mendelson syndrome.⁽³⁾ Investigations showed that the quantities of aspirate as well as its acidity were the major determinant factors.

pH is a important factor than volume to determine the risk of developing aspiration pneumonitis. So various measures were taken to reduce the volume as well as acidity of gastric contents.

The particulate antacids are effective in raising the gastric pH above 2.5, but they are short acting and also increase the gastric volume. Most of these antacid preparations are colloidal suspension which on aspiration cause pneumonitis.

Non particulate antacid like sodium citrate can be used, but it is poorly absorbed in the body and increase pH as well as gastric volume.^(4,5)

The Hydrogen ion is secreted in stomach by the gastric parietal cell. H_2 receptor antagonist like ranitidine is shown to increase the gastric pH by inhibiting acid secretion. Effectiveness of H_2 receptor antagonists were increased when used along with antacids.⁽⁶⁾ Proton pump inhibitors like omeprazole and pantoprazole which can inhibit the H^+K^+ ATPase enzyme can also effectively inhibit the acid secretion even when used it alone.

Esomeprazole is a newer drug and is claimed to be longer acting and more potent than H_2 receptor antagonist and other proton pump inhibitors.

So, in our study we planned to evaluate the effects of prophylactic oral tablet esomeprazole and pantoprazole when compared to placebo on gastric pH and volume in elective procedures.

Aim and Objectives

To evaluate the effects of prophylactic oral Esomeprazole, Pantoprazole and Placebo on

- Gastric pH
- Gastric volume

At induction (post-induction) and at recovery (pre-extubation), in fasting patients undergoing surgical procedure under general anaesthesia.

Patients and Methods: Sixty patients of ASA physical status 1 or 2, aged between 18–65 years, of either sex, scheduled for elective surgery under general anaesthesia, were enrolled for the study. The study protocol was approved by the dissertation committee of the department and Ethical committee of the hospital, and informed consent was obtained from all patients. Patients were explained about the possibility of receiving a placebo with no possible beneficial actions during the study.

Inclusion Criteria: All patients aged between 18–65 years, weighed between 45–65 kg belonging to ASA physical status 1 or 2 of either sex, scheduled for elective short surgical procedures under general anaesthesia were enrolled for the study.

Exclusion Criteria: Pregnant, non-ambulatory patients, patients receiving drugs known to affect gastric motility and secretion, Patient with known acid peptic disease, gastric, renal or hepatic diseases history, known smokers and alcoholics were excluded from the study. Patients fasted for more than 6 hours after premedication and administration of atropine during anaesthesia were excluded from the study.

Anticipating difference of two units (0.2) in pH, with a standard difference of 2.7, for a 80% power and 5% level of significance, sample size of 20 was required in each group calculated by analysis of variance. Each group consisted of 20 patients.

Statistical analysis of the data was done using SPSS version 11.5 for windows.

There were two observers in our study. Observer 1- Primary investigator, anaesthesia postgraduate who was blinded to the type of drug used for premedication, did the preoperative assessment and collected the data. Observer 2- Anaesthesia consultant who inserted the endotracheal and Ryle's tube, measured the total volume of the gastric fluid aspirated, and sent the same sample of gastric content to lab for its pH measurements.

Patients were divided into three groups of 20 each and were randomly assigned to one of the three groups, GROUP pantoprazole(P), GROUP esomeprazole(E), and Placebo(PB), using a computer generated random number table.

Depending on randomisation, patient received following premedication in the night before surgery with sips of water. Group (P_B) patients received Tablet becosules [oral] B 'complex forte with vitamin C I capsule (Becosules Capsules, Pfizer limited, Navi Mumbai, India)], Group (P) patients received Tablet pantoprazole 40 mg [Pantodac-40 mg, (Astra Zeneca Pharmaceuticals Limited, India)] and Group (E) patients received Tablet esomeprazole 40 mg [Neksium-40 mg, (Astra Zeneca Pharmaceuticals

Limited, India)] orally each with 100 ml of water, two hours before induction of general anaesthesia.

On arrival in the operation room, the patients were questioned as to the time of premedication by (observer 1) and NPO status was confirmed. Anaesthetic techniques were standardised for all the patients, ECG, NIBP, SPO₂, ETCO₂ monitors were connected, IV line was secured. Preoxygenation was done for 3 minutes. General anaesthesia was induced, with intravenous fentanyl 2 µg/kg, given for analgesia, intravenous induction done with propofol 2–3 mg/kg (loss of verbal contact was taken as the end point of induction), monitoring the cardio-respiratory system, and trachea was intubated with appropriate size endotracheal cuffed tube, after paralyzing with muscle relaxant (0.1 mg/kg) vecuronium, and after checking ability to mask ventilate. Anaesthesia was maintained with oxygen, nitrous oxide in the ratio of 33: 66 and Isoflurane upto MAC of 1. An orogastric multiorifice 14 F Ryle's tube was passed into the stomach and its position confirmed by auscultation over the epigastrium for insufflated air and aspiration of gastric contents. Gastric aspiration was done with a 20 ml syringe (by the observer 2) with the patient in supine, and 30 degree head up and head down position, as well as in the right and left lateral position to ensure complete aspiration of gastric contents.

The gastric contents measurements, with respect to pH and volume were made twice, once after induction of general anaesthesia, and other before extubation during recovery of anaesthesia. The volume of the fluid aspirated was measured and pH was determined with a pH meter (Eutech cyber scan 510 pH) in the lab. The investigator aspirating the sample (observe 2), was unaware of the group to which the patients had been assigned.

After the completion of the study decoding was done and the values were tabulated and analyzed statistically using one way analysis of variance by Anova for comparison of volume, age and weight between various groups. Comparison of actual number of patients at risk, between different study groups, was done using 'chi' square test and inter group comparison was done by post hoc test, P-value less than 0.05 was taken as significant (s), less than 0.01 as highly significant (HS), and 0.001 as very highly significant (VHS).

A difference of 25% (more or less than) was taken as clinically significant

Results

The participants in three groups were compared in terms of Age, weight, premedication to intubation time, premedication to extubation time and duration of surgery was statistically insignificant

Table 1: Comparison of gastric volume at post-induction(V1) and pre- extubation(V2)

| Time of Sampling | Group | Volume Mean±SD (Range) |
|--------------------|------------------------|------------------------|
| V1(Post Induction) | esomeprazole(E) (n=20) | 6.95±3.71 (0-15) |
| | pantoprazole(P) (n=20) | 7.75±4.28 (0-15) |
| | placebo(PB) (n=20) | 12.30±7.17 (0-25) |
| V2(Pre-Extubation) | esomeprazole(E) (n=20) | 6.10±2.73 (0-10) |
| | pantoprazole(P) (n=20) | 6.65±3.63 (0-15) |
| | placebo(PB) (n=20) | 10.25±4.29 (0-20) |

One Way ANOVA

(Post HOC TEST) p-value

- esomeprazole with pantoprazole= 0.881(NS)
- placebo with esomeprazole = 0.006(HS)
- placebo with pantoprazole= 0.023(S)

V2

- esomeprazole with pantoprazole = 0.88(NS)
- placebo with esomeprazole = 0.002 (HS)
- placebo with pantoprazole= 0.007 (HS)

Table 1) shows post induction (V1) and pre extubation (V2) volume [gastric volume (Mean ±SD)] in the placebo, pantoprazole and esomeprazole group.

Both V1 (post- induction) and V2 (pre - extubation) in esomeprazole group the reduction in gastric volume was statistically ($P<0.01$) and clinically significant ($>40\%$) when compared with placebo group.

In pantoprazole group also, the reduction in gastric volume was statistically ($P<0.01$) and clinically significant when compared with placebo. However, when comparing with esomeprazole and pantoprazole there was no significant difference between the two groups.

In V1 (post- induction) the maximum volume obtained in placebo, pantoprazole and esomeprazole groups were 25ml, 15ml, and 15ml, respectively whereas in V2(pre-extubation) the maximum volume for placebo, pantoprazole and esomeprazole were 20ml, 15ml and 10 ml respectively. In fact we failed to obtain any gastric aspirate in one patient in each groups.

Table 2: Comparison of gastric pH at post induction(pH1) and pre-extubation (pH2)

| Time of pH Estimation | Group | pH Mean ±SD (Range) |
|-----------------------|------------------------|---------------------|
| pH1(Post Induction) | esomeprazole(E) (n=20) | 5.27±1.53 (0-7.24) |
| | pantoprazole(P) (n=20) | 4.00±1.48 (0-5.9) |
| | placebo(PB) (n=20) | 1.65±0.62 (0-2.85) |
| pH2(Pre Extubation) | esomeprazole(E) (n=20) | 5.22±1.62 (0-7.2) |
| | pantoprazole(P) (n=20) | 3.93±1.47 (0-5.3) |
| | placebo(PB) (n=20) | 1.79±0.73 (0-3.79) |

One Way ANOVA

(POST-HOC Test)p-value

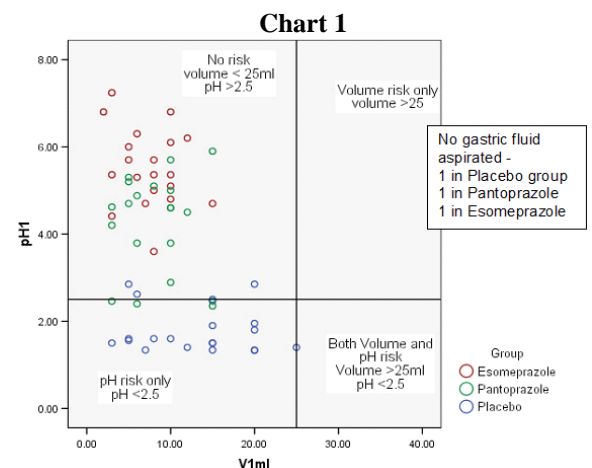
pH1

- esomeprazole with pantoprazole = 0.007 (HS)
- placebo with esomeprazole = <0.001 (VHS)
- placebo with pantoprazole= <0.001 (VHS)

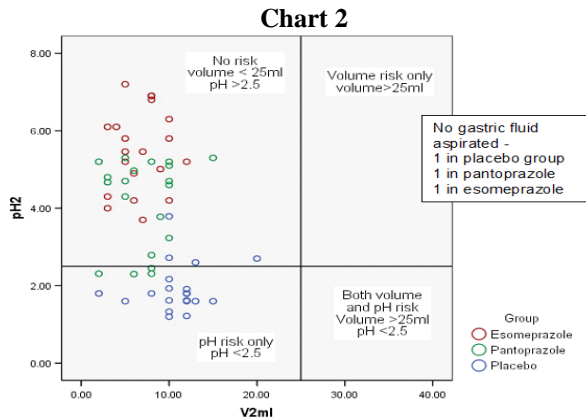
pH2

- esomeprazole with pantoprazole = 0.009 (HS)
- placebo with esomeprazole = <0.001 (VHS)
- placebo with pantoprazole= <0.001 (VHS)

Table 2 shows the gastric pH [Mean(pH±SD)] in the placebo, pantoprazole and esomeprazole groups. Both post-induction(pH1) and pre-extubation (pH2)pH In esomeprazole group, the increase in gastric pH was statistically($P<0.001$) and clinically significant when compared with placebo. In pantoprazole group also, the increase in gastric pH was statistically and clinically very highly significant when compared with placebo. Also when comparing esomeprazole and pantoprazole; esomeprazole was more effective in increasing gastric pH which was statistically significant ($P<0.01$).



The volume (V1) and pH(pH1) of the gastric contents of all the 60 patients in the three GROUPS - Post-Induction.



The volume (V2) and pH(pH2) of the gastric contents of all the 60 patients in the three groups -Pre-Extubation

Discussion

Aspiration pneumonitis is a possibility when pulmonary aspiration occurs with a gastric volume greater than 25 ml or ($>0.4\text{ml/kg}$) and pH less than 2.5.⁽⁷⁾ Several means of decreasing the risk of aspiration have been studied by decreasing the volume, increasing the pH so that risk of Aspiration pneumonitis can be reduced to absolute minimum.⁽⁶⁾ Although gastric volume and pH are major determinants of risk of developing aspiration pneumonitis, recent evidence suggest that pH is more critical than volume.⁽⁷⁾

Healthy patients coming for elective surgery commonly have gastric fluid volumes greater than 25ml and pH less than 2.5 despite endured prolonged fasting, so even elective fasting patients are at risk of acid aspiration syndrome.^(3,10) Pulmonary aspiration of large volume with very low pH resulted in high mortality than lower volume with high pH.⁽¹¹⁾

The patients at risk are pregnant ladies,^(21,22) patients with full stomach as in emergency surgery, ascites etc., who need to be taken care of before taking up for general anaesthesia, so we have to have an effective, safe and easy means of decreasing not only the risk of regurgitation and aspiration of gastric fluid but also of aspiration pneumonitis.

The H_2 receptor antagonists have been found to be more effective in reducing the risk of aspiration pneumonitis by decreasing the gastric volume and pH but with no effect on gastric emptying.⁽⁸⁾ In addition to H_2 receptor antagonists other methods like cricoid pressure and gastric emptying by means of nasogastric tube prior to induction, have been found to be very effective though not 100% protective.⁽⁷⁾ Effectiveness of H_2 receptor antagonists were increased when used along with antacids. Unlike H_2 receptor antagonists, proton pump inhibitors like omeprazole and pantoprazole can also effectively inhibit the acid secretion even when used it alone.

Among the proton pump inhibitor, esomeprazole is claimed to be better than pantoprazole in reducing

gastric acidity.^(12,13,14,15) Moreover Esomeprazole proved to reduce the night time burn and GERD related sleep disturbances.⁽¹⁷⁾ This is the reason we choose esomeprazole to compare its effectiveness with pantoprazole in our study.

In our study we found that both esomeprazole and pantoprazole decreased the risk of aspiration by decreasing the gastric volume which was clinically significant. Esomeprazole decreased the volume of the gastric aspirate to a greater extent than pantoprazole which was statistically significant. In our study mean gastric volumes were never greater than critical level in all the fasting patients in each of the three groups as in study of *Radev et al.*⁽⁹⁾ Only one patient in placebo group had gastric volume of 25 ml.

The number of patients with pH less than 2.5 were 17 (85%) during post -induction and 16 (80%) during pre-extubation period in the placebo group which was clinically very highly significant when compared with esomeprazole and pantoprazole groups. Pantoprazole group had 4 (20%) patients with pH <2.5 both during post -induction and pre -extubation period which was clinically & statistically significant when compared to esomeprazole group, which had none with pH less than 2.5.

In esomeprazole group, both during post- induction and pre- extubation period number of patients with pH less than <2.5 were none, and patients with pH >2.5 were 20 (100%).

None of the patients had volume $>25\text{ml}$ in all the three groups during post -induction and pre- extubation period.

Our study findings are comparable with those of *J. Labenz* and with *Miehlke*,⁽¹⁸⁾ who observed that esomeprazole 40 mg orally was more effective in increasing gastric pH (reducing gastric acidity) when compared with pantoprazole 40 mg orally.

In our study, we observed that one patients in each group had no gastric aspirate both during post-induction and pre- extubation periods.

The study drugs were given in such a way that the duration of action coincided with the study period and decreased the mean gastric volume more than ($>40\%$) in esomeprazole and pantoprazole groups, which was clinically and statistically significant ($P<0.001$) when compared to placebo, even though the mean volumes were much less than the critical levels in all the three groups as observed in the study conducted by *Radev et al.*⁽⁹⁾

In our study the pH was consistently high in both esomeprazole and pantoprazole group when compared with placebo ($>50\%$). They were both clinically and statistically significant ($P<0.001$).

The number of patients with volume risk were nil in all groups where as 4 (20%) and 17 (85%) patients in pantoprazole and placebo group respectively had pH risk during post induction period, which was clinically significant. 4 (20%) patients in pantoprazole group and

16 (80%) patients in placebo group had PH risk, during pre-extubation period. All the patients in esomeprazole group had no volume and pH risk during both periods. These findings were observed both during post - induction and pre- extubating samples. These results are comparable with the study of *J. Labenz* and *S. Miehke*.⁽¹⁸⁾

The reason for low gastric volume in all the patients in the three groups might have been due to the type of premedication used during the pre-operative period which requires further elucidation.

Our study is similar to *T. Labenz et al*, where in a randomized comparative study of esomeprazole 40mg versus pantoprazole 40mg for healing erosive oesophagitis, esomeprazole 40 mg is more effective than pantoprazole 40 mg with respect to reduction in gastric acidity.⁽¹⁸⁾

Our study is similar to *Robert J Hoogen doorn* (Auckland) where he did a selected study on dutch patients receiving PPIs (esomeprazole, pantoprazole, rabeprazole) and found that switching to esomeprazole was associated with a positive effect on patients satisfaction with treatment.⁽¹⁹⁾

Our study is similar to *S. Miehke* where he has found that esomeprazole 40mg twice daily provided better and more consistent intragastric acid control than pantoprazole 40mg twice daily. Esomeprazole provided significantly higher intra gastric pH values over the 24hr period (median intragastric pH 6.4 for esomeprazole and 5.1 for pantoprazole).⁽¹²⁾

So we, recommend Tablet esomeprazole 2hr prior to induction of anaesthesia, as esomeprazole increases gastric pH more effectively than pantoprazole.

Limitations

The aspiration technique of estimating gastric fluid volume is still controversial. The volume aspirated using the blind technique may under estimate true gastric volume, but it is the method which is commonly used in several studies.^(20,23) The true effect of drug in reducing the gastric volume is difficult to demonstrate by using blind technique.

Our study was done in ASA grade 1 and 2 physical status patients who were scheduled for elective surgery and so further study is required to know whether the results we got can be extrapolated to patients at high risk for e.g. obese and pregnant ladies and patients scheduled for emergency surgery.

Conclusions

Both esomeprazole and pantoprazole when administered orally are effective in reducing gastric volume and increasing pH as compared to placebo. Tablet esomeprazole and pantoprazole are comparable with respect to reduction in gastric volume but tablet esomeprazole increase the gastric pH more effectively than pantoprazole.

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