Analgesic and antacid properties of i.m. tramadol given before Caesarean section under general anaesthesia

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**Background.** Intramuscular (i.m.) tramadol increases gastric pH during anaesthesia similar to famotidine. We investigated the antacid analgesic value of a single dose of i.m. tramadol given 1 h before elective Caesarean section performed under general anaesthesia.

**Methods.** Sixty ASA I parturients undergoing elective Caesarean section were included in a randomized double-blind study. The patients were randomly allocated to receive i.m. tramadol 100 mg (n=30) or famotidine 20 mg (n=30) 1 h before general anaesthesia.

**Results.** At the beginning and the end of anaesthesia, patients receiving tramadol had a median gastric fluid pH of 6.4, which was not significantly different from those treated with famotidine (median 6.3). The infant well-being, as judged by Apgar score, cord blood gas analysis, and neurobehavioural assessment showed no significant difference between the two groups. Nalbuphine consumption in the first 24 h after operation was reduced by 35% in the tramadol group. Pain intensity score on sitting and sedation were significantly greater in famotidine group up to 24 h after surgery. There was no significant difference in incidence and severity of nausea and vomiting between the two groups.

**Conclusion.** A single i.m. dose of tramadol is useful pre-treatment to minimize the risk of acid aspiration during operation, and in improving pain relief during 24 h after surgery.


**Keywords:** anaesthesia, obstetric; analgesics opioid, tramadol; antacid, famotidine

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Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It is a central analgesic with a low affinity for μ opioid receptor. It inhibits serotonin and norepinephrine neuronal reuptake.1 Tramadol is less likely to cause neonatal respiratory depression and hence it has been recommended for analgesia in parturients undergoing vaginal delivery.2

Tramadol also inhibits type-3 muscarinic receptor (M₃); which primarily mediates gastric gland secretion and smooth muscle contraction.3 Approximately 30% of women undergoing elective Caesarean section have a significant amount of acidic contents in their stomach unless they receive antacid within 1 h before surgery.4 The aim of this study was to assess the antacid and analgesic value of single dose of i.m. tramadol given 1 h before elective Caesarean section performed under general anaesthesia.

**Methods**

We studied 60 ASA I women undergoing elective Caesarean section. The study was approved by the hospital Ethics Committee and all participants gave informed consent to this double-blind study. Patients with a history of gastritis, gastric or duodenal ulcers were excluded from study.

The patients fasted from midnight (8 h fast). They were randomly allocated (using a computer generated random number) to receive either tramadol 100 mg or famotidine 20 mg i.m. 1 h before induction of anaesthesia. The medication was given by the ward nurse. The patients were transported to the operating theatre in the lateral position and 15° left lateral tilt was maintained on the operating table. An 18-gauge i.v. cannula was inserted into forearm, and ECG, pulse oximeter and indirect arterial pressure monitor (Dinamap) attached.

After 3 min of pre-oxygenation, general anaesthesia was induced with propofol 2 mg kg⁻¹ followed rapidly by succinylcholine 1 mg kg⁻¹. Cricoid pressure was applied after loss of consciousness and maintained until airway was secured using a tracheal tube. After tracheal intubation, a 16-French gauge multi-orifice, vented Salem nasogastric
tube was inserted and its correct position was confirmed by epigastric auscultation of injected air. Gastric content measurement (volume and pH) was made twice: after induction of anaesthesia and at the end of anaesthesia. The pH was measured using a pH meter.

Anaesthesia was maintained with a mixture of nitrous oxide 50% and halothane 0.5% in oxygen. After recovery from succinylcholine, muscle relaxation was maintained with vecuronium 0.1 mg kg\(^{-1}\). Lungs were mechanically ventilated and normocapnia (end-tidal carbon dioxide) was maintained. Systolic, mean, and diastolic arterial pressures and heart rate were recorded every 2 min for the first 20 min. An infusion of compound lactate solution 500 ml was given over the first 10 min. The times from induction of anaesthesia until delivery of the newborn (I–D time) and from the uterine incision to the delivery (U–D time) were recorded. Also, maternal oxygen saturation and end-tidal carbon dioxide concentration at the time of delivery were recorded.

After the umbilical cord was clamped, an infusion of oxytocin 20 units in 500 ml of 5% glucose was started, nalbuphine 0.25 mg kg\(^{-1}\) was given i.v. and nitrous oxide was increased to 67%. Halothane was discontinued at the start of skin suture and nitrous oxide was stopped 2 min later. Residual neuromuscular block was antagonized with a mixture of neostigmine 0.05 mg kg\(^{-1}\) and atropine 0.02 mg kg\(^{-1}\). The surgeon graded uterine relaxation on an unmarked 10-cm visual analogue scale; 0 indicated none and 10 severe relaxations. In combination with the need for supplementary doses of oxytocin, this gave a clinical indication of the degree of uterine relaxation. The mother’s haemoglobin concentration and packed cell volume (PCV) were recorded before and after (24 h) operation. All mothers were questioned during the first postoperative day about intraoperative dreaming or awareness.

All neonates were assessed each time by the same paediatrician who was unaware of the treatment group. Apgar scores were recorded at 1 and 5 min. Umbilical venous and arterial blood gas analysis were performed at delivery. After 24 h the neurobehavioural responses of the neonates were evaluated.

For postoperative analgesia, patients received nalbuphine by PCA, delivering i.v. nalbuphine 0.05 mg kg\(^{-1}\) with lock-out time of 20 min. For escape analgesia, patients were given a bolus of i.v. nalbuphine 10 mg. An anaesthetist, blinded to the treatment groups, visited the patients at 6, 12, 18, and 24 h after surgery. The patients were asked to record the intensity of abdominal pain at rest, on deep inspiration, and on sitting up, on a 10-cm analogue scale ranging from 0 for no pain to 10 for the worst pain imaginable. The cumulative nalbuphine consumption was recorded. A four-point verbal rating score (awake, drowsy, rousable, or deep sleep) was used to assess sedation. The frequency and severity of nausea and vomiting were also assessed as follows: (0) no nausea, (1) mild-moderate nausea, (2) mild vomiting (once per observation period) with severe nausea, (3) moderate vomiting (twice per observation period), (4) severe vomiting (3–4 times per observation period), (5) persistent vomiting that needed treatment with antiemetic agent.

Power analysis revealed a sample size of 30 patients per group was sufficient to achieve a power of 80% and an \(\alpha\) of 0.05 to detect a mean difference of 0.5–0.7 in pH and volume variables or 30% reduction in total opioid consumption. Statistical analysis was performed using Student’s \(t\) test, \(\chi^2\) 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.

### Results

There were no differences in patient characteristics between the groups (Table 1). There were no differences in mean baseline values of systolic arterial pressure or heart rate between the two groups. The values of these variables increased after tracheal intubation in both groups (\(P<0.01\)) and returned to baseline level by 4–6 min in the tramadol group and 7–10 min in the famotidine group.

The total dose of nalbuphine was significantly greater at 24 h in the famotidine group [mean (SD) 46.5 (1.7) mg] than

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tramadol group (n=30)</th>
<th>Famotidine group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29.8 (22–39)</td>
<td>32.0 (23–38)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.3 (9.5)</td>
<td>76.0 (11.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.0 (6.6)</td>
<td>163.4 (7.0)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>38.8 (1.3)</td>
<td>39.1 (1.5)</td>
</tr>
<tr>
<td>F(_{\text{CO2}}), at delivery (%)</td>
<td>99.1 (0.7)</td>
<td>98.8 (1.1)</td>
</tr>
<tr>
<td>E(_{\text{CO2}}), at delivery (kPa)</td>
<td>30.4 (3.5)</td>
<td>30.6 (3.3)</td>
</tr>
<tr>
<td>I – D time (min)</td>
<td>12.1 (2.2)</td>
<td>11.6 (3.1)</td>
</tr>
<tr>
<td>U – D time (min)</td>
<td>1.5 (0.2)</td>
<td>1.6 (0.1)</td>
</tr>
<tr>
<td>Anaesthetic time (min)</td>
<td>49.2 (10.4)</td>
<td>44.6 (9.2)</td>
</tr>
</tbody>
</table>

![Image](image.png)  
Fig 1 Mean (st) hourly consumption of nalbuphine in the tramadol (T) and famotidine (F) groups. *\(P<0.05\), **\(P<0.01\).
in the tramadol group [30.3 (7.5)] \( (P<0.05) \). Analysis of nalbuphine used in 6-hourly epochs revealed a significantly greater use in the famotidine group at 6–12 \( (P<0.05) \) and 18–24 h \( (P<0.01) \) after operation compared with the tramadol group (Fig. 1). The median time to first request for analgesia was increased from 21 to 46 min in the tramadol group. Pain intensity scores on sitting were significantly lower in tramadol group at 6–12 \( (P<0.05) \) and 18–24 h \( (P<0.01) \) after operation than in famotidine group (Fig. 2). The scores for sedation were significantly lower in tramadol group at all time intervals \( (P<0.05) \) (Table 2). There was no significant difference between the two groups in pain intensity score at rest or on deep respiration, incidence and severity of nausea and vomiting, or rescue antiemetic consumption over 24 h after surgery (Table 3).

There was no significant difference between the two groups in surgeon’s assessment of relaxation, requirement of additional oxytocin, the haemoglobin concentration and PCV values before and after operation. Umbilical blood gas analysis and neonatal Apgar scores were satisfactory and similar between groups (Table 4). The neurobehavioural assessment of the neonates, 24 h after delivery, did not show any difference between the two groups. None of the mothers complained of intra-operative dreams or awareness.

Gastric pH and volume at the beginning and end of anaesthesia and the number of patients at risk for aspiration did not differ significantly between the two groups (Table 5).

Discussion
We have found that administration of single dose i.m. tramadol 1 h before Caesarean section increased gastric pH during operation similar to famotidine, and reduced nalbuphine consumption and pain intensity on sitting during first postoperative day with less sedation. 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 analgesia.\(^5\) This may explain relative haemodynamic stability during induction–delivery time, reduction in opioid consumption and better pain relief on sitting after operation in the tramadol group in present study. Tramadol and its metabolite noncompetitively inhibit the NMDA receptors, which may contribute to its analgesic effects.\(^6\) As we reported previously, pre-medication with a NMDA-receptor antagonist reduced pain provoked by movement, enhanced postoperative analgesia and reduced postoperative analgesic requirements.\(^7\)

The combination of tramadol with morphine in the postoperative period of painful surgery was found to be infraadditive.\(^8\) A weak opioid agonist tramadol may potentially inhibit the analgesia provided by full agonist morphine, compete for the same effector \( \mu \) receptor. Webb and colleagues\(^9\) 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

![Fig 2](image)

**Fig 2** Mean (SD) pain scores on sitting, for patients in the tramadol (T) and famotidine (F) groups. *\( P<0.05 \), **\( P<0.01 \).

### Table 2

Verbal rating score (VRS) for sedation in tramadol (T) and famotidine (F) groups. The results are presented as number of patients. *\( P<0.05 \)

<table>
<thead>
<tr>
<th>VRS</th>
<th>6 h</th>
<th>12 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>22</td>
<td>13*</td>
<td>24</td>
</tr>
<tr>
<td>Drowsy</td>
<td>3</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Rousable</td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Asleep</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 3

Number of patients with different grades of nausea and vomiting during the first 24 h after operation in the tramadol (T) and famotidine (F) groups

<table>
<thead>
<tr>
<th>Grade</th>
<th>6 h</th>
<th>12 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, No nausea</td>
<td>11</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>1, Mild-moderate nausea</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>2, Severe nausea, mild vomiting</td>
<td>9</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>3, Moderate vomiting</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4, Severe vomiting</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5, Persistent vomiting</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 4

Median (range) Apgar scores at 1 and 5 min, and mean (SD) umbilical arterial and venous blood gas analysis at delivery in the tramadol (T) and famotidine (F) groups. There were no differences between the groups

<table>
<thead>
<tr>
<th>Apgar score</th>
<th>Umbilical arterial pH</th>
<th>( P_{O_2} ) (kPa)</th>
<th>( P_{CO_2} ) (kPa)</th>
<th>Umbilical venous pH</th>
<th>( P_{O_2} ) (kPa)</th>
<th>( P_{CO_2} ) (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>5 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>8 (6–10)</td>
<td>7.26 (0.06)</td>
<td>3.4 (1.0)</td>
<td>6.5 (1.0)</td>
<td>7.30 (0.05)</td>
<td>4.7 (1.4)</td>
</tr>
<tr>
<td>F</td>
<td>9 (5–10)</td>
<td>7.27 (0.04)</td>
<td>3.3 (0.7)</td>
<td>6.6 (4.1)</td>
<td>7.30 (0.03)</td>
<td>4.9 (0.8)</td>
</tr>
</tbody>
</table>

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In the present study, these previously reported effects of the metabolite of tramadol, O-desmethyl tramadol; substantially reduce the analgesic requirement after surgery. That the preventive treatment of postoperative pain may substantially reduce postoperative nausea. The EEG activation changes were dose-dependent EEG activation, increased arterial pressure, pH (approximately 6.00) at the beginning and end of anaesthesia. The inhibitory effects of tramadol on muscarinic receptor (M3) function explain our present results. Tramadol in common with all opioids, delays gastric emptying and can produce uterine vasoconstriction with possible fetal asphyxia. The difference in umbilical blood gas analysis between the present study and the study by Baraka and colleagues could have induced a relative dilatation in the maternal uterine blood vessels, with possible changes in referred maternal and fetal $P_{O_2}$. Also with an i.v. fluid load given over the first 10 min of anaesthesia in the present study, placental blood flow may have been better preserved during delivery. This may explain the lack of difference in the blood gas data between the two groups in the present study.

As reported previously, we found that both famotidine and tramadol produced a similar level of gastric content pH (approximately 6.00) at the beginning and end of anaesthesia. The inhibitory effects of tramadol on muscarinic receptor (M3) function explain our present results. Tramadol, in common with all opioids, delays gastric emptying and can produce uterine vasoconstriction with possible fetal asphyxia. The difference in umbilical blood gas analysis between the present study and the study by Baraka and colleagues could have induced a relative dilatation in the maternal uterine blood vessels, with possible changes in referred maternal and fetal $P_{O_2}$. Also with an i.v. fluid load given over the first 10 min of anaesthesia in the present study, placental blood flow may have been better preserved during delivery. This may explain the lack of difference in the blood gas data between the two groups in the present study.

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scepticism on the usefulness of these figures. Because other studies of aspiration risk reported their data with respect to these criteria, we did so as well to facilitate comparison.

A main criticism of this study may relate to the unlicensed use of tramadol during pregnancy and lactation in some countries. Our present knowledge about the risk of administering medications during pregnancy is incomplete, and the practitioner is left to weigh the risks against the benefits of instituting pharmacological therapy for each individual. In the present study, tramadol was administered in a single i.m. dose near term and not in early pregnancy.

In summary, our study shows that single dose i.m. tramadol 1 h before elective Caesarean delivery is effective in lowering the risk of acid aspiration during operation and improving pain relief during 24 h after surgery. 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.

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