Preoperative Anxiety and Propofol Requirement in Conscious Sedation for Ovum Retrieval

The purpose of the present study was to evaluate the correlation among the trial number of in vitro fertilization (IVF), preoperative anxiety, and propofol requirement for conscious sedation. One hundred and twenty six Korean women undergoing oocyte retrieval were enrolled. The target-controlled infusion by the anesthesiologist was conducted with initial target propofol concentration of 2.5 μg/mL, which was manipulated until the sedation score 3 and desired clinical end point were achieved. A weak correlation was observed between visual analogue scale (VAS) anxiety and the dose of propofol required for the induction of conscious sedation (r=0.22, p=0.0192). A weak correlation was also found between VAS anxiety and the sedation time needed to reach the proper conscious sedation level for the procedure (r=0.181, p=0.0484). Multiple regression analysis showed that VAS anxiety, preoperative baseline prolactin level, and cortisol level had statistically significant effects on the propofol induction dose for target controlled conscious sedation. We concluded that the induction dose and time requirements for propofol in anesthesiologist-controlled conscious sedation be modified based on the preoperative anxiety level and the baseline blood concentration of stress hormone, cortisol and prolactin.

Key Words : *Anesthesia and Analgesia; Conscious Sedation; Anesthetics, Intravenous; Propofol; Anxiety; Test Anxiety Scale*

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INTRODUCTION

Oocyte retrieval with transvaginal ultrasound guided follicular puncture techniques are the routine in many in vitro fertilization (IVF) centers, usually performed as a day-case procedure under some form of analgesia or anesthesia (1). Infertility has been characterized as creating a form of chronic stress, and IVF is a very stressful experience especially for women (2).

In our clinical experiences, larger doses of narcotics or sedatives seemed to be administered to establish and maintain a clinically sufficient hypnotic component of the anesthetic state in anxious females receiving oocyte retrieval, especially those who had experienced the same procedures repeatedly before. Although several studies have investigated the influence of preoperative anxiety upon intra-operative anesthetic requirement (3, 4) and postoperative recovery profiles (5-7), there are some curiosity left about the conscious sedation requirement and the contributing factors in the highly anxious infertility patients.

The present research project sought to address the following questions: 1) Does preoperative anxiety level relate to the number of IVF cycle? 2) Is increased anxiety associated with increased sedation requirement for induction and maintenance? and 3) Do the psychological or the physiological preoperative factors predict higher propofol requirement for ovum retrieval under target-controlled conscious sedation?

MATERIALS AND METHODS

The study was carried out on a sample of 126 Korean women (ASA 1) who had been accessed consecutively on the oocyte retrieval during the period of March to May 2001 at the Infertility Center. The Institutional Review Board approved it, and informed consent was obtained from all patients. Patients with a history of psychiatric illness or patients taking psychotropic medications were excluded. None of the patients had ever had children or lived with a child from the husband's previous relationship.

On the day of surgery, demographic data including age, the trial number of IVF cycle (cycle), the time elapsed since diagnosis (duration), and the type of infertility diagnosis (diagnosis) were obtained from the patients' charts by an anesthesiologist who was not involved in sedation. The clinical backgrounds of the subjects are presented in Table 1. No sedative premedication was offered to any of the patients.

Psychological Measures

Next, psychological measures were evaluated at the isolated

Table 1. Clinical background of subjects (n=126)

Age (yr)	33.8±4.8
Weight (kg)	54.8±8.0
Height (cm)	159.5±4.8
Cycle	4±3.2 (range 1-22)
Duration (month)	59.3±40.9 (range 2-156)
Diagnosis (%)	
Male alone	24.6
Female alone	45.6
Both	21.9
Unknown	7.9
Job position (%)	
Housewife	69.0
Employed	31.0

Values are mean±SD.
Cycle: the trial number of IVF cycle, Duration: the time elapsed since diagnosis, Diagnosis: the type of infertility diagnosis.

Table 2. Sedation scores

Sedation	Score
1	Fully awake and oriented
2	Drowsy
3	Eyes closed, responds promptly to verbal commands
4	Eyes closed, aroused on mild physical stimulation only
5	Eyes closed, not aroused on mild physical stimulation

preparing room. Trait and state anxiety were assessed using the State-Trait Anxiety Inventory (STAI) of Spielberger (8). The STAI is a widely used self-report anxiety assessment instrument. The STAI-State subscale is designed to measure transitory anxiety states, that is, subjective feelings of apprehension, tension, and worry that vary in intensity and fluctuate based on the situation. The STAI-Trait subscale measures relatively stable individual differences in anxiety proneness, that is, differences in the tendency to experience anxiety. The reliability coefficient (Cronbach's Alpha), referring to the Korean adult female normative sample, is 0.91 for state and 0.82 for trait (9).

The visual analogue scale (VAS) for subjective feeling of anxiety was measured, which consists of a 10 cm line anchored at one end by a label such as "not anxious" and at the other end by a label such as "anxious as can be".

Physiological Measures

Cortisol and prolactin are known to be sensitive indicators to stress because they may play roles as the mediators of psychological stress. Blood samples were taken for the assay of prolactin and cortisol concentrations at the early follicular phase of the treatment cycle (day 3) and in the morning of the day of oocyte retrieval shortly before the anesthetic induction. All blood samples were collected between 0830 and 1200 hr. The corresponding blood samples were centrifuged immediately, and the serum was stored at -20°C until required for assay.

Serum cortisol was assayed using the kits for solid-phase radioimmunoassay of Diagnostic Products Corporation (Los Angeles, CA, U.S.A.). The intraassay and interassay precision, expressed as the coefficient of variation of two pools of serum, were 4.8% and 5.2%. Serum prolactin was measured using immunoradiometric assay (Daiichi, Tokyo, Japan), intraassay and interassay precision of the two serum pools were 2.6% and 3.6%, respectively.

Target-Controlled Conscious Sedation by an Anesthesiologist

After obtaining the baseline recording of electrocardiogram, heart rate, noninvasive arterial blood pressure, and SpO_2, a standardized sedation regimen was initiated. The Target-Controlled Infusion (TCI) system runs on a microcomputer connected to an infusion pump (Becton-Dickinson infusion system, Le Grande Chemin, France). An infusion of propofol with a preset target concentration of 2.5 μg/mL was started until the patient had reached and maintained sedation level 3 on a 5-point sedation scales (Table 2). Cooperation and treatability were additional end points. If these clinical end points were not reached within 3 min (inadequate sedation), the target concentration was increased in steps of 0.2 μg/mL until treatment could be performed. Once sedation score 3 was reached, the propofol target level was maintained unless signs of oversedation became apparent (sedation score 4), as indicated by diminished communication or decreasing SpO_2. In that event, the target concentration was decreased in steps of 0.2 μg/mL and the procedure was temporarily halted until the desired sedation level was achieved. Similarly, when a noninhibitory type of oversedation was present (agitation, excitement, restlessness, and lack of cooperation), the target concentration was decreased in the same way. The targeted propofol concentrations were based on clinical trials in the patient population. Routine oxygen was administered. Positive pressure ventilation was available as required in the event of hypoxemias ($SpO_2 <$ 90%). No opioids were administered.

Induction time of sedation (time consumed to sedation level 3), sedation dose (dose required to sedation score 3) and total intraoperative dose of propofol, target-concentration, calculated-concentration, and effective site-concentration of propofol on the TCI-system at sedation score 3 achieved were recorded.

Statistical Analysis

The main associations we examined were the number of IVF-cycle versus the level of preoperative anxiety, and the level of anxiety versus the amount of propofol required for the induction and maintenance of conscious sedation. Data were analyzed with the use of SPSS version 10.0 (SPSS Inc., Chicago, IL, U.S.A.).

The sample was divided into three subgroups according to the cycle: (i) women who were undergoing their first IVF

cycle, (ii) women who were undergoing their second or third attempt, and (iii) women who were in their fourth or more attempt. In order to evaluate the association between the number of IVF cycle and psychological, hormonal, physiological anxiety parameters, or others, we referred to the analysis of variance (ANOVA). For a more detailed analysis of the phenomena, we considered diagnosis and duration. For diagnosis, there were four subgroups: (i) male factor, (ii) female factor, (iii) both of the couple, and (iv) unknown factor. Referring to the median of infertility duration, we classified the subjects into two subgroups, those suffering for less than 54 months (short-term group), and those more than 54 months (long-term group). We used unpaired t-test for the comparison.

The associations of preoperative anxiety to propofol requirements for conscious sedation and serum concentration of propofol on TCI system were evaluated by Spearman's correlation analysis.

Finally, a stepwise linear regression analysis was used to determine which of the variables could predict the sedation requirement of propofol. All regression models were performed using the SPSS computer program. Comparisons were considered significant if $p<0.05$.

RESULTS

One hundred and twenty six patients were enrolled in this study. The patients were 26-46 yr old (34 ± 4, mean$\pm$SD). The mean duration of infertility was 59.3 ± 40.9 months, the median was 53.5 months. Preoperative state-anxiety of all patients, as assessed by STAI was 40.0 ± 9.7, and the trait-anxiety was 42.6 ± 7.9. Self-report anxiety expressed by VAS was 4.7 ± 2.3. The average propofol induction dose required for the sedation was 1.2 ± 0.4 mg/kg. An average of 0.23 ± 0.05 mg/kg/min total propofol was required intraoperatively. The mean propofol infusion time was 13.1 ± 2.5 min, and the mean sedation time to reach sedation score 3 from the start of propofol was 2.2 ± 0.8 min.

In the subgroups of the cycle variables, there were no significant differences in the state, trait-anxiety score, VAS of anxiety score, and serum prolactin and cortisol level (Table 3). In the subgroup of the duration variable, no significant difference was found in the anxiety values or in the hormonal levels (Table 4). Among the anxiety values and the hormonal levels, there was no significant difference in the comparison made among the diagnosis of infertility ($p>0.05$).

As expected, the patient's state and trait anxieties correlated significantly with each other (r=0.45, p=0.000). We found that increased preoperative state anxiety did not correlate sig-

Table 3. Anxiety scores, stress hormones, and induction quality for the cycle subgroups

	Cycle I (n=57)	Cycle II (n=39)	Cycle III (n=30)	p
Anxiety Scores				
STAI-State	44.6±7.2	43.8±8.4	43.7±7.9	0.626
STAI-Trait	39.4±6.3	40.0±7.6	40.4±7.4	0.302
VAS	4.1±2.0	3.4±2.3	3.4±2.1	0.593
Stress Hormone (μg/mL)				
Prolactin-OPD	9.6±4.0	7.8±3.5	8.0±4.0	0.079
Prolactin-OR	9.2±3.4	8.3±4.6	8.8±2.4	0.670
Cortisol-OPD	27.4±14.0	22.0±12.5	21.7±13.3	0.080
Cortisol-OR	13.2±4.6	12.9±6.0	14.0±4.0	0.684
Induction Quality				
Sed-Dose (mg/kg)	1.23±0.4	1.15±0.4	1.22±0.4	0.651
Total-Dose (mg/kg/min)	0.24±5.9	0.23±5.2	0.23±5.1	0.696
Sed-Time (sec)	137.2±86.6	124.8±81.5	126.4±77.4	0.732

Values are mean±SD.
Cycle I: women who were undergoing their first trial of IVF cycle, Cycle II: women who were undergoing their second or third attempt and Cycle III: women who were in their fourth or more attempt. Prolactin-OPD: blood prolactin concentrations at the early follicular phase of the treatment cycle (day 3), Prolactin-OR: blood prolactin concentrations in the morning of the day of oocyte retrieval shortly before the anesthetic induction, Cortisol-OPD: blood cortisol concentrations at the early follicular phase of the treatment cycle (day 3), Cortisol-OR: blood prolactin concentrations in the morning of the day of oocyte retrieval shortly before the anesthetic induction. Sed-Dose: propofol dose required for induction of sedation, Total-Dose: total propofol dose for the procedure, Sed-Time: induction time reached to sedation score 3 from start of propofol. There were no significant differences in all variables.

Table 4. Anxiety scores and stress hormones for the duration subgroups

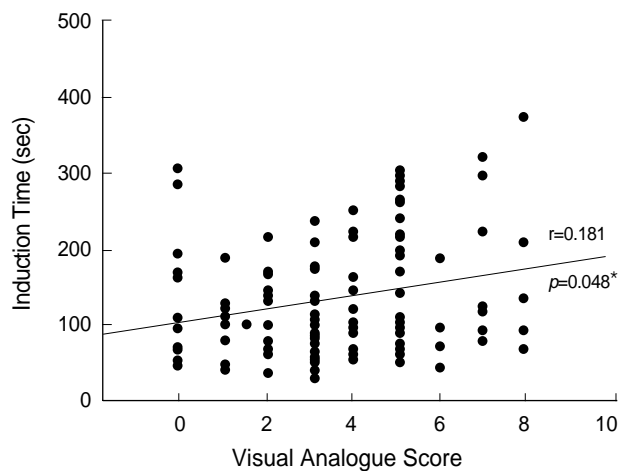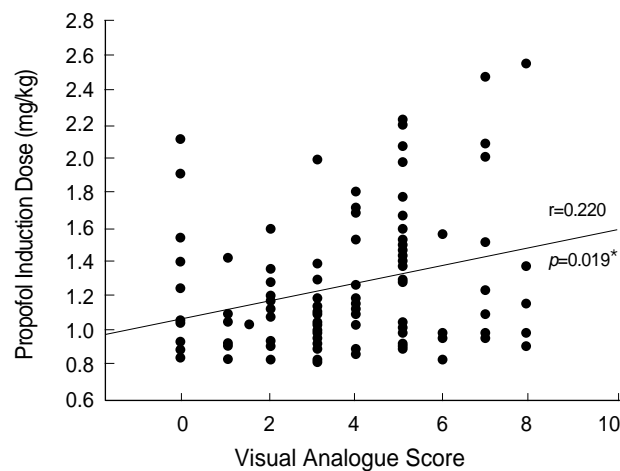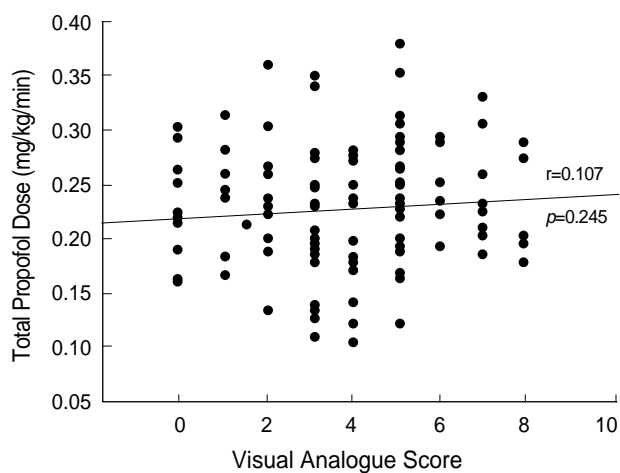|	Short-term Group	Long-term Group	p
Anxiety Scores			
STAI-State	44.2±7.3	44.0±8.1	0.662
STAI-Trait	40.7±7.1	38.8±6.6	0.725
VAS			
Stress Hormone (μg/mL)			
Prolactin-OPD	8.45±4.6	7.66±3.4	0.054
Prolactin-OR	8.74±3.5	9.00±3.9	0.719
Cortisol-OPD	24.3±13.7	25.0±13.5	0.946
Cortisol-OR	13.4±4.3	13.2±5.6	0.118
Induction Quality			
Sed-Dose (mg/kg)	1.24±0.4	1.18±0.4	0.478
Total-Dose (mg/kg/min)	0.24±5.8	0.23±5.3	0.437
Sed-Time (sec)	131.3±84.9	132.5±81.4	0.633

Values are mean±SD.
Short-term group: those suffering for less than 54 months, Long-term group: those more than 54 months. Prolactin-OPD: blood prolactin concentrations at the early follicular phase of the treatment cycle (day 3), Prolactin-OR: blood prolactin concentrations in the morning of the day of oocyte retrieval shortly before the anesthetic induction, Cortisol-OPD: blood cortisol concentrations at the early follicular phase of the treatment cycle (day 3), Cortisol-OR: blood prolactin concentrations in the morning of the day of oocyte retrieval shortly before the anesthetic induction. Sed-Dose: propofol dose required for induction of sedation, Total-Dose: total propofol dose for the procedure, Sed-Time: induction time reached to sedation score 3 from start of propofol.

nificantly with the propofol required for the induction of conscious sedation, nor was the total intraoperative propofol infusion dose required for maintenance. Trait anxiety did not correlate with the propofol for the induction, nor for the maintenance. However, a weak correlation was observed between VAS anxiety and the propofol dose required for the induction of conscious sedation, but not between VAS anxiety and total dose of propofol. In addition, a correlation was found between VAS anxiety and the sedation time, which means the time from the start of propofol infusion to the time proper seda-

tion level was reach for the procedure (Fig. 1).

Statistically significant correlations were found in preoperative serum cortisol level and two STAI scores (Table 5). Prolactin levels just before the procedure had significantly negative correlation with STAI-state only. Interestingly, there were no significant correlations between VAS anxiety score and these two stress hormones.

We found that preoperative VAS anxiety, state anxiety, and trait anxiety were not correlated with the target concentration, calculated concentration, nor effective site concentration of propofol on TCI system for conscious sedation.

To evaluate the unique contribution of each variable to the prediction of intraoperative sedation requirements, two stepwise multiple regression models were constructed. In the first, the propofol required for induction was the dependent variable, and the independent variables included state-anxiety, trait-anxiety, VAS anxiety, cycle, and prolactin and cortisol concentration. In the second model, total propofol dose for the procedure was a dependent variable. Multiple regression analysis showed that VAS anxiety (F=5.644, p=0.019), preoperative baseline prolactin level (F=4.611, p=0.035), and preoperative baseline cortisol level (F=7.308, p=0.008) had

Table 5. Correlation between the anxiety scores and the stress hormones

		Cortisol		Prolactin	
		OPD	OR	OPD	OR
STAI-State	r	0.099	0.221	-0.117	-0.194
	p	0.422	0.016*	0.347	0.035*
STAI-Trait	r	-0.024	0.203	-0.145	-0.072
	p	0.844	0.027*	0.241	0.435
VAS	r	0.113	0.033	-0.019	0.063
	p	0.365	0.724	0.877	0.497

*: $p < 0.05$.

Fig. 1. A weak correlation is observed between VAS anxiety and the propofol dose required for the induction of conscious sedation (sedation score 3), but not between VAS anxiety and total dose of propofol. A weak correlation is also found between VAS anxiety and the sedation time, which means the time from the start of propofol infusion to the time proper sedation level was reached for the procedure.
*: $p < 0.05$.

significant effects on the propofol induction dose for conscious sedation. So, the patients with increased VAS anxiety scores, with elevated preoperative concentrations of prolactin and cortisol could require more anesthetics for conscious sedation.

DISCUSSION

Our main goals were to assess the relationship among the trial number of IVF cycle, preoperative anxiety, and intraoperative sedation requirement of propofol. We found that there were no significant psychological measurements, hormonal values, and sedation dose between women who underwent their first cycle and women who underwent a repeated cycles. Though there is a difference in opinion (10), we shared the views of some authors. The cross-sectional study of Beaurepaire and colleagues (11) showed that both men and women experience anxiety during an IVF treatment, independent of the number of cycles. Reading et al. studied psychological reactions in 37 women over the course of IVF, and found that there were no significant differences between women with first time or repeated cycles (12). However, concerning mood, scores on anger and confusion increased significantly over time. In an exploratory survey of an Italian sample, the number of IVF cycles did not appear to match significantly with the anxiety state (13). Among the other variables such as diagnosis, duration of infertility and pregnancy outcome, significant differences were noted. In their sample, a longer duration of infertility, rather than the repetition of the cycles, may help in coping with oocyte retrieval with less tension. These results do not agree with Berg and Wilson's finding (14) and ours. We believe that this is due to the different criterion used in subdividing the sample in our study and theirs. Although we could not find the effect of infertility duration on the anxiety scores, unusual persistence with which women cling desperately to treatment despite the length tend to bring about "chronic feelings of unhappiness". Chiba and co-workers suggested that the psychological symptoms of infertile women seem to be close to the level of neurosis, and long-term infertility might aggravate their neurotic tendency rather than anxiety itself (15).

With regard to the sedation requirement, we could not observe any correlation between STAI considered "Gold Standard to assess anxiety" and sedation requirement of propofol. In contrast, interestingly, a weak but significant correlation was observed between VAS anxiety and the propofol dose required for the induction of conscious sedation. In addition, a weak correlation was also found between VAS anxiety and sedation time. It is assumed from clinical experience including ours that larger doses of anesthetics are required in the anxious patients to induce and maintain a clinically sufficient sedation for various procedures. Previous studies published in the psychological and anesthesia literatures have yielded contradictory findings. Parris and others suggested that increased anxiety before surgery is associated with increased

intraoperative anesthetic requirements (16). Williams et al. reported highly anxious patients require a greater amount of sodium thiopental to induce anesthesia than less anxious patients (17). Goldman et al. assessed state anxiety in 53 women presented for gynecological surgery who underwent general anesthesia (3). The investigators reported that preoperative anxiety seems to correlate with the amount of methohexitone required, but this relationship was not statistically significant. Maranets and Kain demonstrated that there was a moderate correlation between trait anxiety level and the amount of propofol required for the induction and maintenance of anesthesia (4). They found that situational (STAI-state) anxiety immediately before surgery was not associated with intraoperative anesthetic requirements. In contrast, high baseline (STAI-trait) anxiety did predict increased intraoperative anesthetic requirements. Our assessment of both STAI did not appear to correlate with the amount of propofol required for induction or maintenance. Meanwhile, we found that the VAS anxiety score with which the patients self-expressed their own anxiety had a significant correlation to the sedation requirements and time requirements for the induction with propofol. According to our interesting result, however, we do not know exactly why, we could suggest that preoperative VAS anxiety self-recorded score predict the dose and time requirements for conscious sedation with propofol. The best-known tool for anxiety evaluation is Spielberger's STAI, which was referred to recently in a major anesthesia journal as the "gold standard" for measuring preoperative anxiety (18). So, the discrepancies to the previous reports may in part be explained by the fact that the patients took the procedure under different conditions in general anesthesia or conscious sedation. Careful interpretation of the results may be needed. Generally "general anesthesia" is suggested to consist of unconsciousness, lack of recall, analgesia, and muscle relaxation. The words used to describe 'sedation' have been confused to 'calmness', 'anxiolysis', 'somnolence', 'drowsiness', or 'sense of well-being'. The aim of conscious sedation in this specific group of patients is to alleviate anxiety, thus enabling anxious patients to accept treatment and to experience no more than minimal discomfort, and easing technically difficult procedures for the operator. This may reflect the fact that the quality of sedation tends to depend on the subjective feeling of anxiolysis, and the quality of general anesthesia depends on the anesthetic components. It is unclear how and which factors control the patient's anxiety. There are complicating factors including the type of operation, patient's subgroup, individual patients characteristics such as personality dimension, self-esteem, marital satisfaction, religion, motivation, compliance, locus of control, and reaction to pain. However, it is equally unclear how these allow patients to cope with their procedure and control the anxiety under light sedation. It may be interesting in future studies and more careful approach may be needed.

Although we used validated measures to assess anxiety, our anesthetic technique consisted of only one variable, and we

also controlled the surgical procedure and the patients, the important limitation concerning the design of our study was addressed. We responded to changes just in sedation level by changing the target-concentration of propofol. In addition, the sedation scale we used could not accurately determine the subtle change in the level of sedation, and sedation might be interrupted by the check. Measuring and monitoring of the hypnotic component like a bispectral analysis would have been more helpful for the present study.

In conclusion, we demonstrated that there are significant correlations between preoperative VAS anxiety and the amount of propofol and the consuming time required for the induction of conscious sedation in this study. Among the anxiety values and the hormonal levels, there was no significant difference in the comparison made among the trial number of cycle, duration of infertility, or diagnosis of infertility. Therefore, we suggest that the induction dose and time of propofol for anesthesiologist-controlled conscious sedation should be modified based on the preoperative anxiety level exhibited by each patient.

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