DOI: https://doi.org/10.53350/pjmhs211571760

**ORIGINAL ARTICLE**

# Comparison of effect of Various Combinations of four drugs i.e IV Ondansetron, Ranitidine, Metoclopramide and Omeprazole, to reduce Gastric Fluid Residual Volume and Gastric Acidity in Elective Laparoscopic-Cholecystectomy patients

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## ABSTRACT

**Background:** Inhaling of gastric contents in lower respiratory tract and larynx results in developing of pulmonary aspiration. The acidity of aspirate contents and its volume determines severity of aspiration and is major cause of post-anesthetic mortality.

**Objective:** To compare the effect of four drugs (ranitidine, IV ondansetron, metoclopramide, omeprazole and metoclopramide) in all possible four combinations, to decrease gastric fluid residual volume and gastric acidity in undergoing laparoscopic-cholecystectomy.

**Design:** It was a clinical randomized trial.

**Study Settings:** Trial was conducted at Department of Anesthesiology and ICU, Sheikh Zayed Hospital, Lahore, for a period of 6 months from 01-07-2019 to 31-12-2019.

**Patients and Methods:** A total of 308 patients from both the genders undergoing laparoscopic cholecystectomy were included in this study. Four equal groups were made by random division of patients. Group A: ranitidine & ondansetron, group B: ranitidine & metoclopramide, group C: omeprazole & ondansetron and group D: omeprazole & metoclopramide. Pre-anesthetic medicine was given to all the patients two hours before surgery. For assessing volume of gastric fluid and its pH, an oro-gastric tube was passed. An informed written informed consent was taken from all the patients.

**Results:** Mean age in this study was 36.40±9.15, 33.23±9.13, 36.82±9.37 and 36.57±9.49 years respectively for Group A,B,C and D. Aspirate had mean quantity of 12.56±5.60 ml/kg, 12.65±5.39 ml / kg, 13.68±5.76 ml/kg and 14.34±6.85 ml/kg and he aspirate mean pH was 2.56±0.55, 2.47±0.58, 2.51±0.57 and 2.45±0.58 respectively for group A,B,C and D. Among both the trial groups, this different was insignificant (p-value > 0.05) for both outcomes.

**Conclusion:** All the drug combinations had no significant difference. However, comparatively less pH and volume of gastric fluid was shown by combination of ranitidine plus ondansetron. Therefore, this combination is recommended before general anesthesia for reducing gastric fluid aspirate in patients undergoing surgery.

**Keywords:** Laparoscopic cholecystectomy, Omeprazole, Ranitidine, Metoclopramide, Ondansetron, gastric fluid acidity, pH, gastric fluid volume

## INTRODUCTION

In pulmonary organs inhaling of gastric substance in larynx and lower respiratory tract results in aspiration of gastric counts. The volume and acidity of the aspirate and predisposing factors determine its severity.[1] Gastric acid [HCL] is produce by parietal cells, located in the body of stomach, which secretes HCL and intrinsic factor into the lumen of stomach. In the parietal cells CO2 and H2O are converted to H+ and HCO3- , catalyzed by carbonic anhydrase. H+ is secreted into the lumen of stomach by H+--K+ pump [H+-K+- ATPase] .Cl- is secreted along with H+ thus the secretion product of parietal cells is HCL.[2,3] 25ml or above gastric volume and less than 2.5 pH of gastric volume have been determined as critical factors for causing damage to pulmonary tissues. In practice of anesthesia, protection of airway is advocated by the use of prophylactic pharmacological therapy. Normal gastric emptying occurs within 3 hours, slower for high fat meals and quicker for liquids. During fasting, the stomach secretes approximately 500 to 1500 mL; in the fed state, about 2,500 mL per day. [4,5]

For reducing acidity level and gastric volume various measures have been adopted i.e use of various agents like antacids, pro-kinetics, H2 receptor antagonist and proton pump inhibitors. Most of the anesthesiologist use metoclopramide and ondansetron particularly in diabetic patients having gastroparesis.[4] Ranitidine and omeprazole are supposed to reduce gastric fluid acidity. Anesthesiologists most commonly use metoclopramide and ondansetron particularly in diabetic patients. Ranitidine and omeprazole are used for reducing gastric fluidity acidity.[6-8] In 1990, ondansetron was used for the first time and it is indicated to prevent surgical vomiting and nausea and can be administered in any mode. Its side effects include

Received on 02-01-2021
Accepted on 09-06-2021

flushing, fatigue, hiccups, headache, rashes, faintness, diarrhea and QT interval prolongation. Its quick IV administration results ototoxocity.[8,9]

Matsota et al.[10] reported 1% extrapyramidal side effect of metoclopramide but witnessed its 85% significance in reducing residual gastric fluid volume when it was administer IV 15-30 minutes prior to surgery. H2 receptor antagonism is action mechanisms of ranitidine. It is commonly used prophylactic agent for minimizing acid aspiration syndrome prior to administration of anesthesia. Amongst its side effects are diarrhea, abdominal pain, constipation, headache and fatigue. Hong J-Y et al.[1] studied combination of ranitidine and metoclopramide versus placebo to see its effect on gastric volume. Metoclopramide 10mg and ranitidine 50mg were IV administered 15 minutes before inducing anesthesia. In placebo group gastric fluid was 2.7 ± 2.0 while the combination therapy group had 6.1 ± 1.9. As regards aspirated gastric volume, it was 15.3 ± 10.4 in the former group while the later had 6.9 ± 10.0 indicating that IV administration of the combination had better effect in reducing residual volume and stomach acidity in patients who were undergoing laparoscopic surgery.

For treating gastro-esophageal reflux syndrome, omeprazole is used which is a proton pump. Simbolon et al.[9] conducted a double randomized controlled trial by adding omeprazole to ondansetron for avoiding vomiting and nausea after chemotherapy. The failure ratio was 18% in ondansetron-omeprazole group while in ondansetron-placebo group it was 50% p-value = 0.01. There was no local published data. So, the purpose of this study was to repeat this clinical study in local population and see the efficacy of various combinations of all the four drugs in reducing residual volume of gastric fluid and its acidity.

## PATIENTS AND METHODS

This clinical randomized trial was conducted at Department of Anesthesiology & ICU at Sheikh Zayed Hospital, Lahore for a period of 6 months i.e 01.07.2019 to 31.12.2019. Patients were selected on non-probability, consecutive sampling method. A sample size of 308 patients was estimated at 95% condolence level, 90% power of test by taking expected Volume > 25ml and frequency of pH < 2.5 in ranitidine and omeprazole as 12.5% & 0% respectively. As various combinations of the drug results four groups, so the sample population was divided on random basis in four groups with 77 patients in each group, having ASA I & II class, belong to both genders and in age range of 20-50 years. But, patients with fistula and intestinal obstruction or those using medicine like proton pump inhibitor, H2-blockers, anti-acids or with history of extra-pyramidal side effect were excluded. An informed written consent was taken. Patients were advised fasting for 6-8 hours and routine medicines were stopped about 6-8 hours before surgery. Four groups were made as: Group A: (ranitidine 50mg I/V with ondansetron 0.15mg/kg), Group B: (ranitidine 50mg with metoclopramide 10mg), Group C: (omeprazole 0.5mg/kg with ondansetron 0.15mg/kg) and Group D: (omeprazole 0.5mg/kg with metaclopramide 10mg). Combination therapy was administered IV in all the groups before two hours of surgery.

As per standard protocols, patients were anesthetized with 3 minutes pre-oxygenation after observing ASA I & II. All patients were pre-oxygenated for 3 minutes. General anaesthesia was standardized for all groups. Then patients were induced with I/V propofal 2mg/kg body weight with I/V lignocain preservative free in concentration of 0.1% 1mg of lignocain into propofal. I/V fentanyl 1mg/kg and I/V actracurium 0.5mg/kg body weight. Anaesthesia is maintained with 100% oxygen and isofloren 1.2 MAC. For induction of anesthesia an orograstric tube was passed to the stomach.

SPSS version 2.0 was used for data analysis. At first, frequency tables were generated for categorizing values of pH and fluid volumes for various combinations and its mean± was calculated. Then, among all groups pH level and aspirated fluid volume were compared by using ANOVA in case of normal distribution but if otherwise then Kruskal-Wallis test. Mann-Whitney U-Test was applied post analysis. In each group data for aspiration pneumonitis was shown by using frequency & percentages and chi-square test was applied for comparison among the groups. P-value ≤0.05 was taken as significant.

## RESULTS

Mean age in this study was 36.40±9.15, 33.23±9.13, 36.82±9.37 and 36.57±9.49 years respectively for Group A,B,C and D.

Table 1: Baseline Characteristics of Study Sample

| Description | Group (n=77 each group) | | | |
|---|---|---|---|---|
| | Ondansetron +Ranitidine | Metoclopramide + Ranitidine | Ondansetron + Omeprazole | Metoclopramide + Omeprazole |
| • Age (Years) | 36.40±9.15 | 33.23±9.13 | 36.82±9.37 | 36.57±9.49 |
| Age Range (years) | 20-50 | 20-49 | 20-50 | 20-50 |
| | ANOVA value=2.552, p-value=0.056 | | | |
| • Gender | | | | |
| Male | 28(36.4%) | 21(27.3%) | 22(28.6%) | 31(40.3%) |
| Female | 49(63.6%) | 56(72.7%) | 55(71.4%) | 46(59.7%) |
| Total | 77 | 77 | 77 | 77 |
| | Chi-square value=4.046, p-value=0.257 | | | |
| • Distribution of ASA Status | | | | |
| I | 36(46.8%) | 32(41.6%) | 39(50.6%) | 40(51.9%) |
| II | 41(53.2%) | 45(58.4%) | 38(49.4%) | 37(48.1%) |
| | Chi-square value=2.017, p-value=0.569 | | | |

Table 2: Comparison of Quantity of Aspirate among the Groups Stratified for Age, Gender & ASA Class.

| Description | Groups | | | | P-value |
|---|---|---|---|---|---|
| | Ondansetron +Ranitidine | Metoclopramide + Ranitidine | Ondansetron + Omeprazole | Metoclopramide + Omeprazole | |
| • Age (n, mean±) | | | | | |
| 20-35 Years | 32 (13.66±5.55) | 45 (12.24±5.44) | 33 (14.36±6.37) | 35 (14.23±6.78) | 0.370 |
| 35-50 | 45 (11.78±5.56) | 32 (13.22±5.35) | 44 (13.16±5.25) | 42 (14.43±6.99) | 0.219 |
| • Gender (n, mean±) | | | | | |
| Mal | 28 (12.11±5.65) | 21 (12.57±5.06) | 22 (13.23±5.55) | 31 (15.16±7.61) | 0.256 |
| Female | 49 (12.82±5.61) | 56 (12.68±5.55) | 55 (13.85±5.89) | 46 (13.78±6.31) | 0.620 |
| • ASA Classification (n, mean±) | | | | | |
| I | 36 (12.56±5.97) | 32 (12.16±5.39) | 39 (14.85±5.61) | 40 (14.68±7.16) | 0.133 |
| II | 41 (12.56±5.32) | 45 (13.0±5.42) | 38 (12.47±5.74) | 37 (13.97±6.58) | 0.657 |

Table 3: Comparison of pH Aspirate among the Groups Stratified for Age, Gender & ASA Class.

| Description | Groups | | | | P-value |
|---|---|---|---|---|---|
| | Ondansetron +Ranitidine | Metoclopramide + Ranitidine | Ondansetron + Omeprazole | Metoclopramide + Omeprazole | |
| • Age (n, mean±) | | | | | |
| 20-35 Years | 32 (2.62±0.47) | 45 (2.53±0.52) | 33 (2.46±0.63) | 35 (2.50±0.49) | 0.667 |
| 35-50 | 45 (2.51±0.61) | 32 (2.39±0.65) | 44 (2.55±0.53) | 42 (2.41±0.64) | 0.580 |
| • Gender (n, mean±) | | | | | |
| Mal | 28 (2.58±0.50) | 21 (2.44±0.70) | 22 (2.49±0.67) | 31 (2.33±0.64) | 0.514 |
| Female | 49 (2.55±0.58) | 56 (2.49±0.53) | 55 (2.52±0.54) | 46 (2.53±0.52) | 0.952 |
| • ASA Classification (n, mean±) | | | | | |
| I | 36 (2.53±0.59) | 32 (2.39±0.63) | 39 (2.41±0.64) | 40 (2.44±0.059) | 0.541 |
| II | 41 (2.58±0.52) | 45 (13.0±5.42) | 38 (2.62±0.48) | 37 (2.46±0.57) | 0.218 |

All the groups were insignificant at base value with regard to age, gender and ASA status as given in Table 1 & 2. There were total 102 (33%) male and 206 (67%) female participants with a male-to-female ratio of 1: 2.01. Aspirate had mean quantity of 12.56±5.60 ml/kg, 12.65±5.39 ml / kg, 13.68±5.76 ml/kg and 14.34±6.85 ml/kg and he aspirate mean pH was 2.56±0.55, 2.47±0.58, 2.51±0.57 and 2.45±0.58 respectively for group A,B,C and D. Among both the trial groups, this different was insignificant (p-value > 0.05) for both outcomes. Among both the trial groups, this difference was insignificant (p-value > 0.05) for both outcomes as given in Table 3.

## DISCUSSION

In treatment of cholelithiasis, a gold standard technique is laparoscopic cholecystectomy as it is effective and safe. Though, acidic contents of gastric lining rarely aspirate into respiratory tract / lungs yet they may disturb and compliance general anesthesia.[11-13] That is why, in routine practice for increasing gastric pH an decreasing gastric volume some pharmacological agents are used. Patients undergoing laparoscopic surgery by applying abdominal gas insufflation are at higher risk of gastric contents aspiration.[14-16] However, none of the studies reported effect of IV medicines on preoperative gastric contents.

In our study, mean quantity of aspirate was 12.56±5.60ml, 12.65±5.39ml, 13.68±5.76ml and 14.34±6.85ml respectively in group A,B,C and D. Among all the groups the difference was statistically insignificant. The aspirate mean pH was 2.56±0.55, 2.47±0.58, 2.51±0.57and 2.45±0.58 the groups respectively. The difference among groups was not statistically significant (p-value > 0.05). Ricci et al. reported 1% extrapyramidal side effect of metoclopramide; however, it had significantly decreased volume of residual gastric fluid i.e. 85% when it was administered IV 15-30 minutes before surgery. In comparison with proton pump inhibitor, pooled statistics have shown that ranitidine prophylaxis is better for reducing volume of gastric content (average = 0.22 ml/kg; 95% CI; 0.04-0.41) and increasing the pH (average = 0.85 pH units; 95% CI; -1.14 to -0.28).[11]

Administration of ranitidine and metoclopramide combination preoperative versus placebo in patients undergoing laparoscopic cholecystectomy, mean pH of ranitidine-metoclopramide combination had a mean pH of 6.1 ± 1.9 mean gastric volume was 6.9 ± 10 ml was

observed better.[26] Aspiration pneumonitis was noticed in any patients in our study.

A double blind randomized controlled trail in 2008 studied use of omeprazole and ondansetron as prophylactic agent for avoiding vomiting and nausea after chemotherapy. The treatment was unsuccessful in 18% patients who were given ondansetron + omeprazole therapy. However, this failure was 50% in placebo +ondansetron group with p-value=0.01, thus proved supremacy of the former group.[9]

Orr et al.[17] studied four groups where oral omeprazole 40 mg was given to the patients a night before surgery and in next morning 2nd dose was given to group 1. Group 2 was given omeprazole 80 mg on surgery morning. A combination of 40 mg oral omeprazole on surgery morning and IM 10 mg metoclopramide one night before surgery was given to the third group. In group 4, twenty minutes before anesthesia, 10 mg IM metoclopramide and 80 mg oral omeprazole was administered. This treatment was reported successful at the time of anesthesia administration as (volume <25 ml & pH 2.5) in 87%, 73%, 100% & 81% in the groups respectively. After surgery, these results were 100%, 88%, 100% & 100%.

Farhat et al.[18] noticed that ondansetron is significantly better when given before surgery as prophylaxis in comparisons with metolcoprmaide and it had less side effects of vomiting and nausea in patients undergoing laparoscopic cholecystectomy.[18] Similar, benefits of combination of ondansetron and ramosetron were ported by Schnadower et al.[19] and Ekinci et al.[20] in combined therapy of ondansetron with dopidole and tropitzerone showed better outcomes.

A very strong limitation to the present study was that various side effects of these treatment combinations could not be observed. Such a study is highly recommended in future research.

## CONCLUSION

All the combinations had no significant difference. However, comparatively less pH and volume of gastric fluid was shown by combination of ranitidine plus ondansetron. Therefore, this combination is recommended before general anesthesia for reducing gastric fluid aspirate in patients undergoing surgery.

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