ORIGINAL ARTICLE

Comparison of acid reducing property of tramadol and ranitidine given before cesarean section under general anesthesia

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ABSTRACT

Introduction: Intramuscular tramadol has been shown to reduce gastric acid secretion. We aimed to investigate its role in reducing the gastric acid contents and compared it with ranitidine in patients undergoing elective cesarean sections under general anesthesia .

Methodology: Sixty ASA-II parturients undergoing elective cesarean section were included in a randomized double-blind study. The patients were randomly allocated to receive either tramadol 100 mg (n=30) or ranitidine 50 mg IM (n=30), 1 hour before general anesthesia . Gastric contents were collected using blind gastric aspiration after induction and at the end of the procedure.

Results: The patients receiving tramadol had a lower mean gastric fluid pH after induction and before recovery as compared to patients treated with ranitidine (3.5±1.7 vs. 5.8±1.5), and the difference was significant (P value=0.001). A significantly higher proportion of newborns had a lower APGAR at 1 min in tramadol group as compared to ranitidine group (P value=0.026). Nalbuphine consumption in first 12 hours after operation was reduced in the tramadol group. There was no significant difference in the incidence and severity of nausea, vomiting or any other side effect between the two groups.

Conclusion: In comparison with ranitidine, the administration of tramadol in patients undergoing elective cesarean sections under GA resulted in significantly greater volume and acidity of the gastric contents, lower neonatal APGAR at 1 minute, reduced post operative opioid consumption and no change in the frequency of PONV.

Key words: Anesthesia; Cesarean section; Opioids; Tramadol; Acid reducing property; Ranitidine.

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INTRODUCTION

Due to various physiological changes occurring in pregnancy, parturients are at a higher risk for regurgitation and pulmonary aspiration.[1] Pulmonary aspiration of gastric contents is the major cause of maternal morbidity and mortality in patients undergoing for cesarean section during general anesthesia. All patients should possibly receive prophylaxis against severe non-particulate aspiration pneumonia 1-2 hours prior to induction.[2] Studies have shown that patients not receiving prophylaxis against aspiration are at a higher risk for developing aspiration pneumonia.[3] Strategies aiming at reducing volume and acidity include pharmacological measures, gastric emptying with a gastric tube and adequate preoperative fasting time. Classically H_2 antagonists, antacids and proton pump inhibitors are used for this purpose.[4]

Tramadol is the phenyl-piperidine analogue of codeine. It binds and activates opioid receptors with preference of μ receptors (weak but full agonist). About 10% of it is metabolized to O-desmethyl tramadol which is an active metabolite having greater affinity for μ receptors and a half life of 9 hours.[5] Tramadol does not cause respiratory depression in equipotent doses of other opioids in adults,[6] and is less likely to cause neonatal respiratory depression

and hence has been used in obstetric patients undergoing vaginal delivery.[7] Tramadol inhibits muscurinic receptors and its active metabolite O-desmethyl tramadol also inhibits type-3 muscurinic receptors which primarily mediate gastric gland secretion and smooth muscle contraction. Hence tramadol may be useful in minimizing the risk of acid aspiration during operations and improving pain relief after 24 hours after surgery.[8,9]

This interventional, quasi experimental study was carried out to test the hypothesis that the volume and pH of the gastric contents in patients pre-treated with tramadol will be comparable to those patients treated with ranitidine.

METHODOLOGY

The study was conducted in Department of Anesthesiology, Hameed Latif hospital, Lahore, from February 2011 to February 2012. 60 parturients between 20-40 years of age were randomly allocated into 2 groups of 30 each. Patients of American Society of Anesthesiologists (ASA) class I and II, gestational age not less than 37 weeks were included in the study. Patients maintained supine position during general anesthesia with wedge placed under her right hip. All patients were excluded from study group who had anticipated/documented difficult intubation, documented history/treatment of gastritis, gastric or duodenal ulcers, morbid obesity, symptoms of gastroesophageal reflux, short elective fasting period or who underwent surgery that lasted >45 min. Diagnosed patients of achlorhydria, Zollinger-Ellisson syndrome or inappropriate gastric acid secretion disease were also excluded.

Data collection: After approval by the hospital ethical committee and written informed consent, patients admitted in the hospital for elective cesarean section and fulfilling inclusion criteria were included in the study. The patients were randomly allocated into either group A or B, using random number table. Group A was given tramadol 100 mg and Group B was given Ranitidine 50 mg IM 1 hour before surgery. The drug was given by preoperative care unit nurse. The patient as well as the anesthesiologist was blinded to the study drugs used. After 3 minutes of pre-oxygenation, anesthesia was induced by thiopentone sodium 5 mg/kg followed by succinyl choline 1 mg/kg. Cricoid pressure was maintained after loss of consciousness until airway was secured with endotracheal tube. After tracheal intubation, a 16G multi-orifice orogastric tube was passed.

Volume and pH of the aspirated gastric contents were measured twice; immediately after induction of anesthesia and at the end. The volume was measured by drawing the aspirate into a 20 cc syringe and pH was measured with pH meter[10] [Hanna HI-98107 Phep pH pocket meter (Figure 1)]. Anesthesia was maintained by standard inhalational technique. Muscle relaxation was maintained by vecuronium 0.07 mg/kg. Monitoring was carried out using pulse-oximetry, non-invasive blood pressure and capnography. After umbilical cord clamping, inj. oxytocin 5 iu was given IV. Inj. Nalbuphine 0.15 mg/kg was used as analgesic. At the end of the procedure residual neuromuscular block was antagonized by neostigmine 0.05 mg/kg and atropine 0.02 mg/kg.

All neonates were assessed by a pediatrician, who was blinded to the study drugs and Apgar scores were recorded at 1 and 5 min.

Rest of the care was provided according to standard departmental protocol.

Figure 1: The pH meter's LCD display shows pH to 0.1pH resolution with an accuracy of ± 0.1 pH. Calibration of pH could be carried out at either 1 or 2 points (usually pH 4 and 7 buffer values) quickly and easily. The electrode part is housed within the pocket sized case and is ready for use after the black plastic cap removal. The pH meter electrode was dipped in gastric fluid to measure and read the pH on the LCD display.

Data analysis: SPSS version 10 was used to analyse the data. Descriptive statistics were calculated. The age, weight, gestational age, pH, volume of gastric fluid and duration of anesthesia were presented as mean and standard deviation. The episodes of nausea/vomiting and Apgar score were presented as percentage. The pH levels and gastric fluid volume after induction of anesthesia and at the end of anesthesia were compared by using paired-t test. Chi square test was used to compare the proportions of episodes of nausea/vomiting in both groups. A value of $P< 0.05$ was taken as significant.

RESULTS

The patients receiving tramadol had a mean gastric fluid pH of 3.5±1.7 after induction and before recovery, which was significantly lower than those treated with ranitidine (5.8±1.5, P value=0.001). There was a significantly higher proportion (P value=0.026) of newborns with lower Apgar at 1 min in tramadol group as compared to ranitidine group. Nalbuphine consumption in first 12 hours after operation was reduced in the tramadol group. There was no significant difference in the incidence and severity of nausea and vomiting between the two groups.

Table 1: Comparative analysis of the demographic data

Factor	Tramadol (Mean ± SD)	Ranitidine (Mean ± SD)	p-value
Age (years)	27.07 ± 3.6	28.57 ± 3.2	0.11
Weight (kg)	77.17 ±14.3	78.80 ± 11.8	0.632
Gestational Age (Weeks)	37.87 ± 0.81	37.77 ± 0.89	0.654
Duration of surgery (min)	57 ±11	58 ± 12	0.7

Table 2: Comparison of mean pH of gastric fluid at the time of induction and at end of anesthesia

Study group	Mean Gastric fluid pH		STD	
	At induction	At recovery	At induction	At recovery
Tramadol	3.5	3.5	1.7	1.7
Ranitidine	5.8	5.8	1.5	1.5

Statistical test applied = t test; t: Value: 5.4; P value: 0.001 (<0.05)

The PH of gastric fluid volume was significantly low with Tramadol as compared to Ranitidine at the time of Induction of anesthesia and at the end of anesthesia

Table 3: Comparison of mean gastric fluid volume at the time of induction and at the end of anesthesia

Study group	Mean Gastric fluid volume (ml)		STD	
	At induction	At recovery	At induction	At recovery
Tramadol	8.9	7.7	6.1	4.1
Ranitidine	6.1	6.6	4.6	5.1

t: Value: At induction: 2.05; At recovery: 0.9 **. P value**: At induction: 0.045 (<0.05); At recovery: 0.36 (>0.05)

The gastric fluid volume was significantly higher with Tramadol as compared to Ranitidine at the time of Induction of anesthesia, but no significant difference at the end of anesthesia

Table 4: Comparison of APGAR at 1 minute and 5 minutes [N(%)]

APGAR	Study group		Total
	Tramadol	Ranitidine	
1 Min APGAR = 7+	23(76.7)	29(96.7)	52(86.7)
1 Min APGAR=<7	7(23.3)	1(3.3)	8*13.3)
5 Min APGAR =7+	30(100)	30(100)	60(100
Total	30(100)	30*100)	60(100)

Statistical test applied = Fisher Exact test

P value for two tailed Fisher's Exact test at 1 minute APGAR : 0.026 (<0.05)

Proportion of newborn with low APGAR at I minute, was significantly higher with Tramadol as compared to Ranitidine, but no significant difference of mean neonatal APGAR at 5 between two study groups

Table 5: Comparison of mean dose of opioid (nalbuphine) consumption in 12 hours between two groups

Study group	N	Mean dose of opioid in (mg)	STD
Tramadol	30	16.07	3.8
Ranitidine	30	26.00	10.3

Statistical test applied = t test; **t: Value** 4; **P value**: 0.001 (<0.05)

Significantly higher dose of opioids were required with Ranitidine as compared to Tramadol

Table 6: Comparison of Nausea vomiting with Tramadol and Ranitidine in recovery area. [n(%)]

Study groups	Nausea/vomiting		Total
	No	Yes	
Tramadol	30(50)	0	30(50)
Ranitidine	29(49.2)	1(3.3)	30(50)
Total	59(100)	1(100)	60(100)

Statistical test applied = Fisher Exact test. **P value for two tailed Fisher's Exact test** : 1.0 (>0.05)

No significant difference for nausea and vomiting between two drugs in recovery area

DISCUSSION

Intramuscular administration of tramadol to parturients readily reaches the neonate, confirming a high degree of placental permeability. The neonates at term possess the full hepatic capacity for breakdown of tramadol into its active metabolites. However, the renal elimination of the active metabolite M_1 is delayed, in line with the slow maturation process of renal function in neonates.[11] In the present study the proportion of newborns with *low* APGAR score at 1 min was significantly higher in tramadol, as compared to ranitidine group.

Baraka and colleagues[12] demonstrated that supplementation of general anesthesia with tramadol in parturients undergoing elective cesarean delivery can result in lower umbilical vein PO_2 and a higher PCO_2 than the corresponding values with fentanyl. Tramadol blocks the reuptake of serotonin and norepinephrine at the nerve terminals and can produce uterine vasoconstriction with possible fetal asphyxia. The umbilical cord blood gas analysis in the study by Baraka and colleagues suggest the unwanted fetal effects. We did not observe any determinant variables described by Baraka and colleagues in our present study.[12] However, we observed significantly

low Apgar in first minute in neonates of tramadol group in present study. The possible mechanism low Apgar may be same as described by Baraka and colleagues.[12] Other studies label it safe analgesic in first stage of labour but the present study showed its adverse effects on Apgar scores, which is alarming.[13,14] Our present knowledge about the risk of medications during pregnancy is incomplete, and the practitioner has to weigh the risks against the benefits of instituting pharmacotherapy in each individual.[15] In the present study, tramadol was administered in a single intramuscular dose near term and not in early pregnancy.

Regarding acid reducing property of tramadol, the results of our study are clearly in contrast with the earlier work, since the cellular mechanism of tramadol on glandular cells muscarinic receptors (M_3) as described by Shiga Y and colleagues.[16] A few clinical trials have been performed and published in different international journals of anesthesiology. First clinical trial was performed by Minami K, et al[9], they included 30 patients who presented for elective surgery for the fracture of upper extremities and mastectomy. They selected 10 patients in each group, administered tramadol as an antacid premedication and compared that group with the famotidine and placebo groups of equal sample size. Probably the small sample size of the treatment group could not distinguish the false positive results among the true positive. The other published clinical trial results by Elhakim et al[8] also supported the previous work. They included 60 patients in their study, divided them into two groups, and compared both groups by giving them tramadol or famotidine as a premedication. They claimed that tramadol is a useful pretreatment to minimize the risk of acid aspiration during operation by increasing the pH value of gastric fluid. The study population in our study was equivalent to the study performed by Elhakim and colleagues[8] but the results of our study have shown a significant difference in tramadol and ranitidine groups. The acidity was higher in the ranitidine treated patients in our study as compared to theirs. We do not have an explanation for this difference except that the population groups belonged to different geographical areas. Hence the hypothesis proposed for this study could not be proved. We did not determine the pH value of the gastric contents before administration of study drug, as it was not feasible in our study design. But in reviewing another study, we found the mean pH value in obstetric and nonobstetric patients 3.11 ± 1.17 and 3.31 ± 1.68 respectively.[17] These values may be taken as reference which seemed close to the values of tramadol group of our study. Other noninterventional trials of the past showed an obvious wide variation but the range of pH values of gastric contents was between 1.31 and 3.9.[18,19]

The value of volume of the gastric aspirate in our study may be an under-estimate as it was done by blind gastric aspiration using orogastric tube with the patient in supine position.

At clinical plasma concentrations tramadol potently suppresses the human 5-HT transporter, whereas it has only a slight effect on the human 5-HT_3 A receptor. The results are compatible with a possible mechanism for tramadol-induced early emesis involving the serotonergic system.[20] But in present study, no patient had a complaint of postoperative nausea and vomiting during their stay in the recovery area. Possible explanation of this may be the single intramuscular dose and intentional gastric emptying.

We also noted that the administration of tramadol 1 hour before cesarean section reduced total nalbuphine consumption and pain intensity during first 12 postop hours. It has been suggested that giving tramadol before the start of surgery may minimize the initiation of pain in the tissues and enhance their effectiveness as analgesic.[21] This may explain the relatively reduced opioid consumption and better pain relief in the tramadol group in our study. Tramadol, a centrally acting analgesic structurally related to codeine and morphine, consists of two enantiomers, both of which contribute to the analgesic activity via different mechanisms. Tramadol and its metabolite, O-desmethyl-tramadol (M1) is agonist at the μ-opioid receptor. Both of these inhibit serotonin and norepinephrine reuptake, thus enhancing the inhibitory effects on pain transmission in the spinal cord. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability.[2] Pain mechanisms are subject to alterations with time and these alterations may involve transition from NMDA to non-NMDA receptor-mediated transmission in central pain pathways. Tramadol and its metabolite non-competitively inhibit the NMDA receptors, which may contribute to its analgesic effects.[23] Pre-medication with an NMDA-receptor antagonist reduced pain provoked by movement, enhanced postoperative analgesia and reduced postoperative analgesic requirements.[24] The combination of tramadol with morphine in the postoperative period of painful surgery was found to be infra-additive. A weak opioid agonist e.g. tramadol, may potentially inhibit the analgesia provided by the full agonist morphine by competing for the same effector μ receptor.[25] But this phenomenon was not observed with the use of nalbuphine and tramadol in the present study.

Webb and colleagues[26] 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. In the present study, patients receiving tramadol one hour before operation had significantly lower pain scores and required less postoperative nalbuphine. Also, combination of non-opioid analgesic action of tramadol with opioid nalbuphine

analgesia was found to be co-additive as part of multi-modal approach in pain relief,[27] as described above. In our present study, a significant reduction in nulbuphine consumption was observed postoperatively for the period of 12 hours in the tramadol group. Regarding lower neonatal APGAR, we could not attribute any problem to tramadol in our patients, although no conclusion can be drawn about safety from the number of patients used in this study.

CONCLUSION

In patients undergoing elective cesarean sections under GA, the administration of tramadol compared to ranitidine, resulted in significantly greater volume and acidity of the gastric contents, lower neonatal APGAR scores at 1 min, reduced postoperative opioid consumption but no change in the frequency of PONV.

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