Original Article

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Three Different Bolus Doses of Propofol Using Total Intravenous Anaesthesia (TIVA) in Patients Undergoing Transvaginal Oocyte Retrieval: on Table Recovery Time and Time to Discharge Using Post Anaesthesia Discharge Scoring System (PADSS)

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Abstract

Background: The patients undergoing IVF treatment are thoroughly evaluated for the cause of infertility, appropriate treatment instituted and the associated co morbidity. Another major challenge for the anaesthetists is to allay the anxiety. The patients presenting in the IVF clinic are under high degree of social and psychological stress. Detailed pre anaesthetic check up was done a day prior to surgery and appropriate investigations were carried out. **Subjects and Methods:** The anaesthetic technique and the questionnaire were explained to the patients and an informed written consent was taken from all the patients.Patients were kept fasting overnight prior to surgery and were premedicated with Tab. Ranitidine 150 mg and Tab. Alprazolam 0.25 mg on the night before surgery and repeated on the next day one hour prior to surgery with sip of water. **Results:** On table recovery time was found to be 6.12 minutes in group P1 (2mg/kg), 5.32 minutes in group P2 (1.5mg/kg) and 5.32 minutes in group P3 (1mg/kg). No statistical difference observed between the 3 groups. Time to discharge was found to be 37.08 minutes in group P1 (2mg/kg), 33.48minutes in group P2 (1.5mg/kg) and 28.88minutes in group P3 (1mg/kg). **Conclusion:** On table recovery time was found to be 6.12 minutes in group P1 (2mg/kg), 5.32 minutes in group P2 (1.5mg/kg) and 5.32 minutes in group P3 (1mg/kg). No statistical significant difference was observed between the three groups.

Keywords: Propofol, On Table Recovery Time, Time to Discharge.

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Introduction

Since the first successful in vitro fertilization (IVF) attempt in 1978 by Louise Joy Brown, there has been an exponential increase in the use of this method in thousands of infertile couples. There has been continuous refinement in the fertility drug protocols and the techniques to retrieve eggs. As a result, IVF success rates began to climb slowly reaching 25-30%.[1]

Assisted reproduction technology (ART) is a complex procedure consisting of various steps starting from stimulation of ovaries to oocyte pick up, sperm processing and the intricate embryology laboratory details for embryo formation and finally its implantation into the uterus. Improvements in the culture technique, laboratory methods, retrieval routes and transfer techniques are responsible for the better results. Although the technique of using vaginal ultra-sound probe is less invasive, easier and faster, it forms one of the most painful components of the entire assisted reproductive treatment.[2]

The patients undergoing IVF treatment are thoroughly evaluated for the cause of infertility, appropriate treatment instituted and the associated co morbidity. Another major challenge for the anaesthetists is to allay the anxiety. The patients presenting in the IVF clinic are under high degree of social and psychological stress.

Pain during oocyte retrieval is caused by the puncture of the vaginal skin and ovarian capsule by the aspirating needle as well as manipulation within the ovary during the entire procedure. Here it becomes customary for the anaesthetist to provide adequate pain relief to immobilise the patient and eliminate the danger of piercing any vessel during the process of oocyte retrieval. The ideal pain relief during oocyte retrieval should be effective and safe, easy to administer and monitor, short acting and readily reversible with a few side effects.[3]

Considering all these observations, Christiaens et al in 1999 performed a study on accumulation of propofol in the follicular fluid. Propofol estimation was done using High Performance Liquid Chromatography (HPLC). Follicular fluid concentrations of propofol correlated closely with the

duration of propofol administration and to the total amount administered. Thus they concluded that propofol based anaesthetic technique resulted in significant concentration of this agent in follicular fluid, which is related to the dose administered and duration of exposure.[4]

Another study conducted by Ben-Shlomo et al in 2000 was designed to investigate the impact of propofol exposure on oocyte quality. Thirty two women who had more than 15 oocytes retrieved under propofol-maintained general anaesthesia had their oocytes cultured separately according to the order of retrieval. No differences were documented in fertilization, embryo cleavage, pregnancy rates between the group of oocytes that was retrieved first (therefore they were exposed less to propofol) and the group of oocytes that was retrieved last. In that study the longest retrieval lasted 20minutes and the shortest 3.5minutes.The maximal follicular concentration of propofol was 0.1µg/ml.[5]

With the above concerns, we must aim at using the minimum dose of propofol possible for TVOR. At the same time we have to ensure that the depth of anaesthesia shoud not be compromised at any time to prevent intra operative complications and awareness.

So in our study we compared 1 mg/kg, 1.5 mg/kg and 2mg/kg of propofol induction dose.

In 1985 Rolly, G. and Versichelen, L compared 1.5 mg/kg of propofol induction dose with 2 mg/kg propofol induction dose and 4 mg/kg of thiopentone in thirty premedicated ASA I or II patients scheduled for minor gynaecological surgery. They observed that 1.5 mg/kg group has lesser apnoeic time, and better hemodynamic stability when compared with 2mg/kg group.[6]

In 2004 Ercan et al did a study titled "Assessing propofol induction of anaesthesia dose using bispectral index analysis" and they compared 2 mg/kg bolus dose of propofol with BIS guided propofol bolus dose. They found that propofol bolus for induction using BIS decreased the total propofol dose by 36-43 % and hence propofol consumption. Better hemodynamic stability was observed in titrated propofol dose group than with the 2 mg/kg group.[7]

Very recently in 2013 M Zitta et al did a study on deleterious effect of propofol on invitro fertilisation and compared 1.5 mg / kg with 2 mg /kg induction dose of propofol. They observed higher pregnancy rate in 1.5 mg/kg group and found no difference in anaesthetic parameter, age, no of oocytes retrieved, fertilisation rate and embryo quality.[8]

However, to the best of our knowledge, there is no literature on 1mg/kg induction dose comparison during TVOR for IVF.

Monitor to ensure adequate depth of anaesthesia like entropy help us to prevent excess drug consumption. Gürses E et al showed propofol requirement assessed by bispectral index analysis during anesthesia induction may decrease the dose and side effects and provide for satisfactory depth of anesthesia.[7] Anne Vakkuri et al. in August, 2005 did a study on entropy assisted titration of propofol, which showed a decreased consumption of propofol, and shortened recovery time in the entropy group.9 However, contradicting results were also obtained by Bhardwaj et al. in January, 2010.[10]

We have used Post Anaesthesia Discharge Scoring System (PADSS) for determining home-readiness of the patients. Once the patients were declared fit for discharge, they were questioned using Modified Brice interview technique for evaluating intra-operative awareness.

Subjects and Methods

75 patients were randomly allocated into 3 study groups of 25 patients by a computer generated randomisation table:

Group P1: propofol 2 mg/kg

Group P2: propofol 1.5 mg/kg

Group P3: propofol 1 mg/kg

PAC: Detailed pre anaesthetic check up was done a day prior to surgery and appropriate investigations were carried out. The anaesthetic technique and the questionnaire were explained to the patients and an informed written consent was taken from all the patients.

Patients were kept fasting overnight prior to surgery and were premedicated with Tab. Ranitidine 150 mg and Tab. Alprazolam 0.25 mg on the night before surgery and repeated on the next day one hour prior to surgery with sip of water.

In operation theatre: Standard pre use checks of anaesthesia workstation and ancillary equipment were performed. After shifting the Patient to OT, Routine monitors like heart rate (HR), blood pressure (BP), and SPO2 (saturation of oxygen)were attached. Commercially available disposable entropy sensor strip was applied after skin preparation as recommended by the manufacturer. Entropy module of the S/5 Anaesthesia monitor (GE Healthcare, Finland: formerly Datex-Ohmeda, Helsinki, Finland) was used.

A 20G i.v. cannula was secured in all patients preferably over the dorsum of the non dominant hand. Basal vital parameters like heart rate (HR), blood pressure (BP), ETCO2 (end tidal carbon dioxide) and SPO2 (saturation of oxygen) were noted in all the groups. Baseline response entropy (RE) and state entropy (SE) values were also noted.

All the patients were given Inj. Midazolam 0.03mg/kg i.v. and Inj Fentanyl 2µg/kg i.v. as a premedication. After 3minutes,

IN GROUP P1: A bolus dose of propofol 2 mg/kg i.v. was administered. The patients received 100% O2 @6-8L/min through Anatomical face mask of suitable size connected with Bain co-axial circuit.

IN GROUP P2: A bolus dose of propofol 1.5mg/kg i.v was administered. The patients received 100% O2 @6-8L/min through Anatomical facemask of suitable size connected with Bain co-axial circuit.

IN GROUP P3: A bolus dose of propofol 1mg/kg i.v was administered. The patients received 100% O2 @6-8L/min through Anatomical facemask of suitable size connected with Bain co-axial circuit.

Subsequently, anaesthesia was maintained with propofol infusion @ 150µg/kg/min i.v. along with 100%O2 in all the groups to maintain entropy values between40-60.

All patients were maintained on spontaneous respiration keeping EtCO2 between 35-45 mmHg. The circuit will be attached to the standard anaesthesia workstation. If at any point of time SPO2 falls ≤95 and/or if there are any signs suggestive of loss of airway, then airway opening manoeuvre with assisted bag and mask ventilation was done. Intraoperative fluid replacement was done with ringer lactate

as per the Holiday segar formula.
Patients were put in lithotomy position. Ovarian follicles were aspirated by ultrasound guided needle probe in both the stimulated ovaries. Thereafter the needle was withdrawn and the vagina was cleaned with betadine soaked gauze. Intraoperatively HR, MAP, RR, ETCO2, SPO2, RE, and SE were recorded every 5 minutes in all patients till the time of their recovery on table.

RESCUE: If at any time during the procedure SE value was found to be >60 or any untoward movement of the patient occurs, a bolus of propofol 0.25mg/kg was given. If the above said parameter continues to remain elevated even after two minutes, we repeated the bolus of propofol 0.25mg/kg. If the RE-SE difference was found to be > 10, then Inj.fentanyl 0.5µg/kg i.v. was given. If the SE is <40, rate of propofol infusion was stepped down by 20µg/kg/min. Number of additional boluses required in each group was also noted.
Bradycardia was treated with Inj.Atropine0.6mg i.v. stat. If the MAP was <20% below baseline additional i.v. fluids followed by stepping down of propofol infusion was done.
Propofol infusion was stopped once the trans-vaginal USG probe was removed in all the patients.
All patients were given 100% O2 till the time of recovery i.e. response to verbal command.
PACU: All patients were transferred to PACU and were monitored every 10 minutes till they achieved modified Post Anaesthesia Discharge Scoring system Score of ≥9, when they were declared fit to get discharged. Time required to achieve this score was also noted in all the group of patients.
Rescue analgesia with Inj.Diclofenac 75mg i.m. and treatment of post operative nausea and vomiting (PONV) with Inj.Ondansetron4mg i.v was given and noted.
At the time of discharge, intraoperative awareness of all patients was assessed by the Modified Brice interview technique.

Results

All the three groups were found to be comparable with respect to Age, Weight, ASA Grade, and Duration of Surgery. And also the groups are comparable with each other.

Table 1: Basic parameters

Group	P1 (2mg/kg)	P2 (1.5mg/kg)	P3(1mg/kg)	p value
No of patients	25	25	25	
Age(yrs) (mean±SD)	28.76 ± 3.972	28.40 ± 3.830	28.04 ± 2.475	0.767
Weight(kg) (mean±SD)	57.52 ± 6.494	60.36 ± 10.677	57.72 ± 7.935	0.427
ASA physical status (I/II)	21/4	22/3	21/4	.899
Duration of surgery (min) (mean±SD)	16.40 ± 6.144	17.24 ± 5.953	17.84 ± 5.749	0.692

The mean age was 28.76 years in group P1, 28.40 years in group P2 and 28.04 years in group P3.
The mean weight was 57.52 Kg in group P1 (2mg/kg), 60.36Kg in group P2 (1.5mg/kg) and 57.72kg in group P3 (1mg/kg).

Table 2: ASA GRADE

Group	ASA 1 patients (%)	ASA 2 patients (%)
P1(2mg/kg)	84	16
P2(1.5mg/kg)	88	12
P3(1mg/kg)	84	16
P value	.899	

4 (16%) patients in group P1 (2mg/kg) were ASA Grade II. These patients were Hypothyroid, controlled on Tab Eltroxin.
3(12%) patients in group P2(1.5mg/kg) were ASA Grade II. These Hypothyroid patients controlled on Tab Eltroxin.
4(16%) patients in group P3(1mg/kg) were ASA Grade II. These included 3 patients who were Hypothyroid, controlled on Tab Eltroxin and 1 patient was Diabetic controlled on Tab Glimiperide

The coexisting illnesses were important to note as these are commonly the causes of infertility in females in India, particularly Hypothyroidism and Tuberculosis.
The duration of surgery was 16.40 ± 6.144 minutes in group P1 (2mg/kg), 17.24 ± 5.953 minutes in P2 (1.5mg/kg) and 17.84 minutes in group P3 (1 mg/kg) and the 3 groups are comparable.

Table 3: On Table Recovery Time

Group	On Table Recovery Time (mean±SD)
P1(2mg/kg)	6.12 ± 2.007
P2(1.5mg/kg)	5.32 ± 1.492
P3(1mg/kg)	5.32 ± 2.286
P value	0.135

On table recovery time was found to be 6.12 minutes in group P1 (2mg/kg), 5.32 minutes in group P2 (1.5mg/kg) and 5.32 minutes in group P3 (1mg/kg). No statistical difference observed between the 3 groups.

Table 4: Time to Discharge

Group	Time To Discharge (min) (mean±SD)
P1(2mg/kg)	37.08±5.992
P2(1.5mg/kg)	33.48±4.234
P3(1mg/kg)	28.88±5.477
P value	0.001

Time to discharge was found to be 37.08 minutes in group P1 (2mg/kg), 33.48minutes in group P2 (1.5mg/kg) and 28.88minutes in group P3 (1mg/kg). Statistically significant difference observed between the 3 groups.

Table 5: Time To Discharge (P1 & P2)

Group	Time To Discharge (min) (mean±SD)
P1 (2mg/kg)	37.08±5.992
P2(1.5mg/kg)	33.48±4.234
p value	.018

Table 6: Time To Discharge (P2 & P3)

Group	Time To Discharge (min) (mean±SD)
P2(1.5mg/kg)	33.48±4.234
P3(1mg/kg)	28.88±5.477
p value	.002

Table 7: Time To Discharge (P1 & P3)

Group	Time To Discharge (min) (mean±SD)
P1(2mg/kg)	37.08±5.992
P3(1mg/kg)	28.88±5.477
p value	.000

Statistical significant difference observed between group P1-P2, P2-P3 and P1-P3 in respect to time to discharge.

Table 8: Intraoperative Awareness: (Brice Questionnaire)

Group	Intraoperative Awareness
P1(2mg/kg)	NIL
P2(1.5mg/kg)	NIL
P3(1mg/kg)	NIL

No Intra operative Awareness was noted in any group.

Table 9: Surgeon Satisfaction

Group	0=not satisfied	1=satisfied	2=fully satisfied
P1(2mg/kg)	20.0%	8.0%	72.0%
P2(1.5mg/kg)	8.0%	16.0%	76.0%
P3(1mg/kg)	4.0%	8.0%	88.0%
P value	0.087		

No statistical significant difference observed between 3 groups in respect to surgeon satisfaction.

Table 10: Patient Satisfaction

Group	Satisfied
P1(2mg/kg)	100%
P2(1.5mg/kg)	100%
P3(1mg/kg)	100%

One patients in group P1 (2mg/kg) and other in group P3 (1mg/kg) complained of nausea and were given Inj ondansetron 4 mg i v.

Discussion

Oocyte retrieval is a routine procedure in IVF that is preferably done in ambulatory setting, which can be done under different types of anaesthesia. However, the administered anaesthetic agent, opiates and local anaesthetic have been detected in follicular fluid and their deleterious effects on oocyte cleavage and fertilisation has been reported in previous studies.

TIVA using propofol is the most common method used in oocyte retrieval. Propofol has its innumerable advantages in this day care setting by virtue of its clear headed speedy recovery and minimal post-operative complication. However, recent studies suggest that there is a dose and time dependent toxic effect of propofol on fertilization of oocytes.

In 1997 J. F. Webb et al did a study on Propofol Levels in Follicular Fluid in Transvaginal Oocyte Retrievals Using Diprivan for Intravenous Sedation and found that Propofol is detectable in follicular fluid in patients receiving Diprivan for sedation for oocyte retrieval. The propofol levels do not appear to be affected by the length of sedation prior to follicle aspiration. Contamination with blood significantly increased propofol concentration.[11]

In a study by Cecile Janssenswillen et al, on the effect of propofol on parthenogenetic activation, in vitro fertilization and early development of mouse oocytes in 1997 showed brief exposure of cumulus-enclosed oocytes to a low concentration of propofol is deleterious to subsequent cleavage. Exposure of unfertilized oocytes to propofol results in a high degree of parthenogenetic activation.[12]

Taking into account the potential negative effect of propofol on human artificial reproductive technique, the total dose of propofol administered during anaesthesia should be strictly limited. Devices measuring depth of anaesthesia like entropy make it possible to tailor drug delivery in order to minimise drug administration, and at the same time, optimise the delivery of drug to each individual patient in order to guarantee loss of awareness.

On table recovery time was found to be 6.12 minutes in group P1 (2mg/kg), 5.32 minutes in group P2 (1.5mg/kg) and 5.32 minutes in group P3 (1mg/kg). No statistical significant difference was observed between the three groups.

The on table recovery depends on context sensitive half life of propofol which inturn depends on the infusion rate and duration. Micheal A hughes et el in 1992 did a study on context sensitive half life of intravenous anaesthetic agent and they concluded that context sensitive half times are a useful predictor of post infusion recovery.[13]

Since we kept our maintenance rate constant in all the three groups and the duration was comparable. Hence no significant difference was observed between the three groups.

Time to discharge as assessed by PADSS was found to be 37.08 minutes in group P1 (2mg/kg), 33.48minutes in group P2 (1.5mg/kg) and 28.88minutes in group P3 (1mg/kg). Statistically significant difference observed between the three groups. Statistically significant difference observed between group P1 –P2 (P=0.018), P2-P3 (0.02) and P1 -P3 (P=0.001) in respect to time to discharge. Hence discharge time is varied directly with the dose.

Saleh et al in 2012 did a study titled 'A comparison of two di□erent regimens of total intravenous anesthesia for transvaginal ultrasound-guided oocyte retrieval' and demonstrated that recovery profile of patients depends on total propofol consumption. They obtained shorter recovery time in a group with less propofol consumption. However they have used modified Aldrette score for discharge.[14]

No Intraoperative awareness was noted in any group when interviewed using the Modified Brice questionnaire.

Since we had Entropy monitoring for evaluation of depth of anaesthesia, it was easier to detect lighter plane and helped us in reducing chances of intra operative awareness.

Myles et al and Ecker et al in 2004 demonstrated significant benefit of depth of anaesthesia monitoring in reducing intraoperative awareness in a larger number of high risk patients. High risk patients for awareness include patients undergoing cardiac surgery, trauma surgery, caesarean section, airway endoscopic surgery or paediatric surgery. Also, in the above mentioned studies the patients were questioned on more than one occasion.

No statistical significant difference observed between three groups in respect to patient and surgeon satisfaction. The Entropy monitoring for evaluation of depth of anaesthesia has helped us to detect lighter plane earlier than surgeon could notice. Hence there were no difference between the groups in respect to surgeon and patient satisfaction.

One patient in group P1 (2mg/kg) and group P3 (1mg/kg) complained of nausea and were treated with Inj ondansetron 4 mg i v.

The fewer incidences of post operative nausea and vomiting in our study was due to propofol infusion. Gan .T Eet al compared ondansetron with propofol and they concluded the maintenance infusion of propofol is equally effective as ondansetron in preventing post operative nausea vomiting.[15] None of the patients required any rescue analgesia since fentanyl dose was adequate.

Conclusion

- On table recovery time was found to be 6.12 minutes in group P1 (2mg/kg), 5.32 minutes in group P2 (1.5mg/kg) and 5.32 minutes in group P3 (1mg/kg). No statistical significant difference was observed between the three groups.
- The on table recovery depends on context sensitive half-life of propofol which in turn depends on the infusion rate and duration.

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