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The Antacid and Analgesic Efficacy of Intramuscular Tramadol in Patients Undergoing General Anaesthesia

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Abstract

Pulmonary aspiration during induction of general anaesthesia is an important cause of anaesthetic mortality and morbidity. Many agents have been tried to reduce this risk. *Aim:* To assess and compare the antacid and analgesic efficacy of a single dose of intramuscular tramadol. *Method:* The study was carried out in 50 patients of either gender, age between 18 to 60 years, belonging to ASA I & ASA II status under going surgical procedures. All patients were randomly allocated to receive either tramadol 100mg or Ranitidine 50mg intramuscularly one hour before induction of anaesthesia. *Results:* Tramadol is equally effective in reducing gastric acid pH compared to ranitidine (3.41±2.34 Vs 3.50±2.54). Even though tramadol decreased gastric volume, the reduction in mean gastric volume was not as much as ranitidine (13.96±11.55ml Vs 11.24±9.49). *Conclusion:* Tramadol can be safely used as a premedicant in patients undergoing for general surgeries.

Keywords: Tramadol Ranitidine; Gastric Volume; Gastric pH.

Introduction

Pulmonary aspiration of acid gastric contents during induction or recovery from general anaesthesia is an important cause of anaesthetic mortality and morbidity. In 1946 Mendelson described an acid aspiration syndrome in obstetric patients and showed experimentally that when gastric juice was neutralized, little reaction was produced in the lungs of affected rabbits [1]. In 1962, Banister and Sattilaro [2], suggested that the critical pH for severe lung damage in human was 2.5 and in 1974 Roberts and Shirley [3] suggested that the critical volume of fluid of pH less than 2.5 was 0.4 ml/kg (about 25 ml in humans). A more recent study in rats has shown pH to be a more important factor than volume in determining mortality [4].

Various pharmacological agents such as H_2 receptor antagonists, antacids, proton pump inhibitors, and metaclopramide has been used in an attempt to reduce the risk of aspiration by decreasing acidity and volume of gastric fluid. Recently it has been shown that premedication with tramadol before surgery is effective in increasing gastric fluid pH similar to H_2 receptor blockers [5,6]. This antacid property is explained by its inhibitory effects on M_3 muscarinic receptor function [7]. It has also been claimed that giving tramadol before surgery may minimize the initiation of pain in the tissues, improve hemodynamic stability during induction time, reduce opioid consumption [8], provide better pain relief during immediate post operative period [9], and cause less pronounced typical opioid side effects like respiratory depression, addiction, and effects on smooth muscles.

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In light of above knowledge and various published reports, it is proposed to do a prospective randomized double blinded comparative study to assess and compare the antacid and analgesic efficacy of a single dose of intravenous tramadol in patients undergoing surgery compared with Ranitidine.

Materials and Methods

Following institutional ethics committee approval, double blind, controlled study was carried out in 50 patients of either gender, age between 18 to 60 years, belonging to ASA I & ASA II status under going surgical procedures with duration of 2 to 4 hours. The cases were randomly divided into two groups (1 & 2), before starting the study, patient written consent was obtained.

Exclusion criteria including use of opioid medication, use of medication that may alter gastric composition or gastric emptying, patients with gastrointestinal diseases, and obese patients who are more than 20% heavier than their ideal body weight. All patients were premedicated with 0.5 mg of alprazolam on the night before surgery. All patients were fasted over night. All patients were randomly allocated to receive either tramadol 100mg or Ranitidine 50mg intramuscularly one hour before induction of anaesthesia.

After securing IV access, all the patients were induced with thiopentone 5 to 6 mg per kg body weight titrated to the loss of eye lash reflex along with fentanyl 2 μg/kg body weight. Patients were intubated after administration of vecuronium bromide 0.08 mg/kg body weight.

All patients were monitored with heart rate, electrocardiogram, non invasive blood pressure (NIBP) monitoring, end tidal concentration of carbon-dioxide, and oxygen saturation (SpO_2).

Anaesthesia was maintained with isoflurane 0.6-2%, in a mixture of nitrous oxide 66% and oxygen34% and vecuronium 0.03mg/kg bolus administration at 30 minutes intervals. No other analgesics were used intraoperatively. After tracheal intubation 16 French gauge multi-orifice, nasogastric tube was inserted and its correct position was confirmed by epigastric auscultation of injected air.

Two measurements of gastric fluid volume were taken. First measurement was taken after induction of anaesthesia and second measurement was taken after extubation. The pH was measured immediately using a digital pH meter, manufactured by Global electronics, model: DPH 504, serial No: 95504355 (Figure 2), which was calibrated by using standard buffers. The time from induction of anaesthesia until extubation was recorded. The volume of gastric contents was measured with a syringe.

At the end of surgery, patients were extubated after antagonism of residual neuromuscular block with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). 0.3 μg/kg/hr fentanyl infusion was started immediately after recovery from anaesthesia (as judged by the ability to open the eyes, grip a finger, and breathe deeply on request). Whenever patients complain pain (Verbal analogue score (VAS) more than three), they were received 0.5 μg/kg of fentanyl as rescue analgesia.

Rescue analgesia was repeated at every six minutes interval until the pain subsides. Age, weight, fasting interval, type of the surgery, duration of anaesthesia, and side-effects during postoperative period were recorded.

SpO_2, NIBP, and heart rate were recorded before start of surgery, immediately after extubation, 1st, 2nd, 4th, 6th hour during postoperative period. Gastric fluid pH, gastric volumes were measured after intubation & after extubation and analgesic requirements. Post operatively SpO_2, NIBP, heart rate, respiratory rate, VAS (0-10) and sedation socres were recorded at 0, 1, 2, 4, 6 hour after extubation.

Level of sedation was measured by means of sedation scoring scales in the following pattern.

Sedation Score

i. Fully awake 1

ii. Somnolent, responds to verbal commands 2

iii. Somnolent, responds to tactile stimulation 3

iv. Asleep, responds to painful stimuli 4

Amount of rescue analgesia, number of doses of rescue analgesia, total analgesic consumption was recorded from infusion pump at the end of 6hours.

Power analysis revealed a sample size of 25 patients per group was sufficient to achieve a power of 80% and an α of 0.05 to detect a standard deviation of 0.5–0.7 in pH. Statistical analysis was performed using Student's *t* test, χ^2 test and ANOVA as appropriate. Proportion of patient for risk of aspiration (pH<2.5 and volume >0.4 ml kg^{-1}) were compared using the $\chi 2$ test with Yate's correction when necessary. A value of $P<0.05$ was considered statistically significant. Statistical evaluation was performed by the SPSS.

Results

This randomized study was a comparison between two groups of 25 each, adult patients. In the first group, patients were given ranitidine 50mg injection intramuscularly, and in the second group, patients were given tramadol 100mg intramuscularly one hour before surgery. Patients were compared for hemodynamic changes at before start of surgery, immediately after extubation, 1st, 2nd, 4th, 6th hour during postoperative period. Patients were also compared for gastric fluid pH, gastric volumes (after intubation & after extubation) and analgesic requirements. As per protocol general anaesthesia was administered to all the patients in the study and the conduct of anaesthesia was standardized. No patient was eliminated from the study.

Demographic Variables in Different Groups

The demographic data was comparable between the two groups as shown in the Table 1.

There were no statistically significant differences between groups regarding age, weight, and duration of anaesthesia.

Comparision of Data within the Groups

I. Group 1 (Ranitidine Group)

• *Gastric Fluid pH and Gastric Volume*

The mean gastric fluid pH and gastric volumes collected at after intubation and after extubation are shown in the table 2.

After extubation, there was statistically significant increase in gastric fluid pH and significant decrease in gastric volumes than the after intubation.

• *Hemodynamic Data*

The hemodynamic variables, which recorded at various time intervals, are charted in the following table. There were no statistically significant differences in all the parameters.

• *Other Observed Variables*

The mean values of respiratory rate, sedation score, and pain scores (VAS) are depicted in the Table 4.

There were no statistically significant differences between respiratory rates, sedation scores, and pain scores at any point of time within the group 1.

II. Group 2 (Tramadol Group)

The mean gastric fluid pH and gastric volumes collected at after intubation and after extubation are as follows.

The gastric fluid pH was significantly increased after extubation when compared to after intubation. Though the gastric volume was lower after extubation but it is statistically insignificant .

• *Hemodynamic Data*

The hemodynamic variables, which recorded at various time intervals, are shown in the table 6.

There were no statistically significant differences in mean values of heart rate or SpO2 or blood pressure between all readings within the group 2.

• *Other Observed Variables*

The mean values of respiratory rate, sedation score, and pain scores (VAS) are as follows.

There were no statistically significant differences between respiratory rates, sedation scores, and pain scores within the group 2.

III. Comparision of Data Between The Group 1 & 2

• *Gastric Fluid pH*

The mean gastric fluid pH values which were collected after intubation and after extubation are as follows.

The gastric fluid pH values are comparable between the two groups after intubation and also after extubation.

• *Gastric Volume*

The mean gastric fluid volumes which were collected after intubation and after extubation are as follows. There was no statistically significant difference in gastric fluid volumes collected after intubation whereas there was statistically significant difference in gastric fluid volumes collected after extubation, in between the two groups and both gastric fluid volumes were more in group 2.

• *Patients at High Risk of Aspiration*

Patients who had gastric fluid pH <2.5 and gastric fluid volume >0.4 $ml.kg^{-1}$ were considered high risk of pulmonary damage in case of aspiration.

After induction of anaesthesia one patient in the group 1, three patients in the group 2 and after extubation none in group 1 and one in group 2 were considered to be at high risk of aspiration because of combination of pH <2.5 and gastric fluid volume >0.4 $ml.kg^{-1}$. In both groups the patients at high risk of aspiration were not statistically significant.

• *Hemodynamic Data*

The hemodynamic variables, which recorded at various time intervals, are depicted in the Table 11.

Though there were slight higher mean values of heart rate or SpO2 or blood pressure after extubation in both groups, these changes were not statistically significant at any point of time.

• *Other Observed Variables*

The mean values of respiratory rate, sedation score, and pain scores (VAS) are shown in the table 12. There was no significant difference between respiratory rate, sedation score, and pain score except for pre operative and after extubation sedation score, in between the two groups. Pre operative and post extubation sedation scores were higher in group 2.

Table 1: The demographic data

Variable	Group 1 (mean ± SD)	Group 2 (mean ± SD)
Age (years)	36.08 ± 7.9	37.91±9.23
Weight (Kg)	61.92±9.6	61.56±8.4
Sex (M :F)	19 :6	17 :8
Duration of surgery	2:14±0.88	2:24±0.78

Table 2: Gastric fluid pH and Gastric volume in group 1

Variable	After intubation (mean ± SD)	After Extubation (mean ± SD)
pH	3.50±2.54*	4.39±2.35*
Volume	11.24±9.49*	6.12±4.19*

*Significant difference ($p<0.05$)

Table 3: Hemodynamic data in group 1

Variable	PRE OP	After Extubation	1st Hr	2nd Hr	4th Hr	6th Hr
HR (mean)	84.44	90.28	85.2	83.44	82.20	83.8
SpO_2 (mean)	99	99.4	99.28	99.24	98.96	99.24
SBP (mean)	127.16	131.96	122.04	128.64	127	128.28
DBP (mean)	79.52	84.92	81.44	79.8	79.96	81.68

Table 4: Other observed variables in group 1

Variable	Pre OP	After extubation	1st Hr	2nd Hr	4th Hr	6th Hr
RR (mean)	18.08	19.8	18.84	18.36	18.6	18.56
SS (mean)	1.04	1.64	1.76	1.64	1.6	1.52
PS (mean)	0.36	3.36	1.84	1.72	1.56	1.48

Table 5: Gastric fluid pH and Gastric volume in group 2

Variable	After intubation (mean ± SD)	After extubation (mean ± SD)
pH	3.41± 2.34*	3.84 ± .42*
Volume	13.96± 11.55	10.08± 7.59

*Significant difference ($p<0.05$)

Table 6: The hemodynamic data in group 2

Variable	PRE OP	After Extubation	1st Hr	2nd Hr	4th Hr	6th Hr
HR (mean)	78.52	85.84	82.08	81.24	78.76	80.4
SpO_2 (mean)	98.72	99.4	99.2	98.72	98.88	98.16
SBP (mean)	128.56	135.84	128.4	126.6	128.12	127.84
DBP (mean)	82.64	86.6	83.72	82.8	81.04	82.04

Table 7: Other observed variables in group 2

Variable	Pre OP	After Extubation	1st Hr	2nd Hr	4th Hr	6th Hr
RR (mean)	17.44	19.36	17.6	16.88	17.72	17.6
SS (mean)	1.56	1.96	1.8	1.84	1.84	1.72
PS (mean)	0.6	3.2	1.56	1.64	1.36	1.24

Table 8: Comparison of Gastric fluid pH

Variable	Group 1 (Mean± S.D)	Group 2 (Mean ± S.D)
pH 1	3.50±2.54	3.41± 2.34
pH 2	4.39± 2.35	3.84 ± .42

Table 9: Comparison of Gastric fluid volume

Variable	Group 1 (Mean ± S.D)	Group 2 (Mean ± S.D)
Volume 1	11.24± 9.49	13.96± 11.55
Volume 2	6.12± 4.19*	10.08± 7.59*

*Significant difference ($p<0.05$)

Table 10: Comparison of patients at high risk of aspiration.

Variable	Group 1	Group 2
pH 1 <2.5 & Volume 1 >0.4ml/kg	1(4%)	3(12%)
pH 2 <2.5 & Volume 2 >0.4ml/kg	0	1(4%)

Table 11: Hemodynamic variables between groups

	Variable	PRE OP	After extubation	1st Hr	2nd Hr	4th Hr	6th Hr
Group1 (Mean)	HR	84.44	90.28	85.2	83.44	82.20	83.8
	SpO_2	99	99.4	99.28	99.24	98.96	99.24
	SBP	127.16	131.96	122.04	128.64	127	128.28
	DBP	79.52	84.92	81.44	79.8	79.96	81.68
Group 2 (Mean)	HR	78.52	85.84	82.08	81.24	78.76	80.4
	SpO_2	98.72	99.4	99.2	98.72	98.88	98.16
	SBP	128.56	135.84	128.4	126.6	128.12	127.84
	DBP	82.64	86.6	83.72	82.8	81.04	82.04

Table 12: Other observed variables between groups

	Variable	Pre OP	After extubation	1st Hr	2nd Hr	4th Hr	6th Hr
Group 1 (mean)	RR	18.08	19.8	18.84	18.36	18.6	18.56
	SS	1.04*	1.64*	1.76	1.64	1.6	1.52
	PS	0.36	3.36	1.84	1.72	1.56	1.48
Group 2 (mean)	RR	17.44	19.36	17.6	16.88	17.72	17.6
	SS	1.56*	1.96*	1.8	1.84	1.84	1.72
	PS	0.6	3.2	1.56	1.64	1.36	1.24

*Significant difference ($p<0.05$)

Table 13: Requirement of analgesia

Variable	Group 1 Mean ± S.D	Group 2 Mean ± S.D
NRA	4.68±2.32	3.6±1.84
TD	248.95± 64.52	220.30± 66.69

Table 14: Complications

Complications	Group 1	Group 2
Nausea& Vomiting	4(16%)	2(8%)
Shivering	11(44%)	1(4%)

As we observe from the table, there was higher incidence in nausea, vomiting, and shivering in group 1 compared to group 2.

• *Analgesic (Fentanyl) Requirement*

The mean values of number of rescue analgesia (NRA), and total dose of fentanyl (TD) given for the first 6 hours of post operative period, were as follows.

The required total dose of fentanyl and the total number of rescue analgesia was relatively more in group 1 though it is insignificant.

Complications

The incidences of complications are depicted in the following table.

Discussion

In our study, we found that in group 1 the mean gastric fluid pH was significantly higher and the mean gastric volume was significantly lower after extubation when compared to after intubation. In group 2 too, the mean gastric fluid pH was significantly higher after extubation when compared to after intubation but the reduction in mean gastric volume was not statistically significant.

We have observed that there was no significant difference between mean gastric volumes after intubation in both groups but there was significant difference in reduction of gastric volumes after extubation in Group 1 compared to Group 2. This explains the clinical effect of tramadol on gastric emptying, may be determined by its weak action at μ opioid receptor and relative inhibitory effects on serotonin and norepinephrine neuronal uptake.

Some others have stated that a pH less than 2.5 is critical factor in the development of pulmonary damage, following aspiration of gastric contents. Volume is perhaps less important, but 25ml or 0.4 $mlkg^{-1}$ is recognized as being the critical volume required before pulmonary damage occurs. In our study patients with gastric contents pH <2.5 and volume >0.4 $ml.kg^{-1}$ were specified as at high risk of pulmonary damage in case of aspiration [10].

The proportion of patients classified as "higher risk" in case of aspiration was 4% in Group 1 and 12% in Group 2 immediately after intubation and none in Group 1 and 4% in Group 2 immediately after extubation. Although the risk of acid aspiration in Group 2 was somewhat higher than Group 1, but the difference was not statistically significant.

Our study revealed that the administration of single dose intramuscular tramadol one hour before surgery increased gastric pH during surgery similar to ranitidine. The inhibitory effects of tramadol on muscarinic receptor (M3) function explain our present results [11]. Shiraishi *et al*. reported that tramadol at clinically relevant concentrations inhibits M_1 receptor function via quinuclidinyl benzilate (QNB)-binding sites [12]. In addition, tramadol inhibits M_3 receptor function via QNB-binding sites at clinically relevant concentrations. These findings suggest that tramadol has anticholinergic effects. The inhibitory effects of tramadol on muscarinic receptor function explain our present results. Both gastrin and histamine strongly stimulate the secretion of acid by parietal cells. In our study, the pH in the group 2 was similar to that in the group 1. It would be relevant to study the effects of tramadol on histamine and gastrin induced secretion of acid.

Common non-steroidal anti-inflammatory drug (NSAID) analgesics are used widely. However, they often cause ulcers, possibly via the inhibition of prostaglandin synthesis in the stomach. Patients with underlying gastric ulcer are at particular risk of NSAID-induced gastric ulcer. Our results suggest that tramadol might be a suitable analgesic for such patients.

As with many other studies concerning gastric fluid properties, we used blind aspiration to measure the volume of gastric contents. This technique may incompletely empty the stomach and, therefore, underestimate gastric fluid volume. The alternative methods include gastric aspiration by using a visually guided gastroscope and the dye-dilution technique. Irritation by the gastroscope or insufflation of air may stimulate gastric secretion. Estimated gastric volume by the dye dilution method has been shown to be similar to aspirated volume by blind aspiration despite being complicated and time consuming [13]. Soreide et al used a gastroscopic technique and found that, on average, a very good agreement between blind gastric aspiration and gastroscopic controlled gastric fluid volume measurements [14].

Our results showed that the group 1 required more number of times of rescue analgesia and hence the total dose of fentanyl given for the first six hours during post operative period was relatively more to tramadol though it is statistically insignificant. From his studies Chiaertti et al has suggested the giving tramadol before the start of surgery may minimize the initiation of pain in the tissues and enhance their effectiveness as analgesia [15]. Tramadol and its metabolite noncompetitively inhibit the NMDA receptors, which may contribute to its analgesic effects. It has been proved that, pre-medication with a NMDA-receptor antagonist reduced pain provoked

by movement, enhanced postoperative analgesia and reduced postoperative analgesic requirements [16]. Elhakim et al have also found that administration of single dose i.m. tramadol one hour before Caesarean section reduced nalbuphine consumption and pain intensity during first postoperative day with less sedation [5]. Webb and colleagues found that patients receiving intraoperative tramadol had significantly better opinions of their pain relief and used significantly less postoperative morphine with no increase in side-effects [17].

We have observed in our study that the sedation scores, preoperative and after extubation, were statistically different between the two groups. We can infer from this that the tramadol which has got mild sedative like action might decrease the required dose of induction agents [18].

In contrast to the other studies, our study had shown difference in decrease incidence of nausea and vomiting, in group 2 than group 1. The initial dose of tramadol, if administered postoperatively, can be associated with an increased incidence of nausea [19]. In the present study, this previously reported adverse effect was avoided effectively by administering tramadol 1 h before the patient was anaesthetized.

Incidence of shivering was significantly less in patients who received tramadol hydrochloride. Similar outcome was reported by De Witte et al using tramadol in the dose of 3 mgkg-1 of body weight [20]. Mathews and Mulla et al1 also reported the use of low dose of tramadol to be quite effective in treating postanaesthetic shivering without increasing side effects [21]. As an inhibitor of the reuptake of serotonin and norepinephrine in the spinal cord, the mechanism of action of tramadol resembles that of nefopam, which may explain the present results [20].

Conclusions

The aim of the study was to assess and compare the antacid and analgesic efficacy of a single dose of intramuscular tramadol in patients undergoing surgery with ranitidine. The study was conducted in 50 patients of either sex of ASA I and II grades posted for various general surgeries, who were randomly allocated into two groups of 25 each. The technique was standardized for all patients.

The following conclusions are drawn from the study.

1. Tramadol is equally effective in reducing gastric acid pH compared to ranitidine.
2. Even though tramadol decreased gastric volume, the reduction in mean gastric volume was not as much as ranitidine.
3. Administration of intramuscular ranitidine and tramadol one hour before surgery may reduce the proportion of patients at risk of significant lung injury in case of aspiration.
4. Even though it is not statistically significant, the total analgesic dose and rescue analgesia required was less with tramadol.
5. Apart from being antacid and analgesic tramadol has got sedative action too which might reduce the dose of induction agents.
6. Tramadol had less number of postoperative complications of nausea vomiting and shivering thereby claiming to be a good premedicative.

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