ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 09, 2022

COMPARATIVE STUDY OF DIFFERENT PROPORTIONS OF PROPOFOL-KETAMINE COMBINATION FOR TOTAL INTRAVENOUS ANESTHESIA IN SHORT GYNECOLOGICAL PROCEDURES

Dr. Anand Babu Naik [1],
Dr. K.Indira priyadarshini [2]
Dr.Emeema Bandrapalli[3]
DrJoel Suraj Nuthalapaty*
1,2:Assistant professor ,Department of Anesthesia, Guntur medical college ,Guntur
3.Designated Associate Professor ,Department of Anesthesia, Guntur medical college ,Guntur
*** MBBS ,Guntur medical college ,Guntur**
CORRESPONDING AUTHOR
DrJoel Suraj Nuthalapaty
MBBS
Guntur medical college
Guntur
joelsuraj302@gmail.com

ABSTRACT :
This was a randomized, double-blinded study conducted on 140 patients in the age group of 18-60 years, belonging to ASA I and II undergoing elective short gynecological procedures of duration less than 30 minutes at Kurnool Medical College.The study population was divided into two groups with patients of Group A receiving ketamine-propofol in the ratio 1:4 and Group B receiving ketamine-propofol in the ratio 1:2. All patients were induced with the study drug at a dose of 0.1ml/kg. The maintenance of anesthesia was with an infusion at 0.3ml/kg/hr for both groups. A bolus of 2ml of the study drug was given when an adequate depth of sedation was not maintained due to surgical stimulus.The study aimed to compare and evaluate the effectiveness of the two drug regimens of ketamine-propofol combination(1:4 and 1:2) with respect to quality of sedation and analgesia in the intra-operative period. The secondary objectives were to compare the change in hemodynamic variables, the need for airway interventions, the time for awakening after the procedure, incidence of post operative nausea and vomiting, incidence of recovery agitation and recall of intraoperative events.
Key words: Propofol,ketamine,two drug regimen,short Gynaecological procedure

Introduction :

The advent of general anesthesia in the 19 th century was considered as a significant event in the history of medicine [1] . Since then there has been a vast development in the field of anesthesia. Procedural sedation using total intravenous anesthesia for short duration surgeries is a convenient technique of anesthesia as it has a faster recovery surpassing the side effects of general anesthesia. A combination of intravenous anesthetic and analgesic drugs can be given when speed and completeness of recovery are important. Although all surgical branches use day care interventions, Gynecology

and Obstetrics use these interventions most often [2] . The commonly used drugs are ketamine or propofol with midazolam or fentanyl indifferent combinations. The drawbacks of these drugs are prolonged sedation, need for bag mask ventilation and emergence phenomenon (ketamine delirium)

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 09, 2022

which occur with the routine dose. The ideal anesthetic drugs should possess the following attributes for these short procedures 3 .

- Rapid and smooth induction
- Provide adequate analgesia
- Good hemodynamic stability
- Sedation easily extendable beyond the expected duration
- Smooth recovery
- Less adverse effects

Since no single drug can provide all the characteristics of an ideal intravenous agent, different drugs are used in varying combinations to provide balanced anesthesia in Total intravenous anesthesia(TIVA), that is, amnesia, hypnosis and analgesia. Propofol is a non opioid, non barbiturate, sedative-hypnotic agent with antiemetic effects. It has a rapid onset and short duration of action. Although it is an amnestic, it has not been shown to be an analgesic. Some of the adverse events with propofol include dose-related cardiovascular and respiratory depression. Ketamine, a dissociative anesthetic of phencyclidine derivative, is known to produce both analgesia and amnesia. Although it causes little or no respiratory and cardiovascular depression, the widespread use of ketamine as a single agent is limited by the emergence phenomena and the concern of inducing vomiting. The opposing hemodynamic and respiratory effects of each drug may enhance the use of this combination thereby increasing both safety and efficacy and allowing a reduction in the dose of propofol required to achieve sedation 4 . Further, the combination may decrease the need for supplemental opioid analgesics and has the potential to provide better sedation with less toxicity than either drug alone 5 . Ketamine and propofol administered in various combinations have offered effective sedation for gynecologic, ophthamologic, orthopedic and cardiovascular procedures in all age groups. Further, the addition of ketamine to propofol provides an analgesic effect that is absent when propofol is used alone. Effectiveness of the two agents – propofol and ketamine in combination mixed inasingle syringe has demonstrated efficacy in operating and ambulatory settings which has not previously been studied in the ratios of 2:1 and 4:1 in short gynecological procedures for providing procedural sedation.

Aim of the study: To compare the sedative and analgesic effects of two different proportions of ketamine and propofol combination in patients undergoing short gynecological procedures.

Objectives of study:

Primary objective:

1. To compare the adequacy of sedation and analgesia in both the groups

2. Time taken for administration of 1 st bolus dose

Secondary objective:

1. To compare the hemodynamic variables between both the groups

2. Airway intervention if any

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 09, 2022

3. Time for awakening

4. Post operative nausea and vomiting (PONV)

5. Recovery agitation 6. Recall of intra operative events

MATERIAL AND METHODS

After approval from the Institutional Ethics Committee and written informed consent from the patients, this randomized prospective double-blind interventional study was conducted between August 2021 and August 2022 in 140 patients posted for short gynecological procedures such as Suction and Evacuation(S and E), Diagnostic hysteroscopy(DH), Diagnostic Hysteroscopy and Endometrial Biopsy(DHEB), Polypectomy, Marsupialization of Bartholin cyst, , Copper T removal and secondary suturing in the Department of Anaesthesiology, GMC,Guntur

INCLUSION CRITERIA: 1. Female patients aged between 18-60 years 2. ASA grade I and II 3. Elective surgeries with duration ≤ 30mins

EXCLUSION CRITERIA: 1. Patient's refusal 2. Patients with ASA grade III or above 3. Patients with a history of allergy to study drugs 4. Patients with behavioral problems 5. Patients with Obstructive Sleep Apnoea

MATERIALS REQUIRED:

- 50cc disposable syringe
- Syringe pump
- Pressure Monitoring line
- 1% Propofol
- Ketamine

METHODOLOGY

A detailed pre-anaesthetic checkup was done and the necessary investigations were ordered for all the patients. Patients were randomly assigned to two groups by computer generated randomization to undergo procedural sedation with either 1:4 or 1:2 ratio of ketamine propofol combination. To ensure blinding, the drug was prepared by another anesthetist who was not involved with the study.

STUDY DRUG PREPARATION:

- 1 ml of 50mg/ml Ketamine added to 20 ml of 1% propofol and 4ml of 5% Dextrose to make a total volume of 25 ml (1:4 ratio of ketamine- propofol) - GROUP A
- 2ml of 50 mg/ml Ketamine added to 20 ml of 1% Propofol and 3ml of 5% Dextrose to make a total volume of 25 ml (1:2 ratio of ketamine- propofol) - GROUP B

All the patients were electively fasted according to the standard Nil Per Oral guidelines. An IV catheter was secured in the preoperative waiting room and premedication of Inj Glycopyrrolate 0.2 mg and Inj Midazolam 1 mg was given to all patients 10 mins prior to induction. The anesthetic machine was checked and resuscitation drugs and equipments were kept ready. After shifting the

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 09, 2022

patients to the operating room, essential monitors were attached which included 5 lead ECG, pulse oximeter and noninvasive blood pressure. Oxygen was delivered to all patients by a face mask at 6 liters/min.

Sedation was induced by bolus intravenous administration of 0.1ml/kg of either 1:4 ratio of ketamine-propofol combination (Group A) or 1:2 ratio of the ketamine- propofol combination (Group B). A Ramsay Sedation Score of 6 was considered satisfactory. If the patient did not achieve the desired Ramsay sedation score, a 2ml bolus of the study drug was administered and then the surgeon was allowed to proceed with the surgery.

The amount of drug administered for induction as well as the time for induction was recorded. Post induction, the anesthesia was maintained with an infusion of the study drug at 0.3ml/kg/hr.

The parameters like systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, heart rate, respiratory rate, oxygen saturation and depth of sedation were assessed at baseline (before injecting the study drug), and every 2 minutes till the end of the procedure. End-tidal carbon dioxide(EtCO2) was monitored continuously by a side stream sampling line inserted into the facial mask. If apnoea occurred, as assessed clinically or by capnography trace or if the peripheral oxygen saturation (SPO2) was $\leq$ 96%, a jaw thrust maneuver was performed by the anesthetist. If effective ventilation did not occur after the initial response, bag-mask ventilation was performed and the need for any airway intervention was documented.

If there was an incidence of movement in lower extremities during the procedure, a 2ml bolus of the study drug was administered. The time duration at which these bolus doses were given after the initial induction dose and the number of such bolus doses were recorded. Induction, maintenance and delivery of bolus doses were done using a single syringe pump.

The awakening time was calculated from the time the infusion was stopped (at the end of the procedure) untill the patient responded to verbal commands. The patient was then transferred to the Post Anesthesia Care Unit (PACU) and monitored until they met discharge criteria assessed by the Modified Aldrete Score of $\geq$ 9.

Incidence of PONV, and recovery agitation were observed untill the patient stayed in PACU and if they experienced PONV, it was treated with Inj Ondansetron 4mg IV. Before the discharge, the patients were asked if there was any recall of intraoperative events, dreams or psychological experience and the same was documented

RESULTS AND OBSERVATIONS

STATISTICAL ANALYSIS:

The sample size was calculated based on the study conducted by Chahyun Oh et al7 where the prevalence of movement in lower extremities was observed as 32.5% and 10% in 1:3 ketofol group and 2:3 ketofol combination respectively. At a 5% level of significance and 90% power, the calculated sample size was 67 in each group so a total of 140 patients (70 in each group) was considered for the study.

For continuous variables, the data was presented as mean ± SD and the categorical variables were presented as frequency and percentage. Chi-square test or Fisher-exact test was used to check the association between the two different groups. Statistical analysis was done using SPSS software version 20.0 and p-value $\leq$ 0.05 was considered as statistically significant.

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 09, 2022

RESULTS

During the study period of August 2021 to August 2022 140 patients were enrolled according to the inclusion criteria and after obtaining written informed consent. The data was obtained and the results were tabulated.

DEMOGRAPHIC VARIABLES			
	GROUP A	GROUP B	p-VALUE
AGE (YEARS)	34.54±8.07	35.91±8.92	0.342
HEIGHT(FEET)	5.10±0.31	5.08±0.277	0.625
WEIGHT(KG)	59.93±7.19	58.24±5.95	0.133
BMI	24.42±2.63	23.89±2.32	0.211
INCIDENCE OF MOVEMENT IN LOWER EXTREMITIES	43(61.4)	30(42.9)	0.028
DURATION TO ACHIEVE RAMSAY SEDATION SCORE OF 6 (Sec)	56.27±8.339	50±10.621	0.000
TOTAL NUMBER OF BOLUS DOSES	1.04±1.055	0.90±1.426	0.502
VOLUME OF DRUG FOR INDUCTION (ml)	8.89±1.584	8.09±1.462	0.002
TIME FOR 1ST BOLUS DOSE (sec)	5.93±2.939	7.03±3.045	0.125
AWAKENING TIME (min)	2.24±1.837	2.31±1.556	0.804
DURATION OF PROCEDURE (min)	11.71±4.867	12.10±4.682	0.633
TOTAL VOLUME OF DRUG USED (ml)	14.37±3.972	13.34±4.596	0.159

Discussion:

Different combinations of propofol and ketamine for procedural sedation have been studied in the past and were proven efficient. The aim of our study was to compare the sedative and analgesic properties of ketamine-propofol combination in the ratios 1:2 and 1:4 in gynaecological procedures as these are one of the most commonly performed surgeries in day to day practice. A study design with these drug regimens for gynaecological procedures had not been previously documented and hence the need for this study.

Our primary outcome was to compare the adequacy of sedation and analgesia in 140 patients divided into two groups of 70 each posted for short gynecological procedures. We assessed the adequacy of sedation and analgesia by the movement of lower extremities during the procedure indicating the need for rescue bolus doses of the study drug.

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 09, 2022

The incidence of this movement was significantly lower in Group B compared to Group A. A similar result was reported in a study conducted by Chahyun Oh et al6 with an aim to reduce patient movement in LEEP. They found that the incidence of adduction motion in lower extremities was significantly lower in patients receiving higher ketofol concentration. Another study conducted by Badrinath et al11, evaluating the sedative analgesic properties of different combinations of ketofol with propofol alone concluded that Ketamine produced a dose dependant reduction in the incidence of patient responsiveness to local infiltration for breast biopsy procedure.

The incidence of movement correlated to the number of bolus doses of the study drug as it was administered when the patient responded to surgical stimulus. In our study, the number of patients requiring bolus doses was significantly higher in group A

compared to Group B. This was in concurrence with a study conducted by Hosni A Salem et Al8 on ketofol combinations where 70% of the patients in lower ketamine concentration required bolus doses compared to 40% of patients in the other group. Daabiss et al7 found that the average ketofol infusion rate which was titrated to treat discomfort during the procedure was higher in lower ketamine concentration which was in consistence with our study. Another study conducted by Badrinath et al11 found that 1:5 and 1:3 ketofol groups required no rescue bolus doses whereas rescue bolus doses were needed for the 1:10 ketofol group.

Time required for the patient to reach a Ramsay sedation score of 6 after an induction dose was found to be significantly higher in group A compared to group B respectively. However, a study conducted by Badrinath et al11 comparing different ketofol combinations found no difference in the time required to achieve the desired Observer Assessment of Alertness score. This could be possibly due to the different concentrations of ketamine in the ketofol groups studied. While they used 1:10, 1:5 and 1:3 proportions of ketofol, our study compared 1:2 and 1:4.

The volume of the drug required to induce the patients was significantly higher in Group A compared to Group B. Similarly, Ghadami Yazdi et al9 conducted a study

on ketofol combinations and observed the volume of drug required to reach Ramsay sedation score of 5 was more 1:3 ketofol compared to 1:2 ketofol group.

Our study showed that the number of bolus doses given when there was a response to the surgical stimulus was insignificant in both the groups though Group A(1.04) needed a higher number of bolus doses compared to Group B (0.90). A similar observation was made in studies conducted by Miner et al12 and Badrinath et al11where they didn't find any statistical difference. However, in a study by Chahyun Oh et al6 comparing two ratios of ketofol with propofol alone as procedural sedation, they observed a statistically significant difference in the number of bolus doses needed during the procedure to maintain the desired Ramsay sedation level; the number of bolus doses being higher in the group with lower ketamine concentration.

The total volume of drug used was not statistically different in our study although it was observed to be lower in Group B. Similarly, in the study concluded by Miner et al12 the total sedative bolus dose requirement was higher in the lower ketamine concentration group.

Our study did not find any statistically significant difference in the hemodynamic parameters measured through out the procedure except at 12 and 14 mins where the MAP was lower in the higher ketamine group. Similarly, previous studies by Badrinath et al26, Salem et al8 and Daabis et al7 found insignificant results. However, Ghadami et al9 found a significant reduction in the RR post drug

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 09, 2022

induction and also at the arrival of the patient to the recovery room in 1:2 ketofol group compared to 1:3 ketofol group. The same study also observed a significantly lower MAP in 1:2 group on the patient's arrival to recovery room.

The need for airway intervention in our study was insignificant between the two groups. Similar results were seen in studies conducted by Hosni et al8and Ghadami et al9. However in the studies conducetd by Chahyun Oh et al6and Daabis et al7 there was a statistically significant difference in the need for airway intervention in the groups receiving higher ketamine in the ketofol mixture. The difference in the findings could be due to the increased salivation with higher dose of ketamine in the ketofol mixture which led to impaired breathing and increased need for airway support.

The awakening time in both groups was statistically and clinically insignificant in our study. Similar results were found in a study conducted by Miner et al27. However, studies conducted by other authors7,9 found significantly longer recovery time.

We noticed recovery agitation in 1 patient of Group B and and none in Group A. It was transient and the patient did not require any restrain or use of opioids or benzodiazepines. Similar results with no difference in the incidence of recovery agitation was found in studies conducted by Salem et al8and Chahyun Oh et al6. however, in studies conducted by Daabiss et a7 and Miner et al27, a higher incidence was found in the group receiving 1:1 ketofol compared to the other group. This could be due to the higher concemtration of ketamine in 1:1 ketofol group.

The incidence in PONV in PACU in our study was found to be statistically insignificant. Similar results were found in studies conducted by previous authors like Hosni et al 8and Ghadami et al9 Daabiss et al7 and Kritagya Shukla et al 13 Badrinath et al11 and Pulak P.Padhi14

One patient of Group A in the entire study experienced recall of intraoperative events which was not statistically significant. Similar results were documented by Badrinath et al11 and Chahyun Oh et al6.

Conclusion :

1. The volume of drug needed to induce the patient was significantly lower in Group B when compared to group A.

2. The time duration required to reach a Ramsay sedation score of 6 was significantly lower in group B compared to group A.

3. The time for administering 1st bolus and the total number of rescue bolus doses were similar in both the groups.

4. The time for awakening was similar in both the groups.

5. The total volume of study drug and the total duration of procedure were not statistically different between the two groups.

6. There were no major adverse effects noted in the study. The incidence of PONV, airway intervention, intra operative recall of events and recovery agitation was similar in the two groups.

REFERENCES:

1. Zimmer M. History of anaesthesia: early forms of local anaesthesia. Eur JAnaesthesiol. 2014 Jan;31(1):1-12.

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 09, 2022

2. Işık, Yasemin et al. “Comparison of propofol and ketofol in minor gynecologicinterventions.” Journal of Clinical and Experimental Investigations(6).2015: 244-9.

3. Chen, Wei-Xing, Hui-Jia Lin, Wei-Fang Zhang, Qing Gu, et al. Sedationandsafety of propofol for therapeutic endoscopic retrograde cholangiopancreatography. Hepatobiliary Pancreat Dis Int(4).2005: 437-40. 4

4. Barash PG, Cullen BF, Stoelting RK, Cahalan MK,Stock MC, Ortega R. Clinical Anesthesi:Seventh edition. Wolters Kluwer Health, 2013.

5. Aouad M, Moussa A, Dagher C, Muwakkit S, et al. Addition of ketamine topropofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemodynamic stability. Acta AnaesthesiologicaScandinavica. 2008;52(4):561-5

6. Oh C, Kim Y, Eom H, et al. Procedural Sedation Using a Propofol-KetamineCombination (Ketofol) vs. Propofol Alone in the Loop Electrosurgical ExcisionProcedure (LEEP): A Randomized Controlled Trial. Journal of Clinical Medicine. 2019 Jun;8(7).

7. Daabiss M, Elsherbiny M, Al Otaibi R. Assessment of different concentrationsof ketofol in procedural operations. Saudi J Anaesth 2009;3:15-9.

8. Salem H. Low-Dose Ketamine and Propofol Combination for Upper Endoscopyin Morbidly Obese Patients. Global Journal of Anesthesiology. 2017;4(1):006-12

9. Ghadami Yazdi A, Ayatollahi V, Hashemi A, Behdad Sh, Ghadami Yazdi E. Effect of two Different Concentrations of Propofol and Ketamine Combinations(Ketofol) in Pediatric Patients under Lumbar Puncture or Bone MarrowAspiration. Iran J Ped Hematol Oncol. 2013;3(1):187-92.

10. Willman EV, Andolfatto G. A prospective evaluation of "ketofol"(ketamine/propofol combination) for procedural sedation and analgesia intheemergency department. Ann Emerg Med. 2007 Jan;49(1):23-30.

11. Badrinath S, Avramov MN, Shadrick M, Witt TR, Ivankovich AD. The use of aketamine-propofol combination during monitored anesthesia care. Anesth Analg. 2000;90(4):858-62.

12. Miner JR, Moore JC, Austad EJ, Plummer D, Hubbard L Gray RO. Randomized, double-blinded, clinical trial of propofol, 1:1 propofol/ketamine, and 4:1 propofol/ketamine for deep procedural sedation in the emergency department.Ann EmergMed2015;65(5):479-88.

13. Shukla, Kritagya and Shaila Surendra Kamath. “Comparison of propofol ketamine versus propofol fentanyl as combination for total Intravenous anesthesia on short gynecological procedures.” Journal of Pharmaceutical Research 12 (2020): 1591-1596.

14. Padhi, Pulak Priyadarshi et al. “Procedural Sedation Using Two Different Proportions of Ketamine-Propofol Combination in Short Gynecological Procedures: A Randomized Controlled Trial.” Cureus 14 (2022): n. pag.