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The effect of anesthetic agents used in oocyte collection on intracytoplasmic sperm injection results in patients treated for infertility due to male factor

The effect of anesthetic agents on assisted reproductive techniques

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Abstract

Aim: Different anesthetic methods and agents are used for transvaginal oocyte retrieval procedures (TORP) in assisted reproductive techniques (ART). In our study, we evaluated prospectively the effect of propofol and thiopental sodium during TORP on intracytoplasmic sperm injection (ICSI) results in the spouses of patients with male factor indication.

Material and Methods: The study was approved by the ethics committee with Protocol No. 2019-21-07 on dated October 28, 2019. Sixty female patients who underwent TORP for intracytoplasmic sperm injection were included in the study. Anesthesia was randomized into two groups according to propofol (GP) or thiopental sodium (GT) used for induction and maintenance anesthesia. Patients' demographic data, effects of the anesthetic drug used on hemodynamics and nausea and vomiting, laboratory parameters including fertilization rate, cleavage rate, optimal embryo rate and implantation rate, and pregnancy outcomes were recorded.

Results: Sixty patients, including the propofol group (n:30) and the thiopental sodium group (n:30), were evaluated. Mean age, body mass index and motile sperm count were similar in both groups. Mean arterial pressures and nausea and vomiting rates were lower in GP ($p<0.05$). Although intracytoplasmic sperm injection, pronucleus, MII oocyte values were statistically significantly higher in GP, B-HCG and clinical pregnancy outcomes were similar in both groups.

Discussion: Our findings revealed that propofol and thiopental sodium, the anesthetic agents used in transvaginal oocyte collection procedure before ICSI treatment, had similar effects on clinical pregnancy. The results of our study are similar to many studies in the literature.

Keywords

Anesthetic Agents, Assisted Reproductive Techniques, Transvaginal Oocyte Retrieval Procedures, Pregnancy

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Introduction

Infertility affects 15-20% of couples worldwide. Male factors play a role in about half of them. Assisted reproductive techniques (ART) make it possible for individuals affected by severe oligospermia or azoospermia to have children for infertility treatments [1]. In-vitro fertilization (IVF) is the fertilization of sperm and egg outside the female body. Under the guidance of transvaginal ultrasonography, oocytes are collected by puncture and aspiration of follicles through the vaginal wall with an aspiration needle. The fertilized oocyte is split and implanted into the female's uterus with the help of a catheter after in vitro fertilization into an embryo [2,3]. In the presence of a male factor, the decision is made to use in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) when previous attempts at uterine insemination or surgical treatment have failed [4]. In the transvaginal oocyte collection procedure, pain is caused by the puncture of the vaginal skin and ovarian capsule with the aspiration needle. Meanwhile, in order to prevent complications such as vascular injury, anesthesia requires the patient to remain immobile without pain [5,6]. Pain causes anxiety in women. Various anesthesia methods are used to minimize pain and anxiety [2,3,7]. Anesthetic agents should be non-toxic to the gamete or embryo, should not affect the preimplantation development of the embryo, should provide minimal adverse effects, good surgical anesthesia and short recovery time [8]. In transvaginal ultrasonography-guided oocyte collection, anesthetic agents were observed in the follicular fluid and their effects on oocytes were investigated [9]. Studies have reported that anesthetic agents do not have any negative effects on oocytes [9,10]. However, there are some studies reporting that anesthetic drugs may enter the follicular fluid and may have negative effects on fertilization rates and embryo development [11]. Although general anesthesia is the most commonly used method for TORP, its effects on the outcome of ART cycles are unclear and there is no consensus on the type of anesthetic [12,13]. Propofol is widely used for anesthesia in ART because it provides rapid recovery due to its short duration of action [14,15]. Thiopental sodium, which is known to be associated with prolonged recovery time and other complications such as nausea and vomiting, is used for general anesthesia in OPU as an alternative to propofol [16]. Some researchers have investigated the fertility, cleavage and pregnancy rate between thiopental and propofol and found no significant difference [17].

We aimed in this study to evaluate the adverse effects, hemodynamic effects and effects of propofol and thiopental use on ICSI results in transvaginal oocyte retrieval procedure.

Material and Methods

This study was planned prospectively using the data of patients who underwent infertility treatment at Kanuni Sultan Suleyman Training and Research Hospital. This study was conducted between October 2019 and April 2020, based on the Declaration of Helsinki, with Bakırköy Dr. Sadi Konuk Training and Research Hospital clinical ethics approval (decision no: 2019-21 - 07, date: 28-10-2019).

The American Society of Anesthesiologists (ASA) score I-II female patients between 18-40 years who underwent intracytoplasmic sperm injection (ICSI) due to infertility problems in their spouses, who did not have fertility problems themselves and who accepted written informed consent were included in the study. Patients were randomized into two groups by closed envelope method: propofol was used for induction and maintenance of anesthesia (Group P), thiopental sodium was used for induction and maintenance of anesthesia (Group T). Two patients in GP were excluded from the study because no sperm was found in their partner by microscopic testicular sperm extraction after oocyte collection. In addition, 8 patients with a total number of oocytes of 1 or 2 were excluded from the study.

Female patients undergoing transvaginal ultrasonography-guided oocyte retrieval procedure were monitored with non-invasive blood pressure (NIBP), electrocardiography (ECG) and peripheral oxygen saturation (SpO_2%) and 5-6 L/min oxygen supplementation was provided. Age, body mass index and ASA score were recorded. For induction and maintenance of anesthesia, Group P (GP) patients were administered propofol 2.5 mg/kg and 1 mcg/kg fentanyl for induction of anesthesia and 0.5 mg/kg propofol intravenously (IV) for maintenance if needed. Group T (GT) patients were administered 5 mg/kg thiopental sodium and 1 mcg/kg fentanyl for induction of anesthesia and 1.0 mg/kg thiopental sodium IV for maintenance if needed. NIBP, ECG and SpO_2 vital signs were recorded before anesthesia (T1) and at 5 minutes (min) (T2), 10 minutes (T3) and at the end of surgery (T4). The number of medications needed for maintenance, postoperative nausea and vomiting, and postoperative 1st hour pain were evaluated and recorded with Visual Analog Scale (VAS).

Before ICSI micromanipulation, the spermatozoa were pre-washed and transferred into a conical test tube for incubation at 37°C for at least 1 hour. An ICSI dish containing twelve 5-ul microdrops of G-MOPS processing medium and 2 microdrops of PVP (Vitrolife) was prepared and the dish was coated with 4 ml of paraffin oil (Vitrolife). The cumulus-oocyte complexes (COCs) were briefly rinsed in hyaluronidase (Vitrolife) under a stereomicroscope and the cumulus cells were removed. Peeled oocytes were washed and MII mature oocytes were subjected to ICSI manipulation. The injected oocytes were transferred to culture medium and cultured in a 37°C incubator (Labotect C200) with 95% humidity, 6% CO2 and 5% O_2. Fertilization was assessed 16-18 hours after microinjection and the cleavage stage and embryo morphology were examined. At 48 hours and 72 hours, embryo morphology was evaluated. Normal fertilization was defined as the formation of two pronuclei (2PN) and the appearance of a second polar body. Abnormally fertilized oocytes exhibiting 1PN or 3PN were excluded. Embryo quality was assessed by the number and size of blastomeres and the percentage of nucleated fragments. Embryos were cultured until day 3 or day 5/6 after oocyte collection and high-quality embryos were selected for transfer. Laboratory parameters including fertilization rate, cleavage rate, optimal embryo rate and implantation rate were recorded. Chemical pregnancy was confirmed by a positive Beta-Human Chorionic Gonadotropin (βhCG) test 14 days after embryo transfer. Clinical diagnosis of pregnancy was made on the basis of a normal intrauterine pregnancy by detecting fetal heartbeat activity 28-35 days

after collection.

Total motile sperm count, basal Anti-Müllerian Hormon (AMH), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH) and Estradiol (E2) values, protocol, FSH, LH and HCG doses and days, total gonadotropin dose, HCG-day E2 value, total oocyte count (M2, M1, GV), number of oocytes ICSI-applied, fertilization rate, embryo transfer day, number and quality of embryos transferred, positive implantation and clinical pregnancy rates of the patients were recorded.

Statistical Analysis

Descriptive data are presented as mean±sd, median (quartiles), and percentages. The Kolmogorov-Smirnov test was used to detect normality. Student-t, chi-square, and Mann-Whitney tests were used for comparisons of groups. For MII/Total oocyte ratio was 20% higher in the propofol group, the number of patients required for each group was determined to be 30 using G-Power 3.1.0 (effect size:0.5, β:0.8:0.05). SPSS version 29 was used for all statistical analyses. p<0.05 was accepted as significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The mean age was 31 and 33 years in the Propofol group and the Thiopental group, respectively (p=0.299). Demographic data and all ovarian stimulation characteristics of groups were similar (Table 1).

After induction of general anesthesia, the additional anesthetic drug repetition required for maintenance of anesthesia was similar in both groups (p=0.142) (Table 2). In the Thiopental group, MAP at the 10th and end of the operation, nausea and vomiting were significantly higher, whereas the number of MII oocytes, MII/Total oocyte ratio, the number of the ICSI, number of embryos with two pronuclei and VAS score were significantly lower than in the Propofol group (p=0.002, p=0.004, p=0.030, p<0.001, p<0.001, p=0.017, p=0.049 and p=0.009, respectively) (Table 2). On the other hand, fertilization rates, β-HCG levels, and clinical pregnancy were similar in both groups (p=0.783, p=0.093, and p=0.761, respectively) (Table 2).

Table 1. Basic and ovarian stimulation characteristics of groups.

	Propofol Group (n=30)	Thiopental Group (n=30)	p
Age, years	31±5	33±6	0.299
BMI, (kg/m^2)	25.0 (22.8-31.3)	25.0 (23.0-29.0)	0.818
ASA	1 (1-2)	1 (1-1)	0.247
Motile sperm count, (x106/ml)	1.5 (0.0-5.1)	2.7 (1.8-5.7)	0.122
Basal levels of hormones			
AMH (mIU/L)	2.8 (1.7-3.9)	2.1 (1.3-2.9)	0.084
FSH (mIU/L)	6.1±1.5	6.3±2.3	0.646
LH (mIU/L)	5.9±2.6	6.5±2.5	0.439
Estradiol (pg/ml)	46±14	41±13	0.172
The dosage of administered hormones before TORP			
FSH (IU)	163 (0-225)	225 (0-244)	0.053
LH (IU)	0 (0-0)	0 (0-0)	0.078
HMG (FSH+LH) (IU)	0 (0-300)	0 (0-300)	0.478
Total HMG (IU)	2100 (1800-2531)	2325 (2025-2700)	0.204
The day of starting antagonist	5 (5-5)	5 (5-5)	0.960
The number of days of using antagonist	6 (5-6)	6 (5-8)	0.063
Estradiol on HCG day, (pg/ml)	2274 (1609-3272)	1693 (1153-2935)	0.171

AMH, anti-mullerian hormone; ASA, American Society of Anesthesiologists; FSH, follicle-stimulating hormone; HMG, human menopausal gonadotropin; LH, luteinizing hormone; TORP, transvaginal oocyte retrieval procedure;

Table 2. Comparison of hemodynamic parameters, embryologic effects, and postoperative complications between the groups.

Drug repetition	Propofol Group (n=30)	Thiopental Group (n=30)	p
n (%)			
None	0 (0.0)	6 (20.0)	
Once	12 (40.0)	9 (30.0)	
Twice	10 (33.3)	9 (30.0)	0.142
3 times	6 (20.0)	4 (13.3)	
4 times	2 (6.7)	2 (6.7)	
Hemodynamic parameters			
MAP, mmHg			
Baseline	91±11	91±8	0.823
5th min	74 (68-83)	82 (73-90)	0.057
10th min	78±9	88±13	0.002
End of the operation	80 (76-84)	90 (80-100)	0.004
HR, /min			
Baseline	87±15	87±14	0.846
5th min	81 (74-87)	83 (74-90)	0.325
10th min	79±13	78±7	0.511
End of the operation	77±14	79±11	0.552
Embryologic scores and IVF results			
Number of total oocytes	12±6	10±5	0.152
Number of MII oocytes	10 (6-12)	4 (2-7)	<0.001
MII / Total ratio, (%)	79 (71-88)	62 (39-75)	<0.001
Number of ICSI oocytes	10 (6-12)	6 (3-10)	0.017
number of embryos with two pronuclei	5 (2-7)	2 (2-6)	0.049
β-HCG, mIU/mL	0 (0-91.4)	0 (0-90.7)	0.093
Embryo transfer day	3 (3-3)	3 (3-3)	0.602
Number of transferred embryos	1 (1-2)	1 (1-2)	1.000
Grade of transferred embryo	2 (1-2)	1 (1-2)	0.576
Fertilization rate, (%)	55±24	56±25	0.783
Clinical pregnancy n (%)	8 (26.7)	6 (20.0)	0.761
Postoperative complications			
VAS score in the 1st hour	4 (2-5)	2 (2-4)	0.009
Nause and vomiting, n (%)	3 (10.0)	11 (36.7)	0.030

β-HCG, beta-human chorionic gonadotrophin; HR, heart rate; MAP, mean arterial pressure; ICSI, intracytoplasmic sperm injection; VAS, visual analog scale

Discussion

In this prospective study, pronucleus and MII Oocyte values were statistically significantly higher in GP compared to GT. However, βhCG and clinical pregnancy outcomes were similar in both groups. Nausea and vomiting, which are known adverse effects of anesthesia, were lower in GP (p<0.05). When postoperative 1st hour (VAS) was evaluated, it was significantly lower in GT.

Intracytoplasmic sperm injection is the most commonly used method in the treatment of untreatable severe male factor infertility [18]. The reason for selecting patients with male

factor in our study was our effort to reach more objective data in terms of evaluating the effect of anesthetic agent on oocyte quality.

Although there are several studies associating general anesthesia with lower pregnancy rates in assisted reproductive techniques, propofol and thiopental sodium are considered safe anesthetic agents [2,13,19]. Many studies have been conducted for possible adverse effects with the detection of some anesthetic agents in follicular fluid. Propofol, which is most commonly used because of its pharmacokinetic profile such as rapid onset of action and rapid recovery time, is considered safe, but it is recommended to be used with caution because it accumulates in the follicular fluid [20]. Christiaens et al. [11] did not find any correlation between propofol concentration in follicular fluid and blood concentration of the drug. Ben-Shlomo et al.'s study [20] showed an increase in propofol concentration from the first follicle to the last follicle, but there was no difference in the proportion of mature follicles, fertilization, cleavage and embryo cell number. With the introduction of propofol, thiopental becomes less preferred. Many studies have reported that both drugs do not affect oocyte quality and fertility rate negatively and there is no significant difference in terms of pregnancy outcomes [6,8, 21]. In our study, although oocyte quality was significantly higher in the propofol group, there was no significant difference in terms of pregnancy outcomes.

Since follicle and endometrial perfusion will decrease due to systemic hemodynamic changes after induction of anesthesia with propofol, it is thought to affect IVF results [13]. Therefore, propofol should be administered slowly with a gradual increase in dose during induction of anesthesia [22]. In our study, although MAP values were statistically significantly lower in GP, this decrease was not at a level to affect perfusion. The mean MAP values were above 75 mmHg in both groups.

Since transvaginal ultrasonography-guided oocyte procedure is a short-term procedure, patients are discharged on the same day. Less nausea and vomiting, which is an important criterion for patient comfort and early discharge, is an important parameter in the choice of anesthetic agent. Jarahzadeh et al. [8] reported that vomiting and nausea were significantly lower in patients receiving propofol compared to patients receiving thiopental. Our findings are similar to this study. Propofol, which has antiemetic properties, may provide early discharge from the hospital by increasing comfort in TORP patients.

Limitation

The limitation of our study is that the concentrations of anesthetic agents in follicular fluid could not be determined. Although there are recent studies showing that anesthetic agents are safe, more studies should be done because of concerns about the detection of drugs in follicular fluid.

Conclusion

The effects of the anesthetic agents propofol and thiopental sodium on pregnancy outcomes in assisted reproductive techniques are similar; however, propofol, which has antiemetic properties, seems to be an advantage in TORP patients undergoing one-day surgery.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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