International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 05, 2020
ISSN: 1475-7192

Effect of TIVA with Propofol Versus Inhalational Anasthesia Plus Ketamine on Fertilization and Clinical Pregnancy Rate in ICSI

Raad Ghazi Reshan, Bashar Ghanim Ameen and
Asmaa Abdulrazzaq Hassan

Abstract--- *Anasthesia is an important part of in vitro fertilization and can be detrimental on the reproductive result due to potential toxicity encountered by the anesthetic drugs used.*

Place and duration of the study: The study is held at the high institute of infertility and ART's in al Nahrin University in Baghdad, Iraq from 1st of April 2018 to the 1st of February 2019.

Material and methods: 80 patients during their ICSI course were randomized blindly at time of oocyte retrieval anasthesia into two groups:40 patient subjected to TIVA(total intravenous anesthesia) with midazolam and propofol (group1),and 40 patient subjected to inhalational anesthesia (isoflurane) with ketamine and midazolam, evaluation of fertilization ,cleavage ,grade 1 embryo and pregnancy rate was done to determine the more beneficial, and less toxic anesthesia for in vitro fertilization patients.

Conclusion: TIVA with midazolam and propofol had better reproductive outcome on fertilization rate cleavage and grade 1 embryo rate with significant higher pregnancy rate than inhalational anesthesia with midazolam and ketamine.

Keywords--- *Vitro Fertilization (IVF), Versus Inhalational, Propofol.*

I. INTRODUCTION

In vitro fertilization (IVF) is important advances in infertility treatment in the late forty years and it has become available on outpatient bases in day care surgical units**.**[(1)]

In general IVF techniques include:

a. Ovarian stimulation.
b. Ultrasound-guided oocyte retrieval.
c. Intracytoplasmic sperm injection.
d. Embryo culture.
e. Embryos transfer of.[(1)]

Transvaginal oocyte retrieval was introduced in assisted reproductive technologies (ARTs) since 1981 avoiding more invasive previous laparoscopic use [(2)]. Pain expressed during aspiration of oocytes is produced by the needle

Raad Ghazi Reshan, High Institute for Infertility Diagnosisand ART's, Al-Nahrain University, Baghdad, Iraq.
E-mail: raadreshan@yahoo.com
Bashar Ghanim Ameen, Senior Anesthetist in Salah-Al-Deen Directorate of Health, Iraqi Ministry of Health.
E-mail: basher.ghanim@yahoo.com
Asmaa Abdulrazzaq Hassan, Lecturer in the Department of Obstetrics and Gynaecology, Collage of Medicine, Mosul University, Iraq.
E-mail :asmaa.sanjary@yahoo.com

DOI: 10.37200/IJPR/V24I5/PR201849
Received: 16 Feb 2020 | Revised: 10 Mar 2020 | Accepted: 23 Mar 2020

inserted through the vaginal wall and ovarian capsules. [3] Adequate pain relief is required to ensure immobilization and eliminates the danger of piercing any vessel and to reduce the stress of the procedure. [2] Various anesthetic modalities and analgesic regimens have been tested in different studies, but no definite conclusion so far been made regarding the preferred technique for anesthesia and pain relief for these procedures.[1]In addition these anesthetic agents have been found in the follicular fluid, and may have detrimental effects on oocyte fertilization and embryonic development.[4]

Exposure to the anesthetic drugs should be the least possible time with least penetration to the follicular fluid.[1]

Various anesthetic modalities used for transvaginal oocyte retrieval include monitored anesthesia care, conscious sedation, general anesthesia GA, regional anesthesia, local injection as a paracervical block (PCB), epidural block, subarachnoid block, total intravenous anesthesia (TIVA), patient-controlled analgesia (PCA), and alternative medicine approach (acupuncture). [5] All may be potentially toxic to the oocyte. studies on GA may be conflicting and few studies relates it to a lower pregnancy rates .There was disagreement about the result mainly due to the use of different anesthetic techniques with different anesthetic agents. the presence of detectable amounts of anesthetic drugs in the follicular fluid still not strongly indicate toxicity to oocyte [6] .

General anesthesia have been used with propofol and 50% oxygen–air mixture , Previous trials shows no toxic effect on oocyte DNA and on fertilization rate and embryo quality despite its accumulating effect in the follicular fluid in high concentration.[7]

Ketamine was presented commercially in 1970 with the manufacturer's description as a "rapidly acting, non-barbiturate general anesthetic" ,With the help of its old unique pharmacological properties and newly found beneficial clinical properties, it has survived the strong winds of time, and it currently has a wide variety of clinical applications .It is a specific intravenous anesthetic agent with a wide range of effects associated with broncho-dilatation, with sympathetic nervous system stimulation.[8]

Ketamine is excreted as norketamine in urine and in faeces and will accumulate with a gradual resistance emerge on repeated dosages. Generally ketamine now a days (0.75 mg /kg) is an accepted as alternative to general anesthesia in oocyte retrieval[9]

II. PATIENTS' MATERIAL AND METHODS

The study was double-blind, randomized clinical trial held at the high institute of infertility and assisted reproductive technique in Al Nahrin Medical University in Baghdad, the study was started at the first of April 2018 till the first of February 2019, 80 patients subjected to ICSI for infertility treatment were included in our study after taking a written informed consent from them for their participation in the study.

Inclusion Criteria

Patients age of 20 - 40 years,

BMI of 22-27 kg/m2

Healthy patients with ASA grade I. (Healthy, non-smoking, no or minimal alcohol use)[10]

DOI: 10.37200/IJPR/V24I5/PR201849
Received: 16 Feb 2020 | Revised: 10 Mar 2020 | Accepted: 23 Mar 2020

Normal AFC, AMH, FSH and LH.

Normal seminal fluid analysis or mild male factor infertility.

No genital tract anomalies.

Female factor infertility with adequate ovarian reserve.

Exclusion Crieteria

Those without the above criteria.

Those with empty follicle syndrome.

Those refuse to participate in the study.

Those not subjected to embryo transfer.

80 patients was evaluated initially during their IVF/ICSI cycle for hormonal and ultrasound examination they start their controlled ovarian stimulation with gonadotrophin, the response for treatment was monitored by repeated ultrasound and estradiol level measurements, when the largest follicles was 14 mm antagonist 0.25mg was administered daily until at least three follicles reach 18mm in size, when oocyte maturation was triggered by 10000 IU subcutaneous HCG.

General Anesthesia during Oocyte Retrieval

Oocyte retrieval guided by ultrasound under general anesthesia was done after 34-36 hours. all 80 patients included in the study were healthy with ASA grade 1 according to the American society of anesthesia they are breathing spontaneously with oxygen face mask, they were, blindly randomized to two groups Group 1 :40 patients managed with total intravenous anasthesia (TIVA) starting with I.V. midazolam 0.05 mg /kg with fentanyl 0.015 mg/kg followed after 5 minutes by I.V. propofol 2 mg /kg total infusion dose start infusion at a rate of 100-150 µg/kg/min in the first 15 minutes then 50-100 µg/kg/min ,then turn off the propofol infusion 5-10 minutes before the desired time of emergence. Group 2 are 40 patients start with midazolam 0.05 mg/kg and ketamine 2mg/kg with maintenance on inhalational anesthesia by isoflurane (mac 1.1)with isoflurane is turned off about 5 minutes prior to the desired time of emergence, measurements of vital signs including ,pulse rate ,blood pressure and respiratory rate .At the embryology laboratory assessment of total number of oocytes. oocyte denudation is done and number of MII and MI assessed and abnormal oocyte including GV, mature oocyte were inseminated by ICSI ,18 hours after ,assessment for fertilization and assessment for grade of pronuclei, then daily follow up for number of blastomeres ,degree of fragmentation ,and grading of embryo. Embryo transfer after 48-72 hours, all patients have one or two Grade 1 embryo transferred, this is determined according to the grades and numbers of embryo available, then luteal phase support by cyclogest suppositories twice daily and primolut depot ampoules 250 µg I.M.twice weekly, 2 weeks later checking for pregnancy is done by serum measurement of hCG and subsequently by ultrasound for assessment of fetal node and viability.

Outcome Measures

Fertilization rate: was defined as total fertilized oocyte number by total number of embryo transferred.

Cleavage rate: was defined as total number of day 3 embryo by total number of fertilized oocytes.[(11)]

DOI: 10.37200/IJPR/V24I5/PR201849
Received: 16 Feb 2020 | Revised: 10 Mar 2020 | Accepted: 23 Mar 2020

Pregnancy rate: number of pregnancy by patients subjected to ICSI embryo transfer attempt.[12]

Result: this is a prospective randomized controlled trial ,80 patients subjected to ICSI randomized to TIVA with midazolam and propofol (Group 1) or midazolam and ketamine with isoflurane inhalational anasthesis(group2, IV plus inhalational anasthesia) as a drugs used for sedation during oocyte retrieval,

Statistical Analysis

The Statistical Analysis System- SAS (2012) program was used to effect of difference factors in study parameters. Chi-square test was used to significant compare between percentage and Least significant difference – LSD test was used to significant compare between means in this study.[13]In this study there was a tendency for higher pulse rate , higher blood pressure and respiratory rate in group 2 compared to group1,with significant difference as its evident in table below (table 1).

Total oocyte retrieved in our was 313 in group 1(TIVA; propofol) treated group) and 299 in group 2 (inhalational + ketamine treated group), MII oocyte forms about 45% of oocyte in group 1(142/313) which is lower than MII oocyte ratio in group2 (57.85%)(173/299)with statistically significant difference in between two groups ,MI oocyte has no statistical difference between both groups ,while abnormal oocyte (Germinal vesicle ,ruptured ,abnormal oocyte) in group 2 is statistically lower than group 1 (100/313 compared to 59/299).

Table 1: Physical Finding for ICSI Patient of both Groups of Patients treated with TIVA or Inhational Anesthesia

Physical finding (mean)	TIVA (Propofol) group1	Inhalational Anasthesia+Ketamine group2	T-Test
Heart rate Beat/minute	102.45 ± 5.38	111.62 ± 7.82	7.819 *
Systolic blood pressure mmHg	125.62 ± 7.07	135.42 ± 9.61	28.51 NS
Diastolic blood pressure (mmHg)	66.5 ± 2.66	81.40 ± 4.27	13.73 *
Respiratory rate Breath /min	14.47 ± 0.52	17.02 ± 1.06	2.16 *
*:significant (P<0.05), NS: non-significant.			

The total oocyte inseminated in group 1 was 198 compared to 203 oocyte in group 2 with an insemination rate of 4.95 oocyte /patient in group 1 and 5.07 oocyte /patient in group 2(table 2).

Table 2: Labarotory Finding of Oocytes of both Groups of Patients Treated with TIVA or Inhalational Anasthesia

Labarotory Finding	TIVA: Propofol group1 Number	TIVA:Propofol group1 Percent/ratio	Inhlational+ Ketamine group2 Number	Inhalational + Ketamine group 2 Percent /ratio	Chi-Square (χ^2)
Total oocyte	313	7.8 /patient	299	7.47/patient	---
MII	142/313	45.36%	173/299	57.85	4.52 *
MI	71/313	22.86%	67/299	22.40%	0.074 NS
Abnormal oocyte	100/313	31.94%	59/299	19.73%	4.85 *
MII:MI ratio	142/71	2.00	173/67	2.58	---
inseminated oocyte	198	4.95/patient	203	5.07/patient	---
* (P<0.05), NS: Non-Significant.					

The fertilization rate and Cleavage rate and grade 1 embryo was higher in group 1 than group 2 (75.25% compared to 71.42%, 76.51 compared to 75.86%, 73.46% compared to 67.27%). Although statistically was not significant. With a statistically significant difference between the pregnancy rate between both groups with higher pregnancy rate in patients with group 1 than group 2, (35% compared to17.5%) (table 3).

DOI: 10.37200/IJPR/V24I5/PR201849
Received: 16 Feb 2020 | Revised: 10 Mar 2020 | Accepted: 23 Mar 2020

Table 3: Reproductive Outcome Result from ICSI Patients Treated with TIVA or Inhalational Anesthesia

Reproductive Outcome	Propofol group Number	Propofol group Rate /ratio	Ketamine group Number	Ketamine group Rate/ratio	Chi-Square (χ^2)
Fertilization rate	149/198	75.25%	145/203	71.42%	0.793 NS
Cleavage rate	114/149	76.51%	110/145	75.86%	0.793 NS 1.602 NS
Grade1 embryo	75/114	73.46%	74/110	67.27%	2.526 NS
Pregnancy rate	14/40	35%	7/40	17.5%	7.194 *
*: significant (P<0.05), NS: Non-Significant.					

III. DISCUSSION

Infertile Patients managed with ICSI when subjected to anesthesia they may suffer from stress, anxiety depression and obesity, they might have been taking a lot of drugs especially like Aspirin and met formine and they might be subjected for repeated intervention and pain especially at time of retrieval of oocyte, and discomfort from hyper stimulated ovaries and from associated ascitis.[(14)] The type of anesthesia should be suitable to the patient clinical state and satisfactory for relieving her anxiety and pain, keeping in mind that these drugs might be eliminated in the ovarian follicular fluids and may affect the oocyte and DNA, interfering with their fertilization embryo grading and subsequent pregnancy.

TIVA by Propofol is the most commonly used agent for general anesthesia ,with fast onset and short elimination time It is beneficial in oocyte retrieval ,and it may cause cardio-respiratory depression which can be improved by addition of fentanyl [(15)] and the patient should be monitored with anesthesiologist or personnel skilled with air ways management .In this study the group receiving TIVA with propofol (group 1) has higher fertilization rate , cleavage rate, and higher percentage of good quality grade 1 embryo with significant higher pregnancy rate and this was also evident in previous study by Izhar Ben-Shlomo 2000[(16)], accordingly TIVA with propofol can be more suitable for GA in oocyte retrieval since it has less effect on fertilization rate embryo quality and pregnancy rate this is especially if prolonged anesthesia is avoided , as till now still there is concern on oocyte quality comes from accumulating concentration of propofol in the follicular fluid especially for the last aspirated follicles supported by a human study by Christiaens *et al*., 1999.[(17)] Although this damaging effect is not confirmed till now but it still possible.

Ketamine with its long use in general anasthesia, can be regarded as ideal anesthetic agent as it produce and it's a good alternative to TIVA with propofol, especially when used with midazolam (minimize its well-known postoperative CNS and psychological side effect[(18)], ketamine as in our study, its known to give lower fertilization rate ,embryo grading and significantly lower pregnancy rate this could be correlated due to its effect on increasing prolactin and β-endorphin levels,[(18)] or due to direct toxic effect on oocyte and its DNA.in addition Isoflurane inhalational anesthetic agent used with ketamine, (as in our study) is also might be responsible for lower reproductive outcome and pregnancy rate in group 2 ,as its found from a previous study due to direct embryo- toxic effect.[(19)] Midazolam was used in both groups in our study, its known to accumulates in the follicular fluid without affecting pregnancy rate .[(20)]

In this study there is higher abnormal oocyte (mainly GV) in group 1 than in group2, with relative decrease in

DOI: 10.37200/IJPR/V24I5/PR201849
Received: 16 Feb 2020 | Revised: 10 Mar 2020 | Accepted: 23 Mar 2020

MII with similar total number of inseminated oocyte/patient ,in our study this differences in the ratio of MII to the immature MI and abnormal oocyte may result from the operator tendency to aspirate all the remaining small follicles towards the end of the procedure to avoid OHSS in patients with large number of follicles .Inspite of this higher rate of inseminated MII in group 2(MII:173), the fertilization, cleavage , and embryo transfer rate were still higher than in group 1(MII:142)with significantly higher pregnancy rate.

Wael S Nossair study in **2017**[21] find significant higher fertilization ,cleavage and grade 1 embryo and pregnancy rate in propofol treated group than ketamine groups, similar to the results of our study although in significant differences. The pregnancy rate is clearly significantly different about double the rate similar to the result of Wael S Nossair, but the pregnancy rate is still higher than in our study in the group 1, this might be due to difference in the pregnancy rate between our center and that center.

There is observed negative effect on fertilization, cleavage and Grade 1 embryo rate in inhalational anesthesia plus ketamine treated group compared to TIVA with propofol, and there is significant effect of isoflurane and ketamine on ICSI outcome and specifically on pregnancy rate compared to propofol, the latter should be regarded as first line anesthetic agent to be used for oocyte retrieval.

Studies on the effect of anesthetic drugs level in the follicular fluid on the oocyte retrieved at early, mid and late in the procedure, gives better confirmation for toxicity, and whether it depends on the duration of exposure.

REFERENCES

[1] Ankur Sharma, AnuradhaBorle, AnjanTrikha Anesthesia for in vitro fertilization. *Journal of Obstetric Anaesthesia and Critical Care* 2015: Vol 5: Issue 2; pp. (72-62).

[2] Kwan I, Bhattacharya S, Knox F, McNeil A. Pain relief for women undergoing oocyte retrieval for assisted reproduction. *Cochrane Database Syst Rev* 2013; 1: CD004829.

[3] Annie S.O. Leunga, Michael H. Dahana, B and Seang Lin Tana, B Techniques and technology for human oocyte collection. *Expert Review of Medical Devices*, 2016: Vol. 13, No.8, pp. 701-703

[4] Hayes MF, Sacco AG, Savoy-Moore RT, Magyar DM, Endler GC, Moghissi KS. Effect of general anesthesia on fertilization and cleavage of human oocytes in vitro. *Fertil Steril* 1987; 48: 975-81.

[5] Vlahos NF, Giannakikou I, Vlachos A, Vitoratos N. Analgesia and anesthesia for assisted reproductive technologies. *Int J Gynaecol Obstet.* 2009; 105: 201-205

[6] Paraskevi Matsota, Eva Kaminioti, and Georgia Kostopanagiotou. Anesthesia Related Toxic Effects on In Vitro Fertilization Outcome: Burden of Proof. *BioMed Research International*, Volume 2015, Article ID 475362.

[7] David H. Chestnut, MD., Cunthia A. Wong MD. Lawrence C. Tsen, MD. Chestnut's obstetric anesthesia: principle and practice. Chapter 15: in vitro fertilization and other assisted reproductive technology. 2014 by Saunders, an imprint of Elsevier Inc: pp. 326-340.

[8] Madhuri S. Kurdi, Kaushic A. Theerth, and Radhika S. Deva.Ketamine: Current applications in anesthesia, pain, and critical care. *Anasth Essays Res.* 2014 Sep-Dec; 8(3): 283–290.

[9] Advisory Council on the Misuse of Drugs. Ketamine: A review of use and harm, 2013. Report. [Last accessed on 2014 Jul 08]. Available from: http://www.gov.uk/government/./ACMD_ketamine_ report_ dec13.pdf .

[10] ASA House of Delegates/Executive Committee ASA Physical Status classification System October 15, 2014

[11] Ann M Mangalraj, K Muthukumar, TK Aleyamma, Mohan S Kamath , and KorulaGeorge.Blastocyst stage transfer vs. cleavage stage embryo transfer *J Hum Reprod Sci.* 2009; 2(1): pp. 23–26.

[12] Lynne S. Wilcox, Herbert B. Peterson, Florence P. Haseltine, Mary c. Martin,

[13] Defining and interpreting pregnancy success rates for in vitro fertilization fertility and strility1993:Vol. 60: No. 1

DOI: 10.37200/IJPR/V24I5/PR201849
Received: 16 Feb 2020 | Revised: 10 Mar 2020 | Accepted: 23 Mar 2020

[14] SAS. 2012. Statistical Analysis System, User's Guide. Statistical. Version 9.1th ed. SAS. Inst. Inc. Cary. N.C. USA.

[15] David K. Gardner DPhil, Ariel Weissman MD Colin M. Howles, Zeev Shoham .Textbook of Assisted Reproductive Techniques Fifth Edition, Volume 2: Clinical Perspectives 2018 by Taylor & Francis Group, LLC. Chapter57: Anesthesia for invitro fertilization, Alexander Izaksanand Tiberiu Ezri: pp.739-746)

[16] Edwards JA, Kinsella J, Shaw A, Evans S, Anderson KJ. Sedation for oocyte retrieval using target controlled infusion of propofol and incremental alfentanil delivered by non-anesthetists. *Anaesthesia* 2010; 65: pp.453–61.

[17] Izhar Ben-Shlomo Roland Moskovich Joanne Golan Vered Eyali Arek Tabak Eliezer Shalev. The effect of propofol anaesthesia on oocyte fertilization and early embryo quality. *Human Reproduction*, Volume 15, Issue 10, 1 October 2000, pp.2197–2199.

[18] Christiaens, F., Janssenswillen, C., Verborgh, C. *et al.* Propofol concentrations in follicular fluid during general anaesthesia for transvaginal oocyte retrieval. Hum. Reprod.1999; 14: pp.345–348.

[19] Ben-Shlomo I, Moskovich R, Katz Y, Shalev E. Midazolam/ketamine sedative combination comparedwith fentanyl/propofol/isoflurane anaesthesia for oocyte retrieval. Hum Reprod1999; 14: pp1757–1759.

[20] E.J.E. Lee, A. Bongso, and A. Kumar, "Evaluation of inhalational anaesthetics on murine in vitro fertilization," *Annals of the Academy of Medicine Singapore* 1994; 23: 4: pp. 479–485.

[21] I. Soussis, O. Boyd, T. Paraschos et al., "Follicular fluid levels ofmidazolam, fentanyl, and alfentanil during transvaginal oocyteretrieval,"*Fertility and Sterility*, 1995; 64: 5: pp. 1003–1007.

[22] Wael S Nossair1* and Ahmed MA Maaty2. Comparative Study among Ketamine, Thiopental and Probofol for Sedation during *In Vitro* Fertilization Procedures. *SM J Gynecol Obstet.* 2017; 3(1): 1020.

DOI: 10.37200/IJPR/V24I5/PR201849
Received: 16 Feb 2020 | Revised: 10 Mar 2020 | Accepted: 23 Mar 2020