Oocyte Pick-up İşleminde Anesteziklerin Oosit Kalitesi ve Gebelik Üzerindeki Etkileri

Özet
Amaç: Overlerden oosit toplanması olarak tanımlanan, oosit pick-up (OPU) işleminde farklı anestezi yöntemleri kullanılabilmektedir. Genel anestezikler folliküllere geçerek oosit kalitesini etkileyebilmektedir. Merkezimizdeki OPU işlemlerinde anestezikler, işlem ve derlenme süreleri ile estradiol (E2) düzeyleri, toplam, matür (M2) ve fertilize oosit sayıları, gebelik oranlarının retrospektif olarak değerlendirilmesi amaçlanmıştı. Günc, Yonem: OPU nedeniyle anestezi uygulanan hastaların demografik verileri (yaş, boy, kili, total prose- dur süresi), anestezikler ve tüketim miktarları, derlenme süreleri, toplam, M2, fertlize oosit sayıları ve gebelik oranları incelendi. Haslar indüksona; same propofol uygulanın (Grup P) ve propofol-ketamin uygulanan hastalar (Grup PK) olarak 2 gruba ayrıldı. Bulgular: Her iki gruptaki demografik veri- ler benzerdi. Propofol tüketim miktarları grup P'de 170 (320-120) mg, grup PK'da 140 (190-110) mg idi (p<0,001). Derlenme süreleri, grup P'de anlamlı şekilde kısa bulundu (srasıyla; 6 (9-5), 7 (10-5)) (p<0,001). Her iki grupta E2 düzeyleri, total, M2, fertlize oosit sayıları benzer olup, istatistiksel fark bulunmadı (srasıyla; p=0,837, p=0,434, p=0,518, p=0,524). Gebelik oran grup P'de 32,7% iken grup PK'da 29,1% bulundu (p=0,720). Tartışma: OPU aneste- zisinde hedef, hızlı derlenme amacıyla optimal dozda anestezik kullanımı sağ- lamaktır. Ancak anesteziklerin follikül sıvısına geçerek zararlı olduklarını bilin- mektedir. Kullandığımız anesteziklerfolliküllerin miktarlarından ölçülmi- ancak fertlize oosit kalitesini belirgin olarak etkilemedi. Sonuç: OPU'da propofol, ketamin, remifentanil ve sevofluran ile yapılan anestezi uygulamasının fertlize oosit kalitesini artırmadığı görüldü. Anahtar Kelimeler
Oosit Pick-Up; Gebelik; Genel Anestezi; Propofol; Ketamin

Abstract
Aim: Different anaesthesia methods can be used in the oocyte pick-up (OPU) procedure. General anaesthetics may affect the quality of the oocytes by passing into the follicles. The aim of this study was to retrospectively evaluate anaesthetics used in OPU in our centre through examination of procedure and recovery times, estradiol (E2) levels, numbers of total, mature (M2) and fertilised oocytes, and pregnancy rates. Material and Method: The demographic data of patients applied with anaesthesia for OPU were examined together with the anaesthetics and amounts used, recovery time, numbers of total, M2 and fertilised oocytes, and pregnancy rates. The patients were separated into 2 groups as Group P, where only propofol was used in induction, and Group PK where propofol+ ketamine was used. Results: The demographic data were similar in both groups. Propofol consumption was mean 170mg (320-120 mg) in Group P and mean 140mg (190-110 mg) in Group PK (p<0,001). The recovery period was statistically significantly shorter in Group P (6 mins (9-3) vs 7 mins (10-5)) (p<0,001). In both groups the E2 levels and numbers of total, M2 and fertilised oocytes were similar with no statistically significant difference determined (p=0,837, p=0,434, p=0,518, p=0,524 respectively). The pregnancy rate was 32.7% in Group P and 29.1% in Group PK (p=0,720). Discussion: The aim of OPU anaesthesia is to provide the use of anaesthetic at the optimal dose with rapid recovery. However, the transfer of anaesthetics to follicular fluid is known to be harmful. Although the follicular amounts of the agents used in this study were not measured, there was seen to be no significant effect on fertilisation, pregnancy rates, and oocyte quality. It can be concluded that the application of anaesthesia with ketamine, remifentanil, and sevofluorane in OPU procedures has no negative effect on fertilisation. Keywords
Oocyte Pick-Up; Pregnancy; General Anaesthesia; Propofol; Ketamine

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Introduction

Invitro fertilisation (IVF) is an important procedure that has been developed to treat infertility. This procedure consists of these stages: controlled stimulation with drugs administered to the ovaries, transvaginal oocyte aspiration from the ovaries under ultrasound guidance, fertilisation, and transfer of the embryo to the uterus [1]. The procedure of collecting oocytes from the ovarian follicles, known as oocyte pick-up (OPU), was previously performed by laparoscopy under general anaesthesia, but is currently performed under transvaginal ultrasound guidance, in a shorter and less invasive manner [2, 3].

If there is pain caused by the penetration of the needle into vaginal mucosa and the ovarian capsule or if there are other stress factors of differing degrees in patients during the procedure, anaesthesia is required [4]. Various applications, from minimal sedation to deep sedation and general anaesthesia can be applied with neuroaxial techniques such as epidural or spinal anaesthesia and regional block techniques such as paracervical/paraovarian block [1]. Although the choice of method varies according to the centre, generally, in OPU, regional anaesthesia methods are preferred when the patient is awake, or conscious sedation when the patient is co-operative [2, 3, 5]. Several clinical and experimental studies have reported that oocyte quality and pregnancy rates are affected by the transfer of general anaesthetic agents to the follicles aspirated in the ovaries [6, 7]. In patients with a high level of anxiety, deep sedation or general anaesthesia methods are usually required; in patients where general anaesthesia is applied, the level of the anaesthetic drug used can be increased according to the level of anxiety [8, 9].

The aim of this study was to retrospectively evaluate the effects of the anaesthetic drugs used in OPU procedures in our centre by examining the demographic data of the patients, the doses of the drugs, total procedure and recovery times, estradiol (E2) levels, numbers of total, mature (M2) and fertilised oocytes, and pregnancy rates. In addition, it was thought that examination of the existing literature, along with an internal evaluation of our newly-opened centre, would be useful to review and improve our accountability by exposing any deficiencies in the application of anaesthesia in OPU.

Material and Method

Approval for the study was granted by the Scientific Research Ethics Committee of Sütçü İmam University, Kahramanmaraş, Turkey (protocol no: 12 – 2016/07). A retrospective review was then made of the records of patients who presented at the Assisted Reproductive Treatment Centre of our hospital between 18/11/2015 and 01/04/2016 for IVF treatment and who were then administered anaesthesia for the OPU procedure. Demographic data such as age, height, weight, and ASA status were noted from the records, together with haemodynamic data, agents used for anaesthesia induction and maintenance and the amounts used, total procedure time (from IV anaesthetic induction to patient awakening with the termination of anaesthetic administered for maintenance following the OPU procedure), recovery time (the period from patient awakening after the procedure to obtaining modified Alderate score ≥ 8 in the recovery unit) and any complications that occurred. The numbers of total, mature (M2) and fertilised oocytes, and pregnancy rates were also recorded. Patients were excluded from the study if no oocytes were collected during the procedure or if embryo transfer could not be made because there had been no fertilisation.

Routine monitoring (non-invasive blood pressure [NIBP], heart rate [HR], pulse oximetry [SpO2], 3-lead ECG) was applied to all patients on admittance to the operating room for OPU procedure in our centre. After completion of necessary preparations, 3 IV agents were selected for routine deep sedation. The patients included in the study were retrospectively separated into 2 groups based on these agents. Group P was only administered propofol and Group PK was administered a propofol-ketamine combination.

Patients in Group P received 2 mg/kg IV propofol (Propofol 1% amp, Fresenius) and 1 mcg/kg IV remifentanil (Ultiva 2 mg flk, Glaxo SmithKline) and those in Group PK received 2 mg/kg IV propofol and 0.25 mg/kg IV ketamine (Ketalar 0.5 gr flk, Pfizer) with 1 mcg/kg remifentanil. In both groups, anaesthesia was maintained with 2% Sevoflurane (Sevoran liquid, Abbott) and a 50%-50% mixture of O2/air applied by face mask.

Throughout the operation, patients in both groups were administered IV push propofol of 10-20 mg as needed. No other anaesthesia method (neuroaxial block, paracervical block, minimal sedation, intubation with general anaesthesia) or drugs were used. Intraoperative and postoperative complications (laryngeal–bronchial spasm, aspiration, massive bleed, etc.) that developed in the patients were noted in the records.

In the statistical analysis of the variables, the SPSS 22.0 (IBM Corporation, Armonk, NY, USA) software program was used. Conformity to normal distribution of the data was evaluated with the Shapiro-Wilk test and variance homogeneity with the Levene test. In the comparison of 2 independent groups, the Independent Samples t-test together with the Bootstrap results was used and the Mann Whitney U-test with the Monte Carlo simulation technique. In the comparison of categorical variables, the Fisher Exact test was applied. Quantitative variables were stated as mean ± standard deviation (SD) and median with range (minimum – maximum) values in the tables. Categorical variables were stated as number (n) and percentage (%). The variables were examined at a 95% confidence interval and a value of p<0.05 was accepted as statistically significant.

Results

The mean age of the patients was 33.66±5.56 years in Group P and 33.04±5.71 years in Group PK. The difference was not statistically significant (p=0.514). With respect to ASA status, no statistically significant difference was determined. ASA I was determined in 59 (58.4%) patients in Group P and 31 (56.4%) in Group PK. ASA II was determined in 42 (41.6%) in Group P and 24 (43.6%) in Group PK (p=0.866). With respect to the other demographic variables, no statistically significant difference was determined between the groups in mean bodyweight (Group P: 68.62±8.36 kg, Group PK: 67.93±11.12 kg) (p=0.671), mean height (Group P: 160 cm (172-155cm), Group PK: 160 cm (170-156cm)) (p=0.0437), or in the mean total duration of the procedure (Group P: 16 mins (24-12 mins), Group PK: 16 mins (28-11 mins)) (p=0.886).

The consumption of propofol throughout the operation was de-
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terminated as median 170 mg (range, 320-120 mg) in Group P and 140 mg (range, 190-110 mg) in Group PK and the difference was statistically significant (p<0.001). The recovery time of 6 mins (range, 3-9 mins) for Group P was statistically significantly shorter than that for Group PK of 7 mins (range, 5-10) (p<0.001).

In the evaluation of the embryological data, the values determined in Group P and Group PK respectively were estradiol (E2): 1343 (14759-168) and 1159 (6639-93), total oocyte count: 8 (57-1) and 7 (52-1), mature oocyte count(M2): 6 (43-0) and 5 (42-0), and fertilised oocyte count: 5 (35-1) and 4 (31-1). No statistically significant difference was determined between the groups in respect to these data (p=0.837, p=0.434, p=0.518, p=0.524 respectively). The pregnancy rates of patients were 32.7% (n=33) in Group P and 29.1% (n=16) in Group PK; the difference was not statistically significant (p=0.720). The demographic data of the patients in the study and all the other data are shown in Table 1.

Discussion

In this retrospective evaluation, the total propofol consumption for general anaesthesia was observed to be greater in the Group P patient group than in Group PK and the postoperative recovery period was shorter in Group P. The mean E2 levels, total, M2 and fertilised oocyte count values, and the pregnancy rates were found to be similar in both groups.

The OPU procedure applied for IVF is generally a short procedure and is applied with several anaesthesia methods. While regional methods with conscious sedation have advantages such as providing verbal communication with the patient and a lower incidence of respiratory tract complications such as aspiration and laryngo-bronchial spasm, the applications of deep sedation or general anaesthesia have been found to be superior such as providing verbal communication with the patient and a lower incidence of respiratory tract complications such as aspiration and laryngo-bronchial spasm, the applications of deep sedation or general anaesthesia have been found to be superior in respect to preventing patient movements, facilitating ovarian aspiration with reduced uterus tonus, and removing anxiety [1, 5, 10]. In a study by Hong et al., the amount of propofol administered for conscious sedation in the OPU procedure in a high-anxiety group was found to be greater than that of a low-anxiety group [9]. Therefore, as the majority of patients at our centre have high anxiety levels, deep sedation and general anaesthesia methods via a face mask were preferred for these patients.

However, in general anaesthesia, muscle relaxant and intubation with mechanical ventilator support cannot be applied. While the majority of IV anaesthetic agents can be used alone or together with inhalation agents, propofol, remifentanil, and alfentanil are used more often because of the short period of their effects and more rapid recovery [4]. In our clinic, propofol, ketamine, and remifentanil are used together with sevoflurane as an inhalation agent. The aim here is to use the optimum dose of a combination of short-effect agents in OPU, a short duration intervention, and rapid recovery.

With the current applications of TIVA or target-controlled infusion (TCI) [10, 11], in our centre in particular, propofol is applied intermittently as IV push. Although TCI seems to be the most appropriate method, as the device is not available in our clinic, it is not applied. The TIVA method was not preferred as it was anticipated that difficulties could be experienced in making adjustments for the optimal dose due to the short duration of the procedure. Another reason was that with the use of a higher dose of propofol, there could be the possibility of follicular fluid transfer. In a study by Christiansen et al. 2mg/kg propofol was administered as IV push followed by 10mg/kg/hr infusion in the OPU procedure [12]. In another study investigating the effect of propofol in OPU on oocyte and early embryo quality, in a similar manner to the current study, a dose of 1.5-2mg/kg propofol was used in induction and, when necessary, repeated doses were applied by IV push [13].

Table 1. Comparison of demographic data and other data related to the procedure

<table>
<thead>
<tr>
<th></th>
<th>P (n=101)</th>
<th>PK (n=55)</th>
<th>Total (N=156)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.66±5.56</td>
<td>33.04±5.71</td>
<td>33.44±5.60</td>
<td>0.514</td>
</tr>
<tr>
<td>Weight</td>
<td>68.62±8.36</td>
<td>67.93±11.12</td>
<td>68.38±9.39</td>
<td>0.671</td>
</tr>
<tr>
<td>Height</td>
<td>160 (172-155)</td>
<td>160 (170-156)</td>
<td>160 (172-155)</td>
<td>0.437</td>
</tr>
<tr>
<td>Total procedure time (min)</td>
<td>16 (24-12)</td>
<td>16 (28-11)</td>
<td>16 (28-11)</td>
<td>0.886</td>
</tr>
<tr>
<td>Total propofol consumption (mg)</td>
<td>170 (320-120)</td>
<td>140 (190-110)</td>
<td>160 (320-110)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recovery time (min)</td>
<td>6 (9-3)</td>
<td>7 (10-5)</td>
<td>6 (10-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E2 value</td>
<td>1343 (14759-168)</td>
<td>1159 (6639-93)</td>
<td>1321 (14759-93)</td>
<td>0.837</td>
</tr>
<tr>
<td>Total oocyte number</td>
<td>8 (57-1)</td>
<td>7 (52-1)</td>
<td>8 (57-1)</td>
<td>0.434</td>
</tr>
<tr>
<td>Mature oocyte (M2) number</td>
<td>6 (43-0)</td>
<td>5 (42-0)</td>
<td>6 (43-0)</td>
<td>0.518</td>
</tr>
<tr>
<td>Fertilized oocyte number</td>
<td>5 (35-1)</td>
<td>4 (31-1)</td>
<td>5 (35-1)</td>
<td>0.524</td>
</tr>
<tr>
<td>ASA</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>59 (58,4)</td>
<td>31 (56,4)</td>
<td>90 (57,7)</td>
<td>0.866</td>
</tr>
<tr>
<td>II</td>
<td>42 (41,6)</td>
<td>24 (43,6)</td>
<td>66 (42,3)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Rate</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68 (67,3)</td>
<td>33 (32,7)</td>
<td>39 (70,9)</td>
<td>107 (68,6)</td>
<td>0.720</td>
</tr>
</tbody>
</table>

Independent T Test(Bootstrap) - Mann Whitney U Test(Monte Carlo) - Fisher Exact Test(Exact) - SD : Standard deviation - Max. Maximum - Min. Minimum (p<0.05 value statistically significant)
Although recent studies have shown no harmful effects of propofol on oocytes [13, 14], earlier animal studies have shown negative effects [7, 15]. Similarly, there are studies that have shown negative effects of other IV anaesthetics and analgesics by the transfer of follicular fluid. Still other studies have shown no harmful effects [6, 16, 17]. It can be seen that there is not yet consensus on this subject. Although there have been fewer studies related to inhalation agents, it has been reported that halotane and isoflurane in particular have harmful effects on oocytes through the transfer of follicular fluid. However, it should be noted that they were animal studies and the surgical procedures applied were lengthy laparoscopic OPU methods [18-20]. Piroli et al. reported similar high rates of fertilisation using general anaesthesia with sevoflurane and with local anaesthesia methods in transvaginal OPU procedure [21]. In the current study, which was conducted retrospectively, the follicular fluid amounts were not measured because that is not a routine procedure for administering the anaesthetic agents. But, similar to other recent studies, fertilisation and pregnancy rates and the oocyte quality were not seen to have been significantly affected. It has been reported in previous studies that propofol and remifentanil are suitable anaesthetic agents because of their positive effects in OPU anaesthesia [14, 22]. The same can be said for patients where ketamine was added. In a study by Ben-Sholomo et al. which compared the general anaesthesia method using propofol, fentanyl, and isoflurane with sedative anaesthesia using ketamine and midazolam, ketamine and midazolam were reported to be appropriate agents in OPU anaesthesia [23]. In the current study, the addition of ketamine slightly prolonged the postoperative recovery period, but this is offset by the reduction in propofol consumption. No abnormal event in the haemodynamic parameters was observed during or after the operation in any patient and no serious complication related to bleeding or the respiratory tract developed. In conclusion, in OPU applied for IVF, the application of anaesthesia with propofol, ketamine, remifentanil, and sevoflurane can be considered a suitable anaesthetic option for this patient group as it did not have any negative effect on fertilisation.

Competing interests

The authors declare that they have no competing interests.

References
