Intra-Operative Analgesia during Cesarean section: A Double Blind Clinical Trial Comparing the Effect of Tramadol versus Fentanyl on Both the Mother and the Neonate

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Abstract

Background: Tramadol had been recommended as an analgesic agent during vaginal delivery. Analgesia during cesarean section stills a matter of controversy on the effect on the fetus and maternal awareness and recall.

Purpose: At this study, tramadol had been tested versus fentanyl as an adjuvant to general anesthesia for patients undergoing caesarian section. The effect on both, the mother (recall or awareness during surgery and post operative nausea and vomiting) and the neonate as the effect on Apgar score and the umbilical cord venous blood gases.

Method: Forty pregnant ladies assigned to have elective cesarean section, had been divided blindly in tramadol group (n=20) and fentanyl group (n=20). Tramadol group had received 100 mg IV. And the fentanyl group had received 100 µg IV. Anesthesia induced by thiopentone sodium in a dose of 3 mg/kg B. wt, suxamethonium chloride 1.5 mg/ kg. B. wt, anesthesia was maintained by 100% oxygen and analgesia by tramadol or fentanyl with incremental on and off 0.5% halothane.

Results: The Apgar score on both groups at 1 and 5 minutes shows no difference, the umbilical vein PO2 of the fentanyl group is higher than tramadol group; the PCO2 of the umbilical vein in tramadol group is higher than fentanyl group. Post operatively, 2 patients in tramadol group shows recall of the child crying during surgery, and four patients from tramadol group suffer from nausea and/or vomiting.

Conclusion: Tramadol is associated with high incidence of maternal recall and awareness, with significant reduction in umbilical vein PO2 in spite of no effect on Apgar score.

Key words: Intra-operative analgesia, umbilical vein gases, Apgar score, postoperative nausea and vomiting (PONV)

Introduction

The safety of the infant and prevention of awareness is a conflicting mater faces the anesthetists in cesarean section [1-3]. The awareness must be prevented, so the mother must be sedated very well, and the depressant effect of the anesthetic agents on the fetus must be spared. All of the anesthetic agents are crossing the placenta, fentanyl in a dose of 1 µg / kg B. wt. when administered prior to cesarean section; carry no adverse effects on the fetus [2].

Fentanyl is a potent agonist at ì opioid receptors, with no effect on monoaminergic neurotransmitters. Tramadol is a centrally acting analgesic agent. It has a low effect on ì opioid receptors, and it also inhibits noradrenaline and 5-hydroxytryptamine at the neurons, so it facilitates their release [4-8]. The analgesic effect of tramadol is mediated by the direct stimulation to the ì opioid receptors and modulation of the monoaminergic inhibitory pain pathway. Tramadol in comparison to other opiates do not cause respiratory depression [8-9], so it is recommended as an analgesic during normal vaginal delivery [9]. 100 mg tramadol is equivalent to 100 mg pethidine with a lower incidence of respiratory depression [10]. All of the above, as a potent analgesic with less or no respiratory depression on the fetus, made tramadol as a suitable candidate to be supplemented as an analgesic agent in general anesthesia for cesarean section.

Aim of study: To compare the effect of tramadol versus fentanyl as a supplementation to general anesthesia for elective cesarean section, with the focus on the fetal safety (respiratory depression) and maternal awareness (postoperative recall) and postoperative nausea and vomiting (PONV).

Method:

Forty pregnant women undergoing elective cesarean section were investigated. All of the patients were classified under group (American Society of Anesthesiologists classification) ASA I and II, with gestational age more than 36 weeks, with no active medical or obstetric problems. The ethical means had been taken into consideration. The patients were allocated randomly into 2 groups according to specialized randomization table.

The tramadol and fentanyl were prepared by an anesthetist in a syringe containing 2 ml of clear solution, and labeled as solution No.1 (100mg tramadol) and solution No.2 (100µg fentanyl) as a matter of blinding for the anesthesiologist who is responsible of the study who will interpret the data collection and analyses in order to avoid bias as much as possible.

In the operation room, a wide bore intravenous catheter was applied, 5% glucose water infusion started, with total 1500 ml of fluid had been infused during the surgical procedure. Pulse rate, non-invasive blood pressure and SPO2 were monitored during the operation continuously. The patient lied in supine position with 15 degrees left lateral tilt to avoid aorto-caval compression. Pre-oxygenation by 100% oxygen...
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applied for 5 minutes before induction. The patients had received randomly either solution No.1 or solution No.2 before induction, during the period of pre-oxygenation. Induction was carried out by 3 mg/kg B. wt thiopentone sodium as a sleeping agent, 1.5 mg/kg B. wt. Suxamethonium chloride as a neuromuscular blocking agent was used to facilitate endotracheal intubation with auffed endotracheal tube. Rapid sequence intubation with cricoids pressure had been applied, to ensure rapid and safe secure of the trachea-bronchial tree. Intermittent positive pressure ventilation was applied. After the effect of suxamethonium chloride effect was abolished, 0.1 mg/kg B. wt pancronium bromide was given as the main neuromuscular blocking agent. Anesthesia was maintained by 100% oxygen with 0.5% halothane. The incision-delivery time (I-D) was recorded and the uterine incision-delivery time (UI-D) too. After delivery of the baby, 5 IU oxytocin infusion started to facilitate uterine contraction, the halothane had stopped, and 50 mg tramadol to group T (tramadol group) and 50 µg fentanyl to group F (fentanyl group) were given to the patients to maintain intra-operative maternal sedation and analgesia. The recovery was carried by giving the patient 20µg/kg B. wt neostigmine with 10µg/kg B. wt atropine as a reversal agent. Extubation applied while the patient lying on the left lateral side after regaining regular and adequate reparatory efforts.

The demographic and preoperative data were collected; the ID time was measured in minutes and the UI-D time in seconds. Apgar score was recorded in 1 and 5 minutes. Umbilical vein blood sample was collected to measure blood gases (PO$_2$, PCO$_2$, HCO$_3$, pH and base deficit).

Chi-square was used to the non-parametric data (Apgar score, recall/awareness and PONV). The quantitative parametric data was analyzed by using Student’s t test. The P <0.05 was considered statistical significant.

The groups had revealed to the anesthesiologist responsible for the study after data interpretation and analysis.

Results:
The demographic data was shown in table 1

Table 1: Demographic and preoperative maternal data

<table>
<thead>
<tr>
<th>Group</th>
<th>Age years</th>
<th>Body weight kg</th>
<th>I-D time minutes</th>
<th>UI-D time Seconds</th>
<th>SPO$_2$%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>24±5</td>
<td>78±7</td>
<td>11±2</td>
<td>92±5</td>
<td>99.2±0.3</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>26±5</td>
<td>73±5</td>
<td>9±4</td>
<td>90±7</td>
<td>98.9±1.3</td>
</tr>
</tbody>
</table>

Umbilical vein blood gases:
The umbilical vein PO$_2$ was lower and PCO$_2$ was higher in tramadol group than fentanyl group. The umbilical vein base deficit was the same in both groups (table2).

Table 2: Umbilical vein blood gas analysis data for both groups

<table>
<thead>
<tr>
<th>Group</th>
<th>PO$_2$ mmHg</th>
<th>PCO$_2$ mmHg</th>
<th>pH</th>
<th>HCO$_3$</th>
<th>Base deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>23±5</td>
<td>52±4</td>
<td>7.31±0.03</td>
<td>24±1.2</td>
<td>-1.0±1.5</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>34.5±5</td>
<td>45±4</td>
<td>7.34±0.01</td>
<td>23.5±1.0</td>
<td>-0.72±1.3</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Apgar score:
There were no differences in Apgar score in both groups at 1 and 5 minutes, the record was ≥7 as shown in table 3

Table 3: Apgar score on both groups at 1 and 5 minutes

<table>
<thead>
<tr>
<th>Group</th>
<th>APGAR score at 1 minute</th>
<th>APGAR score at 5 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>7/10</td>
<td>10/10</td>
</tr>
<tr>
<td>Tramadol</td>
<td>8/10</td>
<td>10/10</td>
</tr>
</tbody>
</table>

Maternal recall and PONV:
No patients in fentanyl group had any intra-operative recall or awareness while in Tramadol group 2 patients had remembered the crying of their newborn babies at delivery time, but still no sensation of pain had been experienced.
In tramadol group, 4 patients had suffered from PONV, while no case had been reported in fentanyl group.

Discussion: During cesarean section, the umbilical vein PO\textsubscript{2} of the newborn is proportional to the maternal PO\textsubscript{2}, in the same time, the maternal PO\textsubscript{2} is increasing with the FiO\textsubscript{2} (fractional inspired oxygen)\textsuperscript{[11]}. In our study the FiO\textsubscript{2} was the same in both groups, but there is a difference in umbilical vein PO\textsubscript{2} and PCO\textsubscript{2}. In the tramadol group, the umbilical vein PO\textsubscript{2} was lower and the PCO\textsubscript{2} was higher than the fentanyl group. The uterine blood flow is important factors that affect the umbilical vein PO\textsubscript{2} and PCO\textsubscript{2}. The uterine blood flow at term is equal to 10% of the cardiac output, as the uterine vascular bed is almost maximally dilated under normal circumstances, with a little capacity to dilate further\textsuperscript{[12]} However it is capable of marked vasoconstriction by α-adrenergic activity. Vasopressor effects by α-adrenergic activity by phenylephrine, noradrenalin or angiotensin show a marked reduction in uterine blood flow and could lead to fetal asphyxia.\textsuperscript{[13][14]} Tramadol block the reuptake of noradrenalin and 5-hydroxytreptamine at the nerve terminals.\textsuperscript{[6-8]} Noradrenalin can result in uterine vasoconstriction, while 5-hydroxytreptamine can potentiate the vasoconstriction effect of noradrenalin\textsuperscript{[15][10]} Accordingly, tramadol may induce uterine vasoconstriction, and consequently reduces the uterine blood flow which will be reflected as a reduction in umbilical vein PO\textsubscript{2} and increase in umbilical vein PCO\textsubscript{2}. 5-hydroxytreptamine acting at 5-HT\textsubscript{3} receptors is an important emetic signal and transmitter at the chemoreceptor trigger zone at the solitary tract nucleus.\textsuperscript{[16]} That point explains the increased incidence of nausea and vomiting associated with tramadol, by the direct effect on inhabiting the neuronal reuptake of noradrenalin and 5-hydroxytreptamine. A major drawback of using tramadol is awareness and recalling of incidents happened during surgery and anesthesia, and this was due to the weak action of tramadol on the opioid agonist receptors, and the preferential analgesic effect of tramadol on monoaminergic pain pathways.\textsuperscript{[7]} The high umbilical vein PO\textsubscript{2} and low umbilical vein PCO\textsubscript{2}, as it had no effect on uterine blood flow, as fentanyl rapidly crosses the foeto-placental blood barrier, but has no effect on uterine tone hence no effect on uterine blood flow.\textsuperscript{[17][19]} Those results are applicable for a patient undergoes elective cesarean section. Fentanyl is a potent agonist at μ opioid receptors, with no effect on monoaminergic neurotransmitters.\textsuperscript{[10]} Accordingly there were no cases recorded of recall or awareness during surgery with no cases reported of PONV although in other studies, fentanyl is blamed for the increased incidence of PONV.\textsuperscript{[20]}

Conclusion This study shows that fentanyl is superior to tramadol as a supplement to general anesthesia for elective cesarean section from the mater of maternal awareness and recall, while their effect on Apgar score is the same with no deference in spite of some statistically significant changes in umbilical vein PO\textsubscript{2} and PCO\textsubscript{2}.

References

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