Evaluation of Plasmatic Concentration of Propofol 2.5µg/ml by TCI using Marsh Modified Model, during oocyte retrieval for IVF in Latin-American women (Venezuelans)

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ABSTRACT

Objective: To evaluate efficacy of Propofol at Cp 2.5 µg/ml administered by Target Controlled Infusion (TCI) using Marsh Modified Model, in pre-medicated with midazolam/fentanyl Latin-American women (Venezuelans) during oocyte retrieval for In Vitro Fertilization.

Methods: Prospective, descriptive study included 72 women, 18-44 years old, ASA I-II, non obese, undergoing oocyte retrieval, pre-medicated with midazolam 0.04 mg/kg and fentanyl 2µg/kg and received anesthesia based in Propofol at Cp 2.5µg/ml by Target Controlled Infusion using Marsh Modified Model. Demographic data, propofol doses, duration of procedure and recovery time was registered using descriptive statistic. Anesthesia efficacy was measured by Biespectral Analysis (BIS), Intra-Operative Movements Scale (0 to 5) graded, Postoperative Pain by Visual Analog Scale (VAS) and nausea/vomits incidence. ANOVA and Pearson Chi2 were used with an error of 0.05.

Results: Age average was 33.04±6 years old, procedure average time 18.06±8min, Propofol total doses 146.64±53 mgs, Propofol infusion doses average 155.2±3µg/Kg/min. During procedure, 70.8% of patients had no movement, 22.2% movement Grade I and 6.9% Grade II. (Grade I-II movement did not interfere with procedure continuity). 70.8% achieved BIS 40-50 and 93.1% had BIS equal or less than 60. There was a statistic significant correlation between BIS 40-50 and no movements. Recovery post-anesthesia time was 25.2±8 min. 98.6% of patients reported excellent comfort.

Conclusion: With midazolam/fentanyl pre-medication, Propofol at Cp 2.5µg/ml by TCI using Marsh Modified Model showed a 93% of effectiveness during oocyte retrieval in Latin-American women subjected to IVF, allowing an ultra-fast recovery time.

Keywords: Propofol, Target Controlled Infusion (TCI), Total Intravenous Anesthesia (TIVA), In Vitro Fertilization (IVF), Latin American women.

INTRODUCTION

In order to optimize the rate of oocyte retrieval, women under advanced assisted fertility treatment are subjected to ovarian stimulation hormonal protocols and guided transvaginal ultrasound under sedation or anesthesia (ASRM/SART, 2002).

Ovarian stimulation produces a series of effects which modifies pharmacokinetics of anesthetic medications such as reducing concentration of plasmatic proteins (albumin, protein α -1- acid), increasing free fraction of drugs in plasma (Tsen *et al.*, 1997), increasing endothelial permeability (Markus *et al.*, 2005; Klonoff-Cohen *et al.*, 2004) and a possible anesthetic sensibility at biofase level (pharmacological action location) (Ramírez-Paesano, 2008).

Worldwide, the most used protocol for sedation/an-

esthesia during transvaginal follicle aspiration has been Total Intravenous Anesthesia (TIVA) based on Propofol (pre-medication Midazolam/Fentanyl) (Vlahos *et al.*, 2009; Ramírez-Paesano, 2004; Muñoz-Cuevas, 2006) given by bolus or continuous infusions. There is little information in the literature reviewed that suggests plasmatic concentration ranges (Cp) of Propofol using Target Controlled Infusion methods (TCI) during follicle aspiration. Likewise, there is very short of published information about depth anesthesia measuring by Biespectral Index (BIS) during trans-vaginal follicle aspiration. BIS monitoring was approved by FDA (USA Food and Drug Administration) since 2003 as a very easy method to estimate depth anesthesia and minimize the possibility of intraoperative awareness by an algorithmic analysis of electroencephalogram (EEG) during anesthesia providing ranges from 0 (EEG silence) to 100 points (totally awake patient). A BIS value between 40 and 60 indicates an appropriate level an anesthesia, recommended by manufacturer.

In a series of Asian patients, some authors have proposed an initial dose of 2.5µg/ml Cp as a proper target average (Hong *et al.*, 2003; 2005). Our objective was to carry out a preliminary descriptive research to evaluate the efficacy of Propofol at Cp 2.5µg/ml administrating by Target Controlled Infusion pump using Modified Marsh Pharmacokinetic Model in Latin-American patients pre-medicated with Midazolam and Fentanyl, evaluating the efficacy by measuring depth of anesthesia by BIS and a scale of patients' movements during procedure.

MATERIAL AND METHODS

Once approved by the ethics commissions of the Sociedad Médica de Clínica "El Avila" and Unifertes which is the Fertility Unit of Clínica "El Avila", in Altamira, Caracas, Venezuela, and previous signing of informed consent, a prospective, descriptive research was performed on 72 patients, ASA I-II, between ages 18 and 44 scheduled for follicle aspiration via transvaginal for oocyte recovery during period January-March 2013. Ovarian stimulation protocol used was following: Recombinant FSH (Puregon, Organon Ireland Ltd) was administrated with or without highly purified hMG (Menopur, Ferring GmbH, Germany). On day 2 or 3 ovarian stimulation, doses varied from 150-300 U/d depending on the patient age, basal hormones, anti-Müllerian hormone, antral follicles and response to previous controlled ovarian stimulations (if performed). From day 6 of stimulation, gonadotropin doses were adjusted according to serum estradiol levels and ovarian response, which was assessed by vaginal ultrasound. A daily dose of 0.25 mg of GnRH antagonist (Orgalutran, Organon Ireland Ltd) administration was initiated on day 6 of stimulation. hCG (Ovidrelle, Merck Serono SpA, Italy) was administrated subcutaneously when at least two leading follicles reached a mean diameter 18 mm. Daily administration of gonado-

Table 1. Intraoperative Movements Scale during Oocyte Retrieval (IOMs)

Intraoperative Movements Scale during Oocyte Retrieval (IOMs)	
Grade 0	no movements
Grade I	Ankles Movements (feet dorso-flexion) Non procedure interferent It could deepen analgesia
Grade II	Knees Movements (legs flexo-extension) (with/without feet movements) Non procedure interference (Aspiration could stop) It could deepen analgesia / anesthesia
Grade III	Pelvis/hips Movements (with/without legs/thighs movements) Aspiration must be stopped Must be deepen analgesia/anesthesia
Grade IV	Rude movements of the pelvis, chest and/or arm Aspiration must be stopped Must be deepen anesthesia

Adapted from Ramírez-Paesano (2008) originally in Spanish, and Handa-Tsutsui & Kodaka (2006)

tropin and GnRH antagonist was discontinued on the day of hCG administration. Transvaginal oocyte retrieval was scheduled 36 hours later. A 17-gauge aspiration needle standard single lumen was used for all aspiration (Cook Medical Australia PTY, LTD). Patients fasted for 12 hours before the procedure.

Vital signs standard monitoring was carried out with non-invasive arterial pressure, continuous electrocardiogram, pulse oximetry and Capnography. A peripheral venous was catheterized with N° 20 catheter and 10 ml/kg of Lactate Ringer was administered.

Ten minutes before initiating anesthesia with Propofol, humid oxygen was started at three liters per minute by facial mask. Next, 0.04mg/kg of Midazolam and 2µg/kg of Fentanyl was administered intravenously.

Propofol at 1% was administered by TCI Infusion Pump (Alaris Pk, Cardinal Health 1180 Switzerland), according to Modified Marsh Pharmacokinetic Model (Ke0 1.21), plasma mode (using real weight) starting at initial target concentration of 1.0µg/ml, and increasing at a rate of 0.5 µg/ml each minute, until Cp 2.5µg/ml. Once the equilibrium was reached at the plasmatic concentration, respiratory rate, spontaneous/regular ventilation, and oxygen saturation above 95% was checked, in order to start follicle withdrawal procedure. Once retrieval was finished, each patient received 100 mg of Ketoprofen intravenously.

Demographic data was recorded, as age, weight (kg), height (m), Corporal Mass Index kg/m², procedure duration (min), total amount of Propofol used in each procedure (mg), Propofol infusion dosage (µg/Kg/min).

The main objective of the research was measuring the anesthetic depth monitored by Biespectral Analysis (BIS) and the presence of intra-operative movements as a reaction to nociceptive stimulus by means of a graded scale from 0 to IV (IOM Scale) (table 1). Regarding BIS results, we initially established a scale of optimum BIS interval values: ≤39 an unnecessary too depth anesthesia, 40 to 50 as excellent depth anesthesia target with very low awareness possibility, 51 to 60 as a good depth anesthesia with low possibility of awareness and finally 61 or more, light level of anesthesia with risk of awareness. However, because the anesthesia technique was based just in Propofol (basically hypnotic) without neuromuscular blockers, with decided to simplify the BIS scale in 3 intervals: ≤39, 40 to 50, and ≥51 in order to focus the evaluation over the interval of excellent depth anesthesia (40 to 50) and ob-

tain a more accuracy when correlating with IOM scale. To measure IOM, we designed the IOM Scale adapted from a scale originally publish in Spanish (Ramírez-Paesano, 2008). Other variables measured were post-anesthesia recovery time (minutes since the ending of the procedure up to the moment of leaving the fertility unit), intra-operative recall (Brice scale / Brice *et al.*, 1970), post-operative pain according to Visual Analog Scale (VAS), incidence of nausea and vomits.

Descriptive statistics were used with mean, median, percentages, averages and standard deviation. As we mentioned before, patients were divided in three groups according to BIS levels: ≤39, 40 to 50, ≥51, and they were compared according to Body Mass Index (BMI), mobility range (IOM Scale), Propofol infusions dosage and recovery time. The percentage of patients ≤ 60 BIS were determined. ANOVA and Pearson Chi2 were used with an error of 0.05 by means of a SPSS 13.0 Windows program for data analysis.

Exclusion criteria were patients with BMI more than 35 kg/m², alcoholic or tobacco habits, drug consumption, medications that could alter BIS or anesthetics requirements such as β-blockers, α-2 agonist, benzodiazepines, neuroleptics, anticonvulsant and antidepressants, presence of gastroesophageal reflux type I, Diabetes or insulin dependent, allergic to any of Propofol components and to non-steroid anti-inflammatories. Patients with signs of severe respiratory depression were excluded. (Respiratory frequency lower than eight respirations per minute and pulse oximetry lower than 90%), or Apnea > 30 seconds requiring ventilation assistance and patients with movements grades III or IV (IOM Scale).

RESULTS

The age average was 33.04 ± 6.03 years old. The minimum age was 20 years old (one patient) and the maximum 44 years old (2 patients). El 83.3 % had BMI between 20 a 29 kg/m²; 9.7% BMI less than 20kg/m² and 7% greater than 30 but less than 35 kg/m².

A total of 644 follicles were punctured and 593 oocytes were retrieved. The oocyte pickup average time (from the first puncture in cul de sac vaginal side until the remove the transvaginal ultrasound transducer) was 18.06 min ± 8.03. The minimum duration of the procedure time was 5 min. A maximum of 40 min. and Percentile (P) 25: 12.8 min., P50:15 min. and P75: 25 min. 90% of procedures

Graphic 1. Percentage Distribution of intraoperative

lasted between 10 to 30 minutes.

The dose of Propofol by procedure was $146.64\text{mg} \pm 53.9\text{mg}$ and median of 150mg (80mg minimum and 400mg maximum). The dose average infusion of Propofol $155.2 \pm 73 \mu\text{g/Kg/min}$, Percentile 25 of $90 \mu\text{g/Kg/min}$, Percentile 75 of $190 \mu\text{g/Kg/min}$. Minimum perfusion was $50 \mu\text{g/Kg/min}$ and the maximum of $390 \mu\text{g/Kg/min}$.

Concerning the movement during the procedure, 51 patients (70.8%) had no movements, 16 patients (22.2%) presented movements grade I and five patients (6.9%) presented grade II movements. No patient presented movements III and IV (Graphic 1).

Table 2. BIS according Body Mass Index (BMI)

BIS	n	BMI(kg/m ²)	S.D
≤39	4	24.27	3.43
40-50	51	23.63	3.32
>50	17	24.53	4.81
Total	72	23.88	3.69

($P=0.67$) No statistically significance correlation

5.6% of patients ($n=4$) had $\text{BIS} \leq 39$, the 70.8% ($n=51$) had BIS between 40-50 and 23.6% ($n=17$) $\text{BIS} \geq 51$ (Graphic 2). The 93.1% of the patients had $\text{BIS} \leq 60$. Although 5 patients showed BIS between 61 to 70, no patients presented intra-operative recall to recover from anesthesia after the release from the fertility unit.

There was no statistically significant difference when comparing the groups of $\text{BIS} \leq 39$, $\text{BIS} 40-50$ and $\text{BIS} \geq 51$

Graphic 2. Distribution (%) according Biespectral analysis (BIS). BIS interval values: ≤39 (less than 40) an unnecessary too depth anesthesia, 40 to 50 as excellent depth anesthesia target with very low awareness possibility, 51 until 60 as a good depth anesthesia with low possibility of awareness and finally 61 to 70 light level of anesthesia with risk of awareness.**Distribution (%) according Biespectral analysis (BIS)** **Table 3.** BIS. According Propofol Infusion ($\mu\text{g/Kg/min}$)

BIS	n	Propofol $\mu\text{g/Kg/min}$
≤39	4	170 ± 80
40-50	51	150 ± 80
>50	17	160 ± 70
Total	72	160 ± 70

($P=0.715$) No statistically significant correlation

with respect to the BMI (Table 2), to the Propofol infusion average ($\mu\text{g/Kg/min}$) (Table 3) and neither the average time of post-anesthesia recovery.

We found a statistically significant association ($P = 0.003$) between no movement (IOM Grade 0) and the BIS level between 40-50; otherwise, patient with $\text{BIS} \geq 51$ had 58.8% of movements (35.3% Grade I and 23.5% Grade II). Half of the patient with $\text{BIS} \leq 39$ (two patients) presented movements grade I (Table 4).

The average time of recovery post-anesthesia was 25.2 ± 8.05 minutes, with a minimum time of 15 minutes to a maximum of 60 minutes. The P75 was 30 min.

Only one patient presented postoperative pain of 5-6/10 point of VAS and received 3mg of intravenous morphine and acetaminophen 650 mg orally, the rest (98.6%) reported an excellent level of comfort and VAS less than 3/10 points.

Two patients had nausea and one threw up once in post-anesthesia recovery room. These two patients received 8mg of Ondansetron and 8mg of Dexamethasone intravenously. All patients tolerated oral (liquid) 1hour after the release of the fertility unit.

DISCUSSION

The most used anesthetic protocol for patients undergoing trans-vaginal follicular aspiration for oocyte retrieval during in vitro fertilization, have been based on Propofol (bolus or infusions) pre-medicated by anxiolytic/analgesic combination of Midazolam and Fentanyl respectively (Ramirez-Paesano, 2004,2008, Vlahos *et al.*, 2009). Such drugs have been submitted to animal and human experimental evaluation, being considered as medications with an adequate profile of cellular bio-security, without evidence of affectation in fertilization rates, cleavage, implantation or incidence in congenital malformations or genetic alterations (Bruce *et al.*, 1985; Swanson & Leavitt, 1992; Chopineau *et al.*, 1993; Gonen *et al.*, 1995; Tontisirin *et al.*, 1996; Alsalili *et al.*, 1997; Rosenblatt *et al.*, 1997; Shapira *et al.*, 1996).

Table 4. Correlation BIS vs. IOM Grades during the follicle aspiration

BIS	Grade 0	Grade I	Grade II	Grade III	Total
≤39	50%(2)	50%(2)	0	0	(4)
40-50	82.4%(42)*	15.7%(8)	2%(1)	0	(51)
>50	41.2%(7)	35.3%(6)*	23.5%(4)*	0	(17)
Total	70.8%(51)	22.2%(16)	6.9%(5)	0	100%(72)

Previous research have demonstrated that Propofol concentrations in follicular liquid increases in a directly proportional way along with Propofol plasmatic concentration and with the duration of the infusion (Ben-Shlomo *et al.*, 2000). Even though Propofol has been cataloged as a secure drug in assisted fertility, anesthesiologist criteria continues to be based on reducing to at maximum the cellular exposure to the drug, increasing bio-security profile by giving the lowest dosage necessary to achieve anesthetic's objectives: hypnosis, amnesia, analgesia, comfort, clinic security and patient immobility, so that, the gynecologist can get a maximum and satisfactory oocyte retrieval.

Nowadays, Propofol administration by TCI gives to the anesthesiologist a better control and predictability in anesthetic act; it avoids complex mathematic calculations and provides a friendly and easy way of application (Leslie *et al.*, 2008; Carrillo-Esper *et al.*, 2007). When it is associated to standard monitoring of vital signs and to the measurement of anesthetic depth by means of Bispectral Index analysis of brain electric function (BIS), the level of anesthesia control achieved by TCI gives the anesthesiologist more confidence and security and provides a reduction in the use of Propofol about 10 to 20%, even with less incidence of awareness. In this same way, post-anesthetic recovery time and discharge is shorter after the procedure (Struys *et al.*, 2002; Handa-Tsutsui & Kodaka, 2007).

In order to optimize the number of ovarian follicles retrieval by trans-vaginal ultrasound, patients are subjected to ovarian stimulation with different medications acting on the ovary-hypophysis-hypothalamus axis. The consequences of anesthetic medications pharmacokinetics are plasmatic proteins reduction (albumin and protein α-1-acid), free drug fraction in plasma increase, sensibility increase to medications in the biofase (Tsen *et al.*, 1997; Ramirez-Paesano, 2008).

According to the above, we could think that Propofol Cp50 and Cp95 in these kinds of patients might be reduced in comparison with general population as well as about anesthetic requirements.

Although Handa-Tsutsui & Kodaka (2007), in 23 patients undergoing oocyte retrieval procedure reported no important decrease of Cp50 (4.1µg/ml) and Cp95 (5.1 µg/ml) using TCI with Diprifusor™, no anxiolytic premedication neither opioid were used in the controls patient, no BIS was used, and intra-operative movement was just graduated in two categories (no movement and movement of the body or extremities), a scale very less detailed in comparison as we did.

There are few international publications suggesting a Cp as recommendable for administering Propofol by TCI in this population with special pharmacokinetic characteristics. There is no publication with Latin American (Venezuelan). Some authors, who have worked with series of Asian patients, have suggested 2.5µg/ml Cp, as initial target reference using TCI by means of Modified Marsh Model, and considered adequate during oocyte retrieval (Hong *et al.*, 2003; 2005).

Our main objective was to carry out a preliminary descriptive research in order to evaluate the clinical effectiveness of 2.5µg/ml Propofol plasmatic concentration

target in Venezuelan patients undergoing follicle retrieval, before a standard anxiolytic medication with 0.04mg/kg of Midazolam and analgesic with 2µg/Kg of Fentanyl. The clinical effectiveness was measured using Intraoperative Movements Grading Scale (IOMs) during the procedure (Ramirez-Paesano, 2008) (Table 1) and anesthetic depth by means of BIS. As we mention before, the BIS scale was finally simplified in three intervals: ≤39, 40 to 50 and ≥51. However, some time we highlight data related to BIS 60 in order to give results related to the BIS manufacture recommendation that takes 60 as awareness cut point.

The 93% of patients showed an adequate immobility condition, IOM grade 0 to grade I. In this group 78% showed mobility grade 0 (complete immobility) and 22% of patients showed mobility grade I, in which the majority of cases coincided with the moment when the bottom of the vagina's lateral sack is punctured with the aspiration needle in order to access the corresponding ovary.

Only 7% of all patients showed grade II movements. These movements coincided with Strong Abdominal Pressure (SAP) maneuver, when the gynecologist asks for "fixing" the ovaries by generating "external contra-traction", in case of difficulties for follicular aspiration in very mobile ovaries, in ovaries that are distant from secure ultrasound field of action to withdraw follicles without damage to another intra-abdominal organs or in order to reach follicles on the ovary peripheral surfaces.

A significant statistic association was found between BIS levels and the absence of movements. Patients with BIS 40 to 50, showed less movements compared with ≥51. When we checked, we found BIS >60 patients had 58% positive movements grade I and II). None of the patients showed grade III movement. However, our number of patients is too small to establish an adequate relation between BIS and intra-operative mobility grade, we recommend, as other authors, to achieve BIS level of 50±5 to monitoring grade of depth anesthesia for oocyte retrieval (Circeo *et al.*, 2011).

Grade I movements do not have clinical importance because they do not interfere with the gynecological procedure.

According to our clinical experience, we recommend to administer Propofol bolus (increasing Cp 0.5 to 1µg/ml) before applying (SAP), in order to increase anesthetic depth and to avoid grade II or greater IOM. Furthermore, when difficult ovary retrieval is foreseen and SAP is needed, the use of 25 to 50 µg Fentanyl bolus can be considered (these measures were not taken during this study because of alteration of our objectives, and grade III and IV were considered exclusion criteria).

In our opinion, the two most intense nociceptive stimulus during oocyte retrieval, were at the moment of vaginal wall puncture at the bottom of the lateral bags, in order to access the pelvic cavity, and application of SAP.

The 76.4% of patients showed BIS 50 or less. In clinical practice, adjusting Propofol Cp in order to obtain BIS ≤50, seems to ensure an adequate IOM profile. 93.1% of patients showed BIS ≤ 60. According to literature and manufacturer, BIS numbers lower than 60, exponentially reduces intra-operative recall probabilities (Carrillo-Esper

et al., 2007; Circeo *et al.*, 2011). In our research, none of the patients reported intra-operative recall, not even one patient that showed BIS values of 70 at some moment of the procedure (5 patients showed BIS between 61 to 70). It is possible that pre-medication with Midazolam could have produced a higher security range in our series, due to the amnesic properties of this Benzodiazepine.

We think that, in our study the premedication with midazolam/fentanyl combination, the use of BIS and an IOM Scale very detailed allowed us the use of Propofol Cp 2.5 µg/ml and obtaining a result of 93% efficacy during follicular aspiration. Liu GW *et al.* using premedication with fentanyl, gets significantly reduction of Propofol requirements and faster awakening and discharge in patients undergoing oocyte retrieval (Liu *et al.*, 2004). It is known that high level of anxiety increase the requirement of Propofol (Hong *et al.*, 2003; 2005). Moreover, the great majority of patients undergoing fertility treatment come up with a high level of preoperative anxiety. Therefore, probably reducing the level of anxiety by premedication, in our series, further contributed to the use of Cp 2.5 µg/ml successfully.

The Remifentanyl has also been shown to have adequate bio-safety profile during follicular aspiration (Matso *et al.*, 2012). Coskun *et al.* (2011) using TCI of remifentanyl (Minto model) from 1.5 to 2.0 ng/ml found a greater reduction in Propofol requirements, (Ce 1.5 µg/ml, Schnider model), but our data are not comparable because they used different models for Propofol TCI and these authors did not use BIS or Midazolam premedication.

No significant statistic differences were found when we grouped patients in three categories according to their response to BIS (≤ 39 , 40-50 and ≥ 51) related to BMI, Propofol infusion dosage in µg/Kg/min and post-anesthetic recovery time.

In first place, this result denotes that the series of patients were homogeneous regarding demographic indexes. Secondly, administering Propofol by means of TCI standardizes the infusion medication dosage, fixing a determined target. Third, there is an inter-personal variability in anesthetic sensibility to Propofol, which affects BIS independently from BMI. Finally, the target of Propofol Cp 2.5µg/ml in patients pre-medicated with Midazolam and Fentanyl, provides very fast post-anesthetic recovery independently from the BIS anesthetic depth achieved during the procedure.

The post-anesthetic recovery time obtained in our research (25±8 min, 15 minimum -60 maximum), suggests that Propofol Cp 2.5µg/ml is a reasonable target to be used in order to achieve ultra-fast discharge protocols. The anesthetic protocol used, is associated to a low pain and post-operative nausea and vomit incidence.

In conclusion, the high percentage of patients with BIS ≤ 60 and low incidence of intra-operative movements, which were obtained in our study (93%), suggests that Propofol Cp 2.5µg/ml administered by means of TCI (Modified Marsh Model) is an adequate target reference to start anesthesia in Latin-American (Venezuelan) patients, who are pre-medicated with Midazolam 0.04mg/kg and Fentanyl 2µg/kg, during trans-vaginal oocyte retrieval in vitro fertilization procedures.

We suggest random research, double blind controlled, comparing Cp 2.5µg/ml Propofol anesthesia with higher concentration target in order to establish differences in BIS levels, IOM grades, post-anesthesia recovery time, Propofol follicle concentrations and relate them to the fertilization and implant rate.

CONFLICT OF INTERESTS

No conflict of interest have been declared.

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