ORIGINAL ARTICLE

Comparison of the Effect of Pre-operative Single Oral Dose of Tramadol and Famotidine on Gastric Secretions pH and Volume in Patients Scheduled for Laparoscopic Cholecystectomy

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Abstract

Objective: To evaluate and compare the effects of pre-operative single oral dose of tramadol and famotidine on gastric secretions pH and volume in patients electively scheduled for laparoscopic cholecystectomy.

Study Design: Randomized control trial.

Place and Duration of Study: Department of Anaesthesia, King Saud University Riyadh, Saudi Arabia, from August 2011 to June 2013.

Methodology: Ninety adult, ASA-I and II patients scheduled for laparoscopic cholecystectomy were included in the study. Patients were randomly assigned to receive pre-operatively either placebo (Group-C, n=30), oral tramadol 100 mg (Group-T, n=30) or famotidine 40 mg (Group-F, n=30). After induction of general anaesthesia, gastric fluid was aspirated through orogastric tube. The gastric secretions volume and pH was measured using pH meter.

Results: There was no statistically difference between groups in age, weight and gender. The gastric secretions mean pH was 2.06 ± 0.22,2.04 ± 0.20, 5.79 ± 0.77 and volume was 0.59 ± 0.17, 0.59 ± 0.14 and 0.28 ± 0.16 ml/kg in Group-C, Group-T and Group-F respectively. There was a significant statistical difference in the mean pH values between Group-C vs. Group-F ($p < 0.001$) and Group-T vs. Group-F ($p < 0.001$). Statistically significant difference was also found in the mean gastric secretions volume between Group - C vs. Group-F ($p < 0.001$) and Group-T vs. Group-F ($p < 0.001$). There was no significant difference in the mean gastric fluid pH values ($p=0.99$) and mean gastric secretions volume ($p=0.99$) between Group-T and Group-C.

Conclusion: As compared to famotidine, pre-operative single oral dose of tramadol was unable to elevate the desired level of gastric fluid pH (> 2.5) and decrease in gastric secretions volume (< 0.4 ml/kg).

Key Words: *Tramadol. Famotidine. Gastric. pH. Volume.*

INTRODUCTION

Perioperative prevention of aspiration of gastric contents is always a challenge for anaesthetist. Different strategies are employed for reducing the gastric secretions volume and pH. Pre-operative fasting and administration of H2 receptor blocking agents are considered to be effective strategies for the prevention of aspiration. Tramadol is an atypical analgesic agent. Its exact mechanism of action is not known. It has 100 times less affinity for mu opioid receptors as compared to morphine and causes less respiratory depression.[1,2] The other suggested analgesic effect of tramadol may be due to inhibition and re-uptake of serotonin and norepinephrine respectively.[3] Tramadol is considered to be a safe analgesic agent for mild to moderate pain and less sedative as compared to other opioid analgesic agents. Recently, it has been reported that tramadol is having antimuscrinic effect on M3 receptors and intraoperative intramuscular and intravenous injection of tramadol is able to increase gastric secretions pH and comparable to H2 blocking agents.[4,5]

The objective of this study was to determine the effect and compared the pre-operative single oral dose of tramadol and H2 blocking agent famotidine on gastric secretions pH.

METHODOLOGY

This trial was conducted at Department of Anaesthesia, King Saud University, Riyadh, Saudi Arabia, from August 2011 to June 2013.

This study was approved by the University Ethics Committee. Ninety adult patients, of either sex, age between 18 - 50 years, ASA physical status I or II presenting for laparoscopic cholecystectomy surgery were included in the study. Patients taking any sedative, tranquillizers, history of acid peptic disease, obesity (body weight more than 20% of the ideal body weight) and any contraindication to tramadol or famotidine were excluded. Informed consent was obtained from all patients. Randomization and drug delivery was done

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through hospital pharmacy. Patients were randomly assigned to receive either tramadol (Group-T, n=30), Famotidine (Group-F, n=30) or placebo (Group-C, n= 30). Patients in Group-C received placebo, Group-T received Tramadol 100 mg and Group-F received famotidine 40 mg orally 3 hours before calling the patient to operating room. General anaesthesia was induced with intravenous propofol 1.5 - 2 mg/kg and fentanyl 2 μ gram/kilogram. The lungs were ventilated with 100% oxygen and sevoflurane using circle breathing circuit with care to avoid inflation of the stomach. Tracheal intubation was facilitated after 3 minutes of administration of cisatracurium 0.2 mg/kg. Ventilation was adjusted to maintain the $PaCO_2$ at 35 to 40 mmHg. General anaesthesia was maintained with 2.0 to 2.5% sevoflurane in combination with 50% oxygen in air. All patients were monitored according to the ASA standard. A new 16-Fr Argyle Salem Sump catheter was inserted into the stomach. Placement of the orogastric tube within the stomach was verified by auscultation over the epigastrium during introduction of 10 ml air. Gastric fluid samples were obtained by gentle aspiration with a 50 mL syringe by an investigator who was unaware of the patient's pre-anaesthetic medication. Aspirations were attempted with the patient held in supine and reverse trendelenburg's position. The pH of the gastric fluid was determined immediately using a pH meter (Horiba F-8L; Horiba, Kyoto, Japan) that was already calibrated using standard buffers at pH values of 2,4, and 7. The pH meter had 0.01 pH units precision over the entire pH range. The gastric fluid pH of more than 2.5 and volume less than 0.4 ml/kg was considered as clinically desirable and significant.

Calculations were performed using SPSS version 21. The results are presented as the mean ± SD and percentage where appropriate. ANOVA table was generated for standard deviation calculation for age, weight, gender, pH and volume. Chi-square test was applied for gender. In case of statistical significance, post hoc tests were conducted with Bonferroni adjustments. A p-value < 0.05 was considered as statistically significant.

RESULTS

A total of 90 patients were studied, 30 patients in each group received either placebo, famotidine 40 mg or Tramadol 100 mg per oral 3 hours before taking the gastric fluid sample under general anaesthesia. There was no significant difference between the groups in age (p=0.937), gender (p=0.956) and body weight (p=0.940, Table I). None of the patient was eliminated from the study because of difficulty in the insertion of orogastric tube. The mean pH values were 2.07 ± 0.22, 2.04 ± 0.20 and 5.79 ± 0.77 for control, tramadol and famotidine groups respectively. The aspirated gastric fluid volumes were 0.59 ± 0.17, 0.59 ± 0.14 and 0.28 ± 0.16 ml/kg for control, tramadol and famotidine groups respectively (Table II). There was statistically significant difference in the mean pH values between Group-C vs. Group-F ($p < 0.001$) and Group-T vs. Group-F ($p < 0.001$). There was statistical difference in the mean gastric juice volume between Group-C vs. Group-F ($p < 0.001$) and Group-T vs. Group-F (p=0.001). There was no significant difference in the mean values of gastric juice pH (p=1.00) and volume (p=0.99) between Group-T and Group-C. The placebo and tramadol was unable to achieve the clinical relevant PH of more than 2.5 and gastric fluid volume less than 0.4 ml/kg.

Table I: Patients demographics, comparison of control, tramadol and famotidine group.
Data presented as mean ± SD and percentages for gender. There is no significant difference between groups ($p > 0.05$).

	Group-C n=30	Group-T n=30	Group-F n=30	p-value
Age (years)	45.73 ± 10.35	45.59± 8.31	45.07 ±8.71	0.937
Weight (kg)	71.11 ± 6.94	71.52± 7.68	71.54 ± 5.64	0.940
Gender				
Male	12 (40%)	12 (40%)	10 (33.33%)	0.956
Female	18 (60%)	18 (60%)	20 (66.66%)	

Table II: Comparison of gastric fluid pH and volume between control (C), tramadol (T) and famotidine (F) group. Data presented as mean ± SD. There is significant difference between groups C vs. F and T vs. F ($p < 0.05$)*.

	Group-C n=30	Group-T n=30	Group-F n=30	p-value
Ph*	2.07± 0.22	2.04 ± 0.20	5.79 ± 0.77	C vs. T 0.99 C vs. F 0.001 T vs. F 0.001*
Volume (m/kg $^{-1}$)*	0.59 ± 0.17	0.59 ± 0.14	0.28 ± 0.16	C vs.T 0.99 C vs. F 0.001* T vs. F 0.001*

** = Post hoc tests was applied, significant difference among the groups (p < 0.05).*

DISCUSSION

Managing perioperative pain and prevention of aspiration of gastric contents during anaesthesia is always a great challenge for the anaesthetist. Different strategies are employed for the prevention of aspiration including following the pre-operative fasting guidelines and use of H2 blocking agents. Tramadol is considered to be an effective analgesic agent for mild to moderate pain and used for pre-operative pain and chronic pain control. Tramadol is an atypical analgesic agent. Its mechanism of action is not fully understood. The suggested mechanism are binding of tramadol and its M1 metabolite to μ-opioid receptors. It has about hundred times less affinity for μ-opioid receptors as compared to morphine.[1,2] The weak affinity for μ-opioid receptor makes it less sedative as compared to morphine. The other antinociceptive action are due to weak inhibition of serotonin and reuptake of norepinephrine.[4,5] The analgesia is dependent upon the

plasma concentrations of tramadol and M1 compounds. Tramadol at clinically relevant concentrations via QNB binding sites is known to inhibit the M3 receptor function. Tramadol competitively affects muscarinic receptor function,[4,5] and bound to adrenal medullary cells and is replaced by atropine.[6] These findings suggest that tramadol at clinical relevant concentrations has anticholinergic effects.

Gastric fluid volume and acidity are two important factors for causing aspiration pneumonia in humans. It is generally considered that gastric pH more than 2.5 and volume less than 0.4 ml/kg decrease the risk of aspiration pneumonitis.[7,8] Tramadol was investigated in search of an effective analgesic agent with antimuscrinic effect at M3 receptors. The anticholinergic effect of tramadol has some effect on gastric motility and secretions. Recently, it has been reported that Intramuscular (IM) and Intravenous (IV) injection of tramadol is able to increase the gastric secretions pH which is comparable to H2 blocking agent.[9-11] In this study, the gastric pH was measured under general anaesthesia 3 hours after single oral dose of placebo or tramadol. In the control group and tramadol group the mean gastric pH remained less than the clinically relevant value of 2.5. It has been reported that after 50 mg of intramuscular injection of tramadol, the maximum plasma concentration reached up to 166 ng/ml in 45 minutes and the corresponding value for intravenous injection dose was 293 ng/ml in 30 minutes. The terminal elimination half-life was 5.5 hours. The minimal effective serum concentrations on an average were maintained for 9 - 10 hours.[9] It has also been reported that after per oral administration of 100 mg tramadol in healthy adults, the achieved mean peak plasma concentration was 136 ng/ml and 55 ng/ml of tramadol and M-1 metabolite respectively.[12] The mean absolute bioavailability of a 100 mg oral dose of tramadol ranges in between 68 - 75%.[13] Time to peak hours was 1.6 and 3.0 hours and half life of 5.6 and 6.7 hours for tramadol and M-1 metabolite respectively.[12] However, the concentration/ time relationship of tramadol in the gastric mucosa remains unknown. It has also been reported that tramadol concentrations are considerably higher in saliva and urine than in serum.[10] This may explain that single oral dose of tramadol failed to achieve the peak plasma concentration as shown in the previous studies. This may reflect the different invasion kinetics and oral modes of administration.[10] There is a possibility of pharmacokinetic disparity between the analgesic and pH elevating properties of tramadol.[14,15] The achieved serum concentrations after single dose of tramadol may be clinical relevant to provide analgesia for short duration but not enough to provide antimuscrinic effects at M-3 receptors.[12]

Pre-operatively famotidine is most commonly used H2 blocking agent and is effective for the prevention of aspiration pneumonitis.[16] Famotidine is a competitive inhibitor of histamine H2 receptors. It suppress and inhibit the gastric fluid secretions and acid concentration. Its antisecretory effects occurred within one hour and reaches to maximum within 1 - 3 hours after oral administration.[17] The bioavailabilty is 40 - 45%. In this study, famotidine was given as single dose 3 hours pre-operatively. Famotidine effectively reduced the gastric secretion volume (< 0.4 ml/kg) and increased the pH (> 2.5) as compared to control and tramadol treated group. These results are comparable to other studies.[10,18-20]

Minami suggested that tramadol may be a good alternative to non-steroidal anti-inflammatory drugs (NSAIDs) due to its ability to raise gastric fluid pH.[10] The authors here suggest that intravenous or intramuscular injection of tramadol may be a good alternative to NSAIDs in patients with risk of gastric ulcers but not oral tramadol. It is not known that the repeated or regular use of oral tramadol may be able to increase the gastric fluid pH or not. This is an area where pharmacokinetic disparity of intramuscular/ intravenous and oral tramadol and its antimuscrinic effect at M3 receptors still need to be further investigated.

CONCLUSION

As compared to famotidine pre-operative single oral dose of tramadol was unable to elevate the desired level of gastric secretions pH (> 2.5) and volume (< 0.4 ml/kg). This may be due to pharmacokinetic disparity between the analgesic and pH elevating properties of tramadol which needs to be further evaluated.

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