EFFECT OF PREOPERATIVE ADMINISTRATION OF INTRAVENOUS PARACETAMOL DURING CESAREAN SURGERY ON HEMODYNAMIC VARIABLES RELATIVE TO INTUBATION, POSTOPERATIVE PAIN AND NEONATAL APGAR

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SUMMARY – Selection of anesthetic drugs for cesarean section requires many considerations. Anesthetic drugs for this purpose must prevent hemodynamic stress due to tracheal intubation, while inducing neonatal complications. This study was conducted to determine the effects of paracetamol given before induction of anesthesia on cardiovascular responses to tracheal intubation and postoperative pain in the mother, and on neonatal Apgar score. This double-blind randomized placebo-controlled trial included 60 women in ASA I, without underlying diseases and fetal distress, who were candidates for elective cesarean section under general anesthesia. Patients were divided into two groups of 30 patients. Patients in the paracetamol group received 1 g intravenous (IV) paracetamol 20 min before the operation, while those in the placebo group received 1 cc normal saline at the same time. In both groups, anesthesia was induced by sodium thiopental and succinylcholine. Maternal systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were measured before and immediately upon induction of anesthesia, and at first and fifth minute after tracheal intubation. Neonatal effects were assessed by Apgar score. Postoperative pain was assessed by use of the visual analog scale (VAS). The dose of analgesic used and the time of the first analgesic request by patients postoperatively were recorded. The SBP, DBP, MAP and HR were controlled significantly better in paracetamol group than in placebo group (P<0.05). The mean 1-min and 5-min Apgar scores of neonates did not differ between the groups. The VAS pain score was significantly lower in paracetamol group than in placebo group at all measuring times (P<0.05). Also, paracetamol caused later first analgesic request and lower dose of analgesic needed to control pain postoperatively (P<0.05). In conclusion, the results of our study suggested IV paracetamol to be an efficacious agent to decrease hemodynamic responses to tracheal intubation, while providing better postoperative pain management without considerable neonatal complications in women undergoing cesarean section in general anesthesia.

Key words: Acetaminophen; Cesarean section; Anesthesia, general; Hemodynamics; Pain, postoperative; Apgar score

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Introduction

Cesarean section is one of the most common surgeries. There are two techniques for anesthesia in this surgery, general and regional anesthesia. Although regional anesthesia is expanding, general anesthesia is indicated in many situations like hemorrhage, coagulopathies, fetal distress and other critical situations, or regional anesthesia refused by the patient. Fetal effect of many anesthesia drugs given during cesarean section must be considered. Using opioids and benzodiazepines before delivery may cause central nervous system depression; therefore, the administration of such drugs is usually delayed until delivery has been completed. Opioids and benzodiazepines are lipid soluble and can be transferred from placenta to affect the fetus; therefore, using drugs that have no adverse effect on the mother and the child is recommended. Previous studies have shown that 30%-40% of patients undergoing cesarean section suffer moderate to severe postoperative pain, which causes fear, anxiety and depression in these patients. Laryngoscopy and intubation are painful stimulations and cause blood pressure and heart rate increase during anesthesia induction in cesarean section; in patients with underlying diseases such as hypertension, coagulopathies, valvular heart disease, intracranial tumors, etc. it may even be life threatening. In addition, undesirable effects of pain on physiologic functions of the cardiac, pulmonary, intestinal and urinary systems cause longer hospitalization and extra costs. Postoperative pain relief is associated with less thromboembolic events, better neonatal care and earlier breastfeeding.

Paracetamol is injecting acetaminophen used as a non-opioid analgesic. Although the exact mechanism is not known completely, several studies have proved its analgesic effects in mild to moderate pains, so it can be administered preoperatively without any major complications. Preoperative paracetamol also decreases the need of postoperative morphine; its antiplatelet activity is much lower than that of non-steroidal anti-inflammatory drugs (NSAIDs) and has no effect on bleeding time. Adverse effects of NSAIDs on gastrointestinal and renal systems are not seen with paracetamol, which causes no nausea, vomiting or respiratory depression seen with opioids either. Acetaminophen overdose causes hepatotoxicity, but not when used in therapeutic doses. Although paracetamol can cross the placenta, there is no known adverse effect on the fetus.

As paracetamol has desirable analgesic effects with no adverse effects on the fetus, we decided to assess the effect of preoperative administration of intravenous (IV) paracetamol for cesarean section on hemodynamics relative to intubation, postoperative pain and neonatal Apgar score.

Material and Methods

Upon approval by the institutional Ethics Committee, this double-blind randomized clinical trial was conducted at the Shahid Sadoughi Hospital, Yazd, Iran, between February and September 2012, including women admitted for elective cesarean section under general anesthesia. A written consent was obtained from all study participants.

Sample size

Based on the 95% confidence interval, study power of 80%, standard deviation for visual analog scale (VAS) 1.1 in paracetamol group and 1.4 in control group, standard error of 1 and referring to previous similar studies, 60 patients were required in total (30 patients per group). Patients were selected by simple method and consequently until the required sample size was reached. Patients were allocated to one of the two study groups based on age and using table of random numbers. Patients were not aware of their study group.

Inclusion criteria

Study participants were selected among pregnant women aged 18-40 and considered candidates for elective cesarean section under general anesthesia. Patients were in American Society of Anesthesiologists (ASA) class I and had no history of fetal distress, opioid or non-opioid analgesic use before surgery.

Exclusion criteria

Women with any underlying chronic disease such as cardiovascular, pulmonary, hepatic and renal diseases, and diabetes were excluded from the study. Also, any fetal anomaly or distress was considered as exclusion criterion. Mothers with preeclampsia, body...
mass index (BMI) >25 or BMI <19 were excluded from the study.

Patients were excluded from the study in case of difficult intraoperative intubation, prolonged intubation, unsuccessful intubation, prolonged surgery for more than 90 minutes, or delivery of fetus with congenital anomaly.

**Anesthesia protocol**

Anesthesia was always induced by the same anesthesiologist. Premedication with 10 mg metoclopramide was administered one hour before the induction of anesthesia. In the operating room, two IV lines were inserted and 1000 mL lactating Ringer’s solution was infused before induction of anesthesia. In paracetamol group, 20 minutes before anesthesia induction, 1 g paracetamol was injected in 500 cc lactating Ringer’s solution and infused, while in placebo group 1 cc normal saline was injected in Ringer’s lactate. The solution was prepared by the resident in anesthesiology and infused by an anesthesia nurse who was not aware of the patient group.

Routine monitoring included noninvasive blood pressure measurement, electrocardiography, pulse oximetry and capnography. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) of the mother were documented before and immediately upon induction of anesthesia, and at first and fifth minute after intubation by using BCI Advisor Vital Signs Monitor. Hemodynamic variables were measured by anesthetic technicians who were unaware of the patient group.

The patients were preoxygenated for three minutes before induction of anesthesia in supine position. General anesthesia was induced using rapid sequence administration of sodium thiopental 5 mg/kg and succinylcholine 1.5 mg/kg. Following direct laryngoscopy and endotracheal intubation within 15 seconds, anesthesia was maintained with 0.7% isoflurane in 50% nitrous oxide with 50% oxygen mixture. Isoflurane concentration was decreased to 0.5% after delivery and a dose of 0.5 mg/kg atracurium was administered as muscle relaxant.

**Data collection**

Data were collected into a form containing study group, demographic variables (age, weight, height, gravidity, etc.) and study variables. Maternal SBP, DBP and HR were documented before induction of anesthesia, immediately upon, and at first and fifth minute after intubation. Apgar score of neonates was recorded at first and fifth minute after delivery. Postoperatively, pain score was assessed at 30th minute after recovery, then at 2 h, 6 h and 12 h after admission to maternity ward. The intensity of postoperative pain was evaluated by a researcher using patient self report and quantified using a 10-cm VAS, where zero indicates no pain at all, and a score of 10 indicates very severe, intolerable pain. Also, the first patient’s request for analgesic and the administered dose of analgesic were recorded during the first 12 hours. If VAS was ≥5, 0.5 mg/kg IV pethidine was administered. The researcher collecting the data was not aware of the patient group.

**Statistical analysis**

All data collected were transferred into the SPSS-19 software and analyzed by Mann-Whitney test and T-test. The level of significance was set at \( P < 0.05 \).

**Results**

Sixty pregnant women, candidates for elective cesarean section under general anesthesia, were enrolled in the study (30 women per group). The mean age of patients in the paracetamol and placebo groups was 28.68±4.53 and 27.96±4.26, respectively \((P > 0.05)\). The mean (±SD) SBP, DBP, mean arterial pressure (MAP) and HR did not differ between the groups before anesthesia induction. However, significant differences were recorded between the paracetamol group and placebo group according to all hemodynamic variables after intubation, at all measuring times after anesthesia induction, immediately after laryngoscopy, one minute after laryngoscopy, and five minutes after laryngoscopy (Table 1).

In terms of pain score, the mean (±SD) VAS score in paracetamol group was significantly lower as compared to placebo group at all measuring times of recovery \((P=0.0001)\), 2 h after surgery \((P=0.0001)\), 6 h after surgery \((P=0.0001)\) and 12 h after surgery \((P=0.019)\) (Table 2).

The mean pethidine use after surgery was significantly lower in paracetamol group as compared to placebo group at 2 h after surgery \((P=0.002)\) and 6 h after surgery \((P=0.001)\), but at 12 h the difference was
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not statistically significant (P=0.236; Mann-Whitney test) despite the lower pethidine use in paracetamol group (Table 2).

The time after surgery when the first dose of an analgesic was requested by patients was 2±1.01 and 1.1±0.30 h for paracetamol and placebo group, respectively (P=0.0001; Mann-Whitney).

Neonatal 1-min Apgar score was 8.93±0.25 and 8.93±0.25, and 5-min Apgar score 9±0.0 and 9±0.0 in paracetamol and placebo group, respectively; the

Table 1. Mean ± SD values of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) at different times of anesthesia induction in study groups and related P values (T-test)

<table>
<thead>
<tr>
<th>Measuring time (SBP) Group/Variable</th>
<th>SBP before anesthesia induction</th>
<th>SBP after anesthesia induction</th>
<th>SBP immediately after laryngoscopy</th>
<th>SBP 1 min after laryngoscopy</th>
<th>SBP 5 min after laryngoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol yes</td>
<td>123.23±10.18</td>
<td>127.13±10.87</td>
<td>14.56±10.62</td>
<td>130.83±13.16</td>
<td>117.53±9.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>123.13±9.52</td>
<td>142.30±10.68</td>
<td>152.50±9.23</td>
<td>145.53±11.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.969</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 2. Mean ± SD for pain based on visual analog score (VAS) and pethidine used at different times after surgery and related P values (Mann-Whitney test)

<table>
<thead>
<tr>
<th>Pain (VAS) Group/Variable</th>
<th>Recovery</th>
<th>2 h after surgery</th>
<th>6 h after surgery</th>
<th>12 h after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol yes</td>
<td>5.66±1.78</td>
<td>5.4±1.16</td>
<td>4.13±1.15</td>
<td>3.37±0.9</td>
</tr>
<tr>
<td>No</td>
<td>8.03±0.88</td>
<td>7.3±1.11</td>
<td>5.76±1.33</td>
<td>3.93±0.83</td>
</tr>
<tr>
<td>P</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean pethidine use Variable</th>
<th>2 h after surgery</th>
<th>6 h after surgery</th>
<th>12 h after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol yes</td>
<td>8.62±12.09</td>
<td>25±6.31</td>
<td>22±8.29</td>
</tr>
<tr>
<td>No</td>
<td>18.75±11.02</td>
<td>33.33±11.98</td>
<td>24.13±4.66</td>
</tr>
<tr>
<td>P</td>
<td>0.002</td>
<td>0.001</td>
<td>0.236</td>
</tr>
</tbody>
</table>
difference was not statistically significant at any time ($P=1.00$; Mann-Whitney).

**Discussion**

Although regional anesthesia is the method of choice in cesarean section, general anesthesia should be considered in some emergency cases such as coagulopathy, previous spinal surgery or mother’s request. In general anesthesia for cesarean section, opioids are avoided because considerable amounts of drugs are transferred through placenta to the fetus. The aim of the anesthesiologist is to minimize the stress due to laryngoscopy, intubation and surgery in the mother, with the lowest possible adverse effect on the fetus.

As satisfactory effects of paracetamol on postoperative pain were confirmed in previous studies, we decided to assess the effect of paracetamol on maternal hemodynamic variables, pain, and neonatal Apgar score. We used 20 g IV paracetamol 20 minutes before anesthesia induction. Results showed that paracetamol decreased SBP, DBP and HR at all times after laryngoscopy and intubation. In fact, 1 g paracetamol had equal effects to 1 μg/kg remifentanil, 10 μg/kg alfentanil, or 5 μg/kg remifentanil, reported in previous studies to decrease hemodynamic stress after laryngoscopy and tracheal intubation.

Analgesic effect of paracetamol was also considerable in our study, similar to the study by Tablov et al., which evaluated the effects of paracetamol on post gynecologic surgery pain and suggested paracetamol to be an effective analgesic with no side effects. In the study by Naga Rani et al., 1 g paracetamol was administered as analgesic in the second stage of labor. This study confirmed paracetamol as an analgesic and antipyretic during pregnancy and labor. These results are similar to our results in terms of analgesic effects and safety for the fetus.

In the present study, significant decrease in pethidine use was seen at 2 h and 2 h postoperatively. In addition, the time of the first analgesic request by the patient was prolonged, confirming the favorable analgesic effects of paracetamol too. The mean pethidine use was not significantly different between the study groups at 12 h postoperatively; this is reasonable because of the 4-6 h half life of paracetamol.

In the present study, there was no fetal complication (which was evaluated by Apgar score). In the study by Elbohoty et al., 1 g paracetamol was administered in the active phase of labor. Their results showed that pain was decreased significantly at 15 min, 1 h and 2 h after delivery, with no effects on Apgar score. These results are consistent with our study results. However, using 0.5 μg/kg remifentanil at the time of anesthesia induction and then 0.2 μg/kg/min infusion of remifentanil, van de Velde has reported respiratory depression in six neonates and acute hypotension in two mothers, besides better control of hemodynamic stress after laryngoscopy. Also, after 1 remifentanil administered at the time of induction, Ngan Kee et al. succeeded to control hemodynamic variability, but two neonates needed resuscitation and naloxone, while in our study none of the neonates had Apgar score lower than 8.

As a general conclusion and based on our study, injection of 1 g paracetamol could control hemodynamic instability following laryngoscopy and intubation, which is one of the most important concerns in general anesthesia. Considering its limited side effects and fetal complications, this drug could be used in cesarean section, where the use of opioids should be limited. Paracetamol is also highly effective in postoperative pain control.

**Acknowledgment**

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**References**


4. AMJADIMANESH J, HATAMIPOOR E, GHEARIAN SHIRAZI HR, MOMBEINI R. Alfentanil effects on neo-
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Sažetak

**UČINAK PRIJEOPERACIJSKOG INTRAVENSKOG PARACETAMOLA TIJEKOM CARSKOG REZA NA HEMODINAMSKE VARIJABLE U ODNOSU NA INTUBACIJU, POSLJEOPERACIJSKU BOL I APGAR INDEKS NOVOROĐENČETA**

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Odabir anestetika kod carskog reza zahtijeva ozbiljno promišljanje. Anestetici koji se primjenjuju za ovu namjenu moraju spriječiti hemodinamski stres zbog traherealne intubacije, ali ne smiju izazvati komplikacije kod novorođenčeta. Cilj ove studije bio je utvrditi učinke paracetamola danog prije indukcije anestezije na kardiovaskularni odgovor na intubaciju trahејe и poslijeoperacijsku bol kod majke, te na Apgar indeks novorođenčeta. U ovo dvostruko slijepo randomizirano placebo kontrolirano ispitivanje bilo je uključeno 60 žena, ASA i, bez osnovnih bolesti i fetalnog distresa, kod kojih je bio predviđen elektivni carski rez u općoj anesteziji. Trudnice su podijeljene u dvije skupine od po 30 žena. Žene u skupini paracetamol dobile su 1 g paracetamola intravenski 20 minuta prije operacije, dok su one u skupini placebo u isto vrijeme primile 1 cc normalne fiziološke otopine. U objema skupinama anestezija je inducirana natrij tiopentalom i sukcinilkolinom. Majčin sistolički krvni tlak (SKt), dijastolički krvni tlak (dKt), srednji arterijski tlak (SAt) и srčana frekvencija (SF) mjereni su prije i neposredno nakon indukcije anestezije te u 1. и 5. minuti nakon trahеalne intubacije. Učinci na novorođenče procijenjeni su pomoću Apgar indeksa. Poslijeoperacijska bol procijenjena je pomoću vizualne analogne ljestvice (VAS). Učinci na novorođenče procijenjeni su pomoću Apgar indeksa. Poslijeoperacijska bol procijenjena je pomoću vizualne analogne ljestvice (VAS). Zabilježena je doza analgetika i vrijeme kad je prvi put zatražen analgetik nakon operacije. Utvrđeno je da su SKt, DKT, SAT i SF značajno bolje regulirani u skupini na paracetamolu u usporedbi sa skupinom koja je primila placebo (P<0,05). Srednji Apgar indeks u 1. и 5. minuti nije se razlikovao između novorođenčadi dviju skupina. Zbroj VAS bio je značajno niži u skupini na paracetamolu nego u skupini na placebo u svim vremenskim točkama mjerenja (P<0,05). Uz to, uz paracetamol je prvi put nakon operacije analgetik zatražen kasnije i bila je potrebna niža doza analgetika za kontrolu boli (P<0,05). Zaključno, rezultati ovoga ispitivanja ukazuju na to da intravenski paracetamol učinkovito smanjuje hemodinamske odgovore na trahеalnu intubaciju, dok istodobno osigurava bolje zbrinjavanje poslijeoperacijske boli bez većih neonatalnih komplikacija kod žena koje se podvrgavaju carskom rezu u općoj anesteziji.

Ključne riječi: Acetaminofen; Carski rez; Anestezija, opća; Hemodinamika; Bol, poslijeoperacijska; Apgar indeks