Effect of Rectal Paracetamol on BIS Guided Intraoperative Sedation and Postoperative Pain in Infertile Women Undergoing IVF Treatment, A Randomized Clinical Trial

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Abstract

Background: In vitro fertilization requires the harvesting of mature oocyte from the ovaries of infertile women under direct sonography, a process for which some form of anesthesia and analgesia is still required.

Objectives: Evaluation the effect of rectal paracetamol on intraoperative sedation using bispectral index monitoring and postoperative pain using numeric rating scale in these group of patients. Pregnancy and implantation rates were also recorded.

Material/patients and methods: Eighty ASA classes I or II women who were scheduled for oocyte retrieval were allocated into two equal groups and received rectal paracetmol or placebo one hour before surgery according to the allocations. Patients anesthetized with fentanyl and propofol and anesthesia was maintained with propofol infusion to achieve Bispectral Index value between 45-65. Demographic data, Intraoperative propofol and fentanyl consumption, postoperative pain score and pregnancy and implantation rate were also recorded and compared between the two groups.

Results: Demographic data were not statistically different between the study groups. Intraoperative propofol consumption was 67.4 ± 38.1 µg/kg/min in paracetamol and 87.0 ± 47.9 µg/kg/min in placebo group (P=0.04). No patient required additional fentanyl during the operation (P=0.06). Thirty two patients in paracetamol group and fourteen patients in placebo group had numeric rating scale ≤ 3 that was statistically significant (P<0.001). There was no difference in pregnancy and implantation rate between the study groups.

Conclusion: Preoperative rectal paracetamol reduced propofol consumption and postoperative pain in infertile women undergoing oocyte retrieval for in vitro fertilization treatment. Pregnancy and implantation rates did not differ in this group of patients.

Keywords: Anesthetics i.v; Propofol; Analgesics opioid; Fentanyl; Monitoring depth of anesthesia; Monitoring; Bispectral index; Paracetamol

Introduction

In Vitro Fertilization (IVF) requires the harvesting of mature oocyte from the ovaries of infertile women. Initially oocyte harvesting was performed by laparoscopy. Development of transvaginal ultrasound allowed the aspiration of the follicles through the vaginal wall under direct sonography. Most centers now use Transvaginal Ultrasound-Guided Oocyte Retrieval (TUGOR) for which some form of anesthesia and analgesia is still required. Nonetheless, some patients experience considerable postoperative pain [1,2].

Non-steroidal Anti-Inflammatory Drugs (NSAIDs), which have peripheral and central analgesic actions, have been shown to be effective analgesics when administered after surgery [3].

Because prostaglandins are involved in embryo implantation, anti-prostaglandin effects of NSAIDs may have a detrimental effect on the endometrium and thus implantation rate [4].

In contrast to NSAIDs, paracetamol is known to be safe when given during pregnancy. There is insufficient information on the efficacy of paracetamol on the outcome of the IVF treatment. On the other hand the analgesic effect of preoperative paracetamol may reduce drug consumption and enhanced sedation during anesthesia [3].

The Bispectral Index (BIS), a variable derived from the electroencephalograph, has the ability to measure the hypnotic component of the anesthetic state. Many studies have evaluated the relationship between BIS and sedation, consciousness and anesthetic concentration, and it has been established that anesthetic titration using BIS monitoring reduces anesthetic requirement and shortens recovery in adult surgical patients [5-8].

Since TUGOR is a short procedure and conducted as an outpatient surgery, we evaluate the effect of rectal paracetamol administration before surgery on intraoperative sedation and drug consumption using BIS monitoring and postoperative pain using Numeric Rating Scale (NRS). The implantation and pregnancy rates were also recorded after following up the patients.

The aim of this study was to evaluate the effect of 500 mg rectal paracetamol on intraoperative drug consumption and postoperative pain.

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Our hypothesis was “paracetamol can reduces intraoperative drug consumption and postoperative pain without any side effects on implantation and pregnancy rate”.

**Methods**

This randomized, double-blind clinical trial was approved by the Ethical Committee of Tehran University of Medical Sciences, Tehran, Islamic Republic of IRAN, protocol number 543 on 20 June 2012. The study was performed at the Center of Reproductive Medicine, Dr. Shariati Hospital, between January to April 2012.

**Allocation**

Eighty six ASA physical status I or II women aged 20–40 yrs scheduled for oocyte retrieval enrolled consecutively in the study of which 6 were excluded (4 patients not meeting inclusion criteria and 2 patients declined to participate). Finally eighty patients were allocated into two equal parallel groups and written informed consent was obtained from all subjects.

The women had normal ovulatory cycles, normal basal levels of serum FSH and LH and a normal uterine cavity as visualized by transvaginal ultrasonography. Women with hydrosalpinges, history of allergy or contraindications to the use of paracetamol or recent use of paracetamol and liver or kidney diseases were excluded.

Randomization was by means of computer generated codes. Sealed envelopes containing the information of the randomization code were kept by the staff not involved in the study. The specific envelope was opened again and kept in the patient’s folder until the end of the study period. All members of the surgical team, nursing staff, patients and the anesthetist were unaware of the allocation. Subject enrollment and allocation is summarized in a CONSORT flow diagram (Figure 1).

Since the onset time of rectal paracetamol is faster than oral route and our operations were conducted as an outpatient surgeries, we preferred to use rectal route. We have not suppository more than 500 mg in our country and we did not want to use more than one suppository so we decided to use the lower dose and evaluate if it has any effect on pregnancy rate, implantation rate and postoperative pain with this lower dose.

After arrival in the operating room, a 20 Gauge IV cannula was inserted for each patient and 3 ml/kg ringer lactate solution was infused. Patients were instrumented with BIS (Aspect monitor, XP version, Nattick, MA,USA) leads (two-channel-referential measurements, fronto-temporal application). Other standard monitoring, including electrocardiogram, arterial oxygen saturation, non invasive blood pressure and end-tidal carbon dioxide monitoring were used throughout the operation.

Before surgery, patients were educated about the numeric rating scale in which; 0=no pain and 10=worst imaginable pain.

All Patients were premedicated with midazolam 0.03 mg/kg and fentanyl 2 µg/kg intravenously.

After induction with propofol 2.5 mg/kg, anesthesia was maintained with propofol 100 µg/kg/min. All patients were oxygenated by facemask and ventilated manually when necessary. The propofol infusion rate was altered to achieve BIS value between 45-65 (deep hypnosis to sedation). Infusion rate of propofol was recorded at each change of BIS and for total time period before the next change. If there were another signs of inadequate anesthesia (HR>20% baseline or movement) additional dose of fentanyl 1 µg/kg was administered.

Total amount of propofol and fentanyl consumption, duration of anesthesia and number of follicles were recorded at the end of operation. Postoperative pain scores using NRS were also recorded one hour after surgery at rest for all patients. NRS ≤ 3 assumed as no pain.

**Follow up**

Forty patients in each group were followed-up and no one was excluded from analysis. Implantation and pregnancy rate were also recorded after following up the patients based on their data in the center of reproductive medicine.

Pregnancy rates were defined by ultrasound evidence of fetal heart rate as a proportion of the number of the patients. Implantation rates were defined by the number of gestational sacs as a proportion of the number of transferred embryos.

Primary outcome of the study was whether rectal paracetamol before surgery caused a reduction in propofol consumption based on BIS monitoring. The reduction in postoperative pain according to NRS measurements in recovery was the secondary aim of the study.

**Sample size calculation**

A sample size of 40 patients would be required in each study group to detect a 25% difference in propofol consumption [average requirement of propofol 100 µg/kg/min (SD 30)] with an alpha error of 0.05 and power of 90% (95% confidence interval). With this sample size, the power of the study to detect 25% difference in postoperative pain was 85%. Normality of distribution was tested by Kolmogorov Smirnov test. Data were analyzed by SPSS version 19. Independent sample t-test and Chi-square test were used for comparing demographic data and intraoperative propofol consumption between the two groups. Fisher’s Exact Test was used for comparing NRS between the study groups.

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**Figure 1:** Consort 2010 Flow Diagram.
Data are presented as mean ± SD; ASA Class: American Society of anesthesiologist Classification

Table 1: Comparing demographic data between the study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Paracetamol group (n=40)</th>
<th>Placebo group (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>31.1 ± 4.2</td>
<td>28.6 ± 4.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.5 ± 10.1</td>
<td>66.0 ± 10.5</td>
<td>0.14</td>
</tr>
<tr>
<td>ASA Class (lll)</td>
<td>128/12</td>
<td>26/14</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Eighty patients enrolled in the randomization and no one was excluded (Figure 1, CONSORT flow diagram). Demographic data were not statistically different between the study groups (Table 1) (Independent sample t-test and Chi-square).

Intraoperative propofol consumption was 67.4 ± 38.1 μg/kg/min in paracetamol group and 87.0 ± 47.9 μg/kg/min in placebo group (p=0.04, independent sample t-test).

Total fentanyl dose requirement was 112.2 ± 85.5 μg in paracetamol group and 115.2 ± 62.4 μg in placebo group according to the first dose of 2 μg/kg and no patient required additional fentanyl during the operation (P=0.06).

Thirty two patients in paracetamol group and fourteen patients in placebo group had NRS ≤ 3 (P<0.001, Fisher’s Exact Test).

The number of follicles retrieved in paracetamol group were 105 compared to 110 in placebo group (P=0.07).

A total of 163 embryos were transferred. Eighty-seven embryos in the paracetamol group and 76 embryos in the placebo group were transferred. Ten gestational sacs in the paracetamol group and nine in the placebo group were visualized, respectively. The pregnancy rate was 20% and 17.5% and the implantation rate was 11.4% and 17.5% in the paracetamol group and the placebo group, respectively (P=0.77, P=0.65, Chi-square test).

Duration of anesthesia was 24.3 ± 8.3min in paracetamol group and 28.3 ± 4.2min in placebo group (P=0.32, Independent sample t-test).

Discussion
This study showed that preoperative rectal paracetamol reduced propofol consumption and postoperative pain in infertile women undergoing oocyte retrieval for IVF treatment. Pregnancy and implantation rates did not affected in this group of patients.

Oocyte retrieval is an invasive procedure that necessitates some form of analgesia anesthesia. A survey of UK practice has revealed many varied analgesia techniques for assisted conception. Out of 70 centers, 14 reported use of diclofenac sodium for analgesia. Some clinicians are wary of using diclofenac sodium as analgesic at oocyte retrieval due to concerns regarding their anti prostaglandin effects [9].

Paracetamol compared to NSAIDS considered safe for postoperative pain in high risk patients because of lower incidence of adverse effects [10].

However, there was no study about using paracetamol alone before anesthesia and oocyte retrieval and its effect on intraoperative sedation and pregnancy and implantation rates.

In a randomized prospective double-blinded study by Dr Kailasam on 381 assisted conception cycles, patients were allocated to either receive diclofenac sodium suppository 100 mg (Voltarol®) at the end of oocyte retrieval or nothing. Use of diclofenac sodium did not significantly compromise the implantation and pregnancy rates. Patients randomized to receive diclofenac sodium had statistically significantly reduced pain scores prior to discharge (P=0.030). Diclofenac sodium did not compromise treatment outcome and reduced post operative pain scores that was correlated to our study. It should be mentioned that in this study diclofenac was given after oocyte retrieval not before, that was different to our study. In this regard the effect of the diclofenac sodium on implantation and pregnancy rate cannot be evaluated correctly [11].

In another study by Akande et al, 74 infertile women were divided in two groups (A and B). Group A (n=38) received 1 g paracetamol and 100 mg diclofenac and group B (n=36) received 1 g paracetamol rectally immediately after the oocyte retrieval. Neither pregnancy nor implantation rates differed significantly between the two groups. While it reduced discomfort and pain associated with oocyte retrieval. Although their results were correlated to our study, they gave all medications after oocyte retrieval that was different to our methods [2].

In a qualitative review article by Hyllested et al. as "comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management” their concluded that paracetamol is a viable alternate to the NSAIDS because of the low incidence of adverse effects [10].

There are a number of limitations for our assessment including: difficulty for satisfying the patients for participating in the study, difficulty for following up the result of pregnancy and implantation rate. The other limitation was absence of paracetamol suppository more than 500 mg in our country, since we did not want to use more than one suppository ,we decided to evaluate a relatively small dose of paracetamol to find if this dose can reduces anesthetic drug consumption and postoperative pain and lower the risk of complications in this group of patients. We suggest further study to compare the effects of different doses of paracetamole, NSAIDs or their combination given before oocyte puncture on postoperative pain and pregnancy and implantation rate in infertile patients undergoing oocyte retrieval.

Conclusion
Administration of 500 mg rectal paracetamol one hour before oocyte retrieval in infertile women can reduce intraoperative propofol consumption and postoperative pain without any side effect on implantation and pregnancy rate.

Implication for Health Policy Makers/Practice/Research/Medical Education
The addition of rectal paracetamol to anesthetic management of patients for In Vitro Fertilization (IVF) surgeries offers clinical advantages. This study will help to formulate policy regarding the safe method of anesthesia and reducing postoperative pain in infertile women undergoing outpatient surgeries for infertility.

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References


