ORIGINAL ARTICLE

Comparison of Acid Reducing Properties of Tramadol and Ranitidine Given before Caesarean Section under G/A

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ABSTRACT

Aim: 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.

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

Results: At the beginning and the end of anaesthesia, patients receiving tramadol had a mean gastric fluid pH of 3.5±1.7 after induction and before recovery, which was significantly different from those treated with ranitidine (mean 5.8±1.5). The infant well-being, as judged by APGAR score at 1st minute and at 5th minutes after delivery, showed significantly higher proportion of newborn with low APGAR at 1st minute with Tramadol as compared to Ranitidine. Nalbuphine consumption in first 12 hours after operation was reduced in the tramadol group. There was no significant difference in incidence and severity of nausea and vomiting between the two groups.

Conclusion: In comparison with Ranitidine, the administration of Tramadol in patients undergoing elective Caesarean sections under GA resulted in significantly greater volume and acidity of the gastric contents, lower neonatal APGAR at 1st minute, reduced post operative opioid consumption.

Keywords: Anaesthesia, Caesarean section; opioids, tramadol; acid reducing property, ranitidine.

INTRODUCTION

Due to various physiological changes occurring in pregnancy, parturient is 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 caesarean section during general anaesthesia. 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 assurance of adequate pre operative 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% is metabolized to O-desmethyl Tramadol which is an active metabolite having greater affinity for μ receptors and half life of 9 hours[5]. Tramadol does not cause respiratory depression in equipotent doses of other opioids in adults[6], and also 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 mediates gastric gland secretion and smooth muscle contraction. Hence Tramadol may be useful in minimizing the risk of acid aspiration during operation and improving pain relief after 24 hours after surgery[8,9].

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PATIENTS & METHODS

Sixty parturients between 20-40 years of age were randomly allocated into 2 groups of 30 in each sample section.

- Patients of American society of anaesthesiologists (ASA) class ll.
- Gestational age not less than 37 weeks.
- All elective Caesarean sections performed in general anaesthesia.
- Duration of surgery between 45 to 90 minutes.
- Patients maintained supine position during general anaesthesia or supine with wedge under her right hip.

Patients with anticipated/documented difficult intubation, with documented history/treatment of gastritis, gastric or duodenal ulcers, with morbid

obesity, having symptoms of gastroesophageal reflux and diagnosed patients of Achlorhydria, Zollinger-Ellisson syndrome and any inappropriate gastric acid secretion disease were excluded.

After approval from the ethical committee of the hospital and written informed consent, patients admitted in the hospital for elective caesarean section and fulfilling inclusion criteria were included in the study. Before the start of study, the entire sample was randomly allocated into 2 groups, 30 in each using Random Number Table. The groups were designated as Group A and Group B. Group A was given Tramadol 100mg whereas Group B was given Ranitidine 50 mg, both as intramuscular injections 1 hour before surgery. Volume was measured by drawing it into a 20 cc syringe, pH meter[10] (Hanna HI-98107 Phep pH pocket meter; see Figure 1) was used to measure the pH. Anaesthesia was maintained by standard inhalational technique. After recovery from succinylcholine, muscle relaxation was maintained by vecuronium 0.07mg/kg. Minimum mandatory monitoring was carried out using pulse-oximetry, non invasive blood pressure and capnography. After umbilical cord clamping, injection oxytocin 5i.u was given intravenously. Injection Nalbuphine 0.15mg/kg was given as analgesic. Inhalational agent was discontinued on start of skin suture and residual neuromuscular block was antagonized by Neostigmine 0.05mg/kg and Atropine 0.02mg/kg.

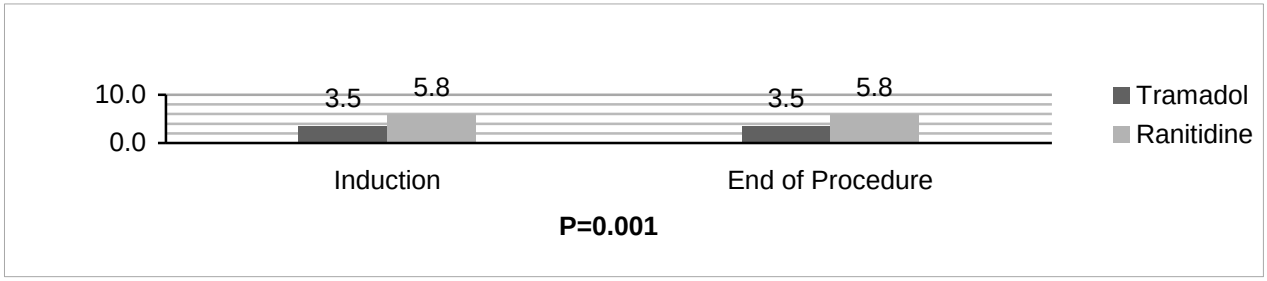
SPSS version 10 was used to analyse the data on computer. Descriptive statistics were calculated. The age, weight, gestational age, pH, volume of gastric fluid and duration of anaesthesia were presented as Mean and Standard Deviation. The episodes of nausea/vomiting and Apgar score were presented as percentage. The pH levels and gastric fluid volume after induction of anaesthesia and at the end of anaesthesia 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

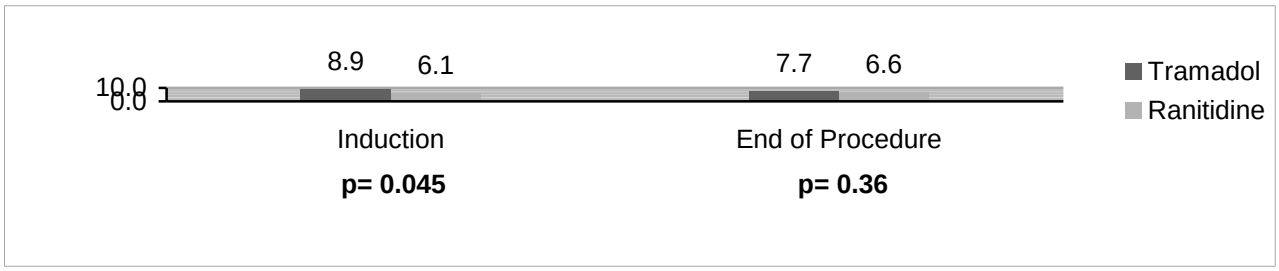
Patient's demographic data analysis:

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

Mean pH:



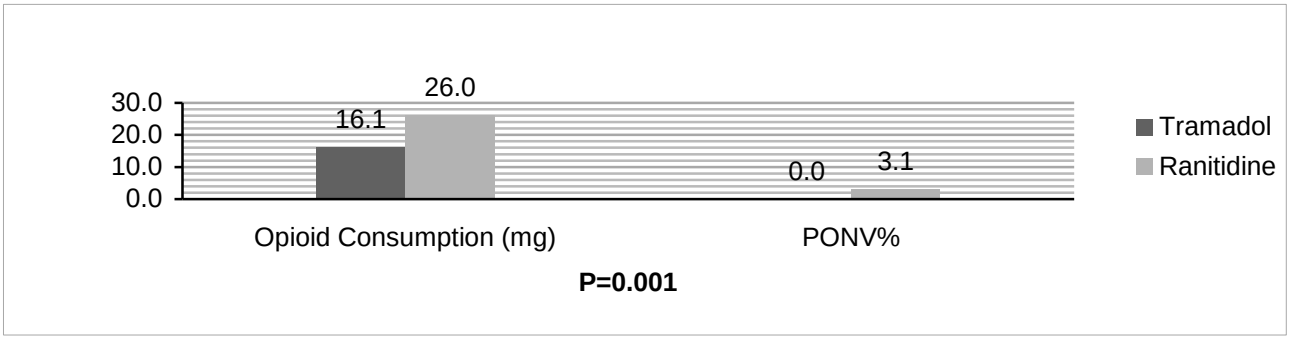
Mean Gastric Volume:



Neonatal APGAR Score:

Neonates with APGAR >7	**Tramadol**	**Ranitidine**	**Statistical Significance (2-tailed Fisher's Exact Test)**
1 min	23(76.7%)	29(96.7%)	p=0.026
5 min	100%	100%	No difference

Opioid Consumption & PONV:



DISCUSSION

Intramuscular application of tramadol in parturients almost freely reaches the neonate, confirming a high degree of placental permeability. The neonates already possess the complete hepatic capacity for the metabolism of tramadol into its active metabolite. However, the renal elimination of the active tramadol metabolite M_1 is delayed, in line with the slow maturation process of renal function in neonates[11]. The proportion of newborn with low APGAR at 1st minute was significantly higher with Tramadol as compared to Ranitidine in the present study.

Baraka and colleagues[12] demonstrated that supplementation of general anaesthesia with i.v. tramadol in parturients undergoing elective Caesarean delivery can result in lower umbilical vein PO2 and higher PCO2 than the corresponding values with i.v. fentanyl. Tramadol blocks the reuptake of serotonin and norepinephrine at the nerve terminals and can produce uterine vasoconstriction with possible fetal asphyxia. 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. Other studies label it safe analgesic in first stage of labour but it could not be proved safe in patients of present study[13, 14]. Our present knowledge about the risk of administering medications during pregnancy is incomplete, and the practitioner has to weigh the risks against the benifits of instituting pharmacological therapy for each individual[15].

Regarding acid reducing property of tramadol, the results of present 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]. 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 famotidine and placebo groups having same sample size. Probably the small sample size of the treatment group could not distinguish the false positive results among the true positive. The next published clinical trial results were by Elhakim et al[8], which 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 pre treatment to minimize the risk of acid aspiration during operation by increasing the pH value of gastric fluid. The study population in present study was same as in study performed by Elhakim and colleagues[8] but the results of our study have shown a significant difference in tramadol and ranitidine groups. But in reviewing the results of previous local non interventional study, we found the mean pH value in obstetric and non obstetric patients 3.11±1.17 and 3.31±1.68 respectively[17]. Other non interventional 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].

At clinical plasma concentrations tramadol potently suppresses the human 5-HT transporter, whereas it has only a slight effect on the human 5-HT_3A receptor. The results are compatible with a possible mechanism for tramadol-induced early emesis involving the serotonergic system[20].

We have also found that administration of single dose intramuscular tramadol 1 hour before Caesarean section does reduce nalbuphine consumption and pain intensity during first 12 hours postoperatively. 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]. Tramadol and its metabolite-O-desmethyl-tramadol (M1) is agonist at the μ-opioid receptor. Tramadol and its metabolite inhibits 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[22]. Pain mechanisms are subject to alterations with time and that these alterations 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 a 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 post-operative period of painful surgery was found to be infra-additive. A weak opioid agonist tramadol may potentially inhibit the analgesia provided by full agonist morphine; compete for the same effector μ receptor[25].

Webb and colleagues[26] found that patients receiving intra-operative tramadol had significantly better opinions of their pain relief and used significantly less postoperative morphine with no increase in side-effects. Further, in the present study patients receiving tramadol 1 hour before operation had significantly lower pain scores and required less post-operative 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].

CONCLUSION

In comparison with Ranitidine, the administration of Tramadol in patients undergoing elective Caesarean Sections under GA resulted in significantly greater volume and acidity of the gastric contents, lower Neonatal APGAR 1 minute, reduced post operative opioid consumption, no change in the frequency of PONV

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