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A COMPARITIVE STUDY OF TWO DIFFERENT DOSES OF KETAMINE/PROPOFOL (KETOFOL) IN DAY CARE GYNAECOLOGICAL PROCEDURES IN INDIA

Srikanth S[1], Manoj Kumar Vallury[2]*

[1]Associate Professor of Anaesthesiology, Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, (Affiliated to Bharath University, Chennai), India
[2]Assistant Professor of Anaesthesiology, Sri Lakshmi Narayana Institute of Medical Sciences, Pondicherry, (Affiliated to Bharath University, Chennai), India

ABSTRACT
The combination of propofol and ketamine (ketofol) is mostly used for short procedural sedation and analgesia. Various combinations of ketamine and propofol doses have been used in this aspect. This study was conducted to compare the two different combinations of ketamine with propofol in providing adequate procedural sedation without limb movement in patients undergoing day care gynaecological procedures. This study also evaluated the hemodynamic stability, sedation level, post procedural analgesia and the time needed to discharge patients from the recovery room. Fifty patients of ASA Physical Status I and II undergoing day care gynaecologic procedures were categorized into 2 groups, each group having 25 patients. Group A patients received 1ml/kg of propofol and ketamine 0.25mg/kg. Group B patients received 1ml/kg propofol and ketamine 0.5 mg/kg. Adequacy of procedural sedation and analgesia was assessed with incidence of limb movements during procedure. In recovery room VAS (Visual Analogue scale) score, modified sedation score, modified Aldrete score and side effects were noted. The results were analyzed using SPSS 16.0. The incidence of limb movements during the procedure was 3(12%) in group B and 9(36%) in group A. Mean VAS score at 1hr was high in group A compared to Group B. Haemodynamic measurements, sedation score and postoperative side effects were comparable. Ketofol(1:2) combination is the most appropriate dose for procedural sedation in day care gynaecological procedures with less postoperative side effects and short recovery time.

Key words: Ketofol, Day Care Gynacological Procedures, Procedural Sedation And Analgesia.

INTRODUCTION

Day care gynaecological procedures, form the most essential component in day to day gynaecology practice. Mostly, the procedural sedation and analgesia (PSA) is preferred than regional anaesthesia for these gynaecological procedures due to rapid recovery and early discharge from the hospital. PSA facilitates the patient to maintain oxygenation and airway control independently.[1] The most frequently used pharmacological agent in PSA is propofol. The effect of propofol is usually augmented with an opioid (e.g., remifentanil, fentanyl, sufentanil) and/or ketamine. So far, none of the available pharmacological agents can be used as a sole anaesthetic agent that could act as an ideal intravenous anaesthetic agent. The combination of ketamine with propofol commonly known as ketofol, reduces the patient movement that can arise due to inadequate sedation and also provides better hemodynamic and respiratory stability. [1, 2]

Ketofol is a combination of ketamine and propofol and this has been recently popularized in the emergency department setting for short procedures. [3] Propofol is a nonbarbiturate sedative-hypnotic agent. Propofol is used as a general anaesthetic in operating

Corresponding Author: - **Dr. Manoj Kumar Vallury**

rooms, also outside operating rooms. It is used as a continuous infusion for sedation in ICU. Propofol is the most commonly used drug in the outpatient setting because of its rapid onset and short duration of action. However, propofol's inability to reliably provide adequate analgesia prevents it from being the sole anaesthetic for any painful procedure.[4] Ketamine provides dose-dependent amnesia like propofol, but it has the additional benefit of bronchodilatation with maintenance of spontaneous respirations and airway reflexes at clinical doses. Ketamine's disadvantages include sympathomimetic reactions, aggravation of laryngospasm, increased intracranial pressures, and worsened postoperative nausea and vomiting (PONV). At higher doses or with rapid infusions, ketamine can paradoxically induce respiratory depression, but this effect is uncommon with levels used for sedation. [5, 6]

Many studies concluded that, ketofol significantly decreases the incidence of hypotension, bradycardia, and respiratory depression while simultaneously improving analgesia when compared to propofol alone. There is an uncertainty about the analgesic dose of the ketamine with propofol that will be appropriate in reducing the patient's limb movements and also minimizing the side effects.

We therefore, conducted this prospective, randomized trial to compare the two different combinations of ketamine with propofol in patients undergoing day care gynaecological procedures. This study also evaluated the hemodynamic changes, sedation level, post procedural analgesia and the time needed to discharge patients from the recovery room.

MATERIALS AND METHODS

The study was approved by the institutional ethics committee from Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry and written informed consent was obtained from each subject. Fifty female patients of ASA physical status I and II aged 20-60 years who underwent day care gynaecological procedures like hysteroscopy, dilatation and evacuation (D&E) and dilatation and curettage (D&C) were included in this prospective randomized double blinded, clinical trial.

Exclusion criteria included allergy or contraindication to propofol and ketamine, patient's refusal, head injury, seizure disorder, psychological disorders, severe hypovolemia, inability to undergo general anaesthesia and chronic narcotic usage. A detailed preanaesthetic checkup of the patients was done before the procedure and they were kept in fasting for 6 hrs. The randomization was performed by computer generated random numbers and allocation concealment was done by prefilled numbered syringes. The standard solutions were 50 mg/ml ketamine and 10 mg/ml propofol. For blinding, transparent syringes containing either 25mg or 50 mg ketamine made up to 1ml normal saline, and then added to 10 ml syringes containing 10 ml of propofol.

This was done by a separate anaesthesiologist who was not aware of the study protocol and data collection during the study. The patients were also not aware of the group allocated to them. Patients were randomly allocated and divided into two groups of 25 each. Group A patients received 1ml/kg of propofol and ketamine 0.25mg/kg. Group B patients received 1ml/kg propofol and ketamine 0.5 mg/kg. In the operating room, an IV line was secured with 20-G venous cannula and Ringer's lactate infusion was started. The baseline monitors like electrocardiogram (ECG), pulse oximetry, noninvasive blood pressure (NIBP) were attached. The baseline values of heart rate (HR), oxygen saturation (SpO_2), blood pressure (BP) were recorded. The patients were premedicated with intravenous 0.2mg injection glycopyrrolate 10 minutes before the procedure and oxygen 6 L/min was given through a face mask. All the patients received fentanyl in a dose of 1.5 mcg/kg IV.

The induction of anaesthesia was done using a prefilled ketofol 1ml/10kg bolus dose to reach modified Ramsay sedation score value of 4-5. The patient's sedation level was evaluated and ketofol was administered by using the Modified Ramsay sedation scale (RSS) throughout the whole procedure.[7] If RSS was < 4 at any time during the procedure and if the patient had any limb movements incremental ketofol dose 2ml was given and repeated after 3 minutes if necessary. The patients were also assessed for apnoea, i.e. the loss of respiratory efforts for more than 20 seconds and oxygen desaturation i.e. SpO2 below 93%.

The parameters like mean arterial pressure (MAP), heart rate, respiratory rate and Spo2 were observed at baseline, 1min after induction and thereafter every 5 min till completion of 30 minutes. Hypotension was defined as a decrease in systolic arterial blood pressure >20% of baseline and was treated with intravenous (IV) 5 mg bolus dose of ephedrine. Bradycardia was defined as heart rate <50 beats per minute and were treated with 0.6 mg bolus dose of atropine. Respiratory depression was defined as respiratory rate <8 and was intervened with bag- mask ventilation.

In the recovery room pain intensity was measured on a visual analog scale (VAS) graded from 0 (no pain) to 10 cm (the maximum pain imaginable). The rescue analgesia was obtained with injection paracetamol 1gm iv over 15 minutes when the pain score was ≥4.The time of first rescue analgesic administration was noted. Postoperative side effects like nausea, vomiting, hallucination, coughing and desaturation were recorded. When the patient had a sedation score of 4 and above, supplement oxygen 4 L/min was administered and an alert was given to the anaesthesiologist. The drug injection ondansetron 4 mg was given slow IV in patients who complained of nausea and vomiting. The patient's recovery from anaesthesia was assessed and the time taken to achieve Modified aldrete score >8 was noted.

Statistical analysis

The data were analyzed using appropriate descriptive and inferential statistics using SPSS 16.0-Software. Normally distributed interval and ratio data were analyzed using the student t test. Categorical data were analyzed using Chi-square or Fischer Exact whichever is appropriate. A p-value <0.05 was considered to be significant.

RESULTS

In our study both the groups were comparable in terms of age, weight, height, body mass index, ASA physical status, type of surgeries and duration of procedure ($p > 0.05$) (Table- 1).

Ratio or interval data are expressed as mean ± SD. ASA I/ II and type of procedures are expressed as numbers. The parameters like heart rate and mean arterial pressure were recorded in two groups at specified intervals are shown in [Table 2], [Figure 1]. There was no significant difference in baseline heart rate and mean arterial pressure among the two groups (p>0.05).

Though Group A patients had higher mean arterial pressure and heart rate at all intervals, the differences were statistically insignificant. There were no difference in SpO2 level and respiratory rate between two groups at all intervals (p>0.05). None of the patients in both groups had developed apnoea or bradycardia.

The incidence of limb movements during the procedure was 3(12%) in group B and 9(36%) in group A. This difference was statistically significant (p<0.05)(Table-3).

There were no statistically significant difference in the time of first rescue analgesia and the time to achieve Modified aldrete score >8 among the two groups (p > 0.05) (Table-3).

Mean VAS score at 1hr was 4.3 ± 1.83 in group A and 3.12 ± 1.13 in group B (Table-4), and this difference was statistically significant (p <0.05). There was no statistically significant in mean VAS scores among the two groups at 2 hr interval and thereafter till the study was completed (P >0.05).

There was no statistically significant difference in mean Sedation scores after the procedure throughout the study period (p >0.05) (Table-5).

The incidence of desaturation, coughing, hallucination and nausea and vomiting (PONV) are shown in Table-6 and the differences between the two groups were statistically not significant (p > 0.05).

Table 1: Patients basic demographic characteristics and clinical data

Variable	Group A (n=25)	Group B (n=25)	P value
ASA I/II (n)	22/3	21/4	>0.05
Age (years)	35.8 ± 8.6	34.3 ± 6.5	>0.05
Weight(kg)	72.3 ± 5.1	74.5 ± 5.9	>0.05
Height (m)	1.63 ± 0.7	1.62 ± 0.8	>0.05
BMI ($m^2.kg^{-1}$)	26.93±1.5	26.12 ± 1.7	>0.05
D&E/D&C/Hysteroscopy	15/4/6	13/5/7	>0.05
Duration of procedure (min)	9.3 ± 2.1	10.36 ± 2.5	>0.05

Table 2: Effect of Ketofol at two difference doses on heart rate

	Group A	Group B	P value
Baseline	101.32 ± 12.07	97.92 ± 13.97	$p > 0.05$
1 min after induction	111.2 ± 11.47	103.44 ± 13.77	$p > 0.05$
5 min	102.68 ± 12	96.96 ± 13.72	$p > 0.05$
10 min	100.04 ± 12.41	96.72 ± 13.52	$p > 0.05$
15 min	100.16 ± 11.77	95.48 ± 13.81	$p > 0.05$
20 min	99.8 ± 12.74	93.56 ± 12.88	$p > 0.05$
25 min	99.8 ± 12.74	95.84 ± 14.34	$p > 0.05$
30 min	98.36 ± 12.77	94.92 ± 13.85	$p > 0.05$

Table 3: Effect of Ketofol at various doses on limb movement, first rescue analgesic time and time for recovery

	Group A	Group B	p value
Limb movement n (%)	9(36%)	3(12%)	p <0.05
Time of first rescue analgesia (Mean± SD)	37.5 ± 5.3	42 ± 4.8	p > 0.05
Time to achieve aldrete score >8 (Mean ± SD)	138.8 ± 34.43	146.4 ± 34.86	P > 0.05

Table 4: Effect of ketofol at two different doses on VAS score

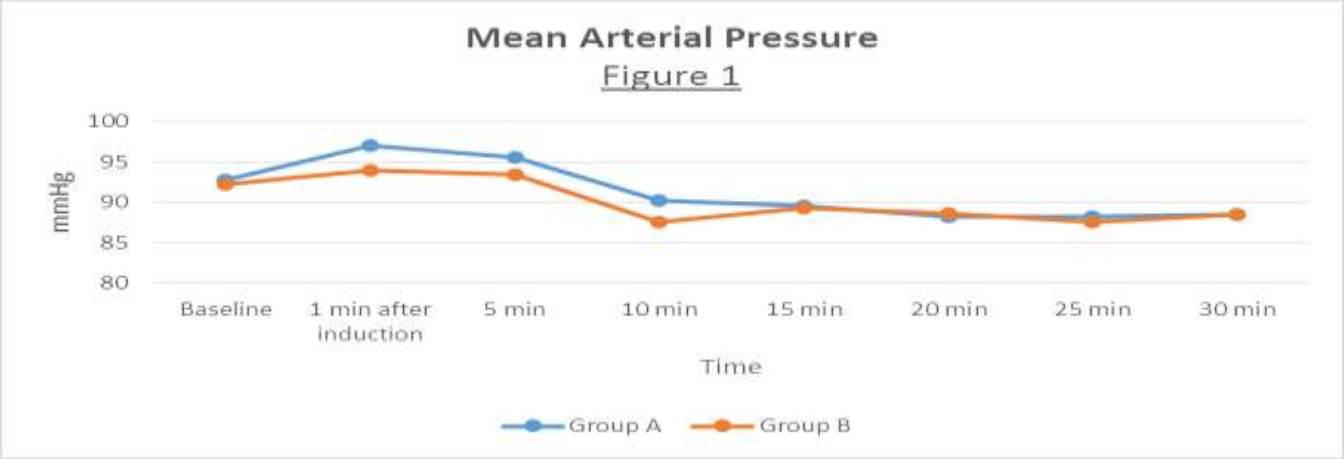
	Group A (Mean ± SD)	Group B(Mean ± SD)	P value
1 hr	4 ±1.83	3.12 ± 1.13	p <0.05
2 hr	3.36 ± 1.85	2.24 ± 2.2	P > 0.05
3 hr	1.36 ±1.35	1.68 ± 1.31	P > 0.05
4hr	0.52 ± 0.92	0.44 ± 0.51	P > 0.05
5 hr	0.48 ± 0.51	0.4 ± 0.58	P > 0.05
6 hr	0.2 ± 0.48	0.2 ± 0.41	P > 0.05

Table 5: Sedation score

	Group A(Mean ± SD)	Group B(Mean ± SD)	P value
1 hr	3.2 ± 1.08	3.92 ± 1.47	P > 0.05
2 hr	2.56 ± 0.51	2.8 ± 0.58	P > 0.05
3 hr	1.28 ± 0.46	2.2 ± 0.58	P > 0.05
4hr	1.08 ± 0.28	1.2 ± 0.41	P > 0.05
5 hr	1.04 ± 0.20	1.12 ± 0.33	P > 0.05
6 hr	1	1	P > 0.05

Table 6: Side effects of two various doses of ketofol in the groups

Side effects	Group A	Group B	P value
PONV	3	5	$p > 0.05$
Hallucination	1	3	$p > 0.05$
Coughing	1	1	$p > 0.05$
Desaturation	1	2	$p > 0.05$



DISCUSSION

The present study identified that there is a significant difference in the limb movements between the two doses of ketofol whereas there is no difference in sedation score, VAS score among the groups. Sedative and analgesic agents are essential components of procedural sedation. Procedural sedation is defined as "a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function.[1] Propofol and ketamine are commonly used for procedural sedation and analgesia in the emergency department.[8]

Propofol possesses amnesic and antiemetic properties. It results in a dose-dependent reduction in mean arterial pressure (MAP) and respiratory drive. When used for deep sedation, propofol have anti-nociceptive properties through suppression of cortical activity and responsiveness.[4] Ketamine is a dissociative analgesic and anaesthetic, it acts primarily through noncompetitive antagonism of the *N*-methyl-D-aspartate receptor. Ketamine is classically associated with a emergence phenomenon which is common in adults. Both midazolam and propofol are used to prevent and treat this undesirable phenomenon.[5,9] The combination of ketamine and propofol (ketofol) lowers the requirement of each agent thereby decreasing undesirable adverse effects of both

agents while maintaining optimal conditions for performing procedures.[9]

Hegazy et al found that the combination of propofol and sub-dissociate dose of Ketamine [Ketofol] was superior to Propofol alone in providing adequate sedation and analgesia for uterine cervical dilation and curettage procedures.[10] These findings support our study. In another study by walravens et al, concluded that ketofol in a 1: 4 ratio appears safe and effective for use in the emergency department procedural sedation.[3] Similarly in our study 0.25mcg/kg ketofol had very few side effects and early recovery observed. A study by kip et al reported that 1:2 combination of ketofol provided better analgesic and sedation with minimum side effects compared to 1:4 ketofol group in dental procedures.[11] These findings were comparable to our study. We also found that statistically decreased limb movements and better analgesia with 1:2 combination of ketofol when compared to 1:4 ketofol.

Ghadami Yazdi *et al* compared two different combinations of Ketofol 1:2 and 1:3, for lumbar puncture or bone marrow aspiration in pediatric patients. They observed that lower doses of ketamine in these combinations caused lower psychomimetic side effects and shorter recovery time. [12] In a study by Salem *et al* compared two different combinations of Ketofol (1:1 and 1:4) for procedural sedation and analgesia in patients undergoing upper gastrointestinal endoscopy procedures. He recommended that, the combination of ketamine and propofol 1:4 dose was associated with a short recovery and less psychotomimetic side effects. [13] In another study by Daabiss *et al* studied two different combination of Ketofol 1:1 and 1:4 in children undergoing procedures esophagoscopy, rectoscopy, liver biopsy and BMA and concluded that 1:4 dose of ketofol combination minimizes the psychomimetic side effects and encourages early discharge from the hospital compared to 1:1 combination of ketofol.[14] In our study also, lower dose of ketofol (1:4) had lesser side effects and short recovery time compared to 1: 2 combination of ketofol. But the patients in 1:4 combination group had significantly higher incidence of limb movements.

Ayatollahi et al performed a study on two concentrations (1:3 and 1:1) of ketamine and propofol in closed reduction of the nasal bones. There was a decrease in recovery time, hallucination, and vomiting in the low dose ketamine group compared with the other group.[15] These findings comparable to our study. Oh et al assessed two different doses of ketofol and propofol alone for PSA in loop electro excision surgical procedure. He concluded that propofol–ketamine combination is more effective than propofol alone. He also found that the incidence of adduction movement was 10% in 0.66mg/kg ketofol compared to 32.5% in 0.33mg/kg ketofol.[16] In our study also limb movements were less in 0.5mg/kg ketofol group compared to 0.25mg/kg ketofol group. Miner et al found a similar frequency of airway and respiratory adverse events leading to intervention between propofol alone and either 1:1 or 1:4 ketofol in emergency department adults undergoing deep sedation.[17] These findings were comparable to our study.

CONCLUSION

We recommend that, the 1:2 combination of ketamine/propofol (ketofol) for procedural sedation in day care gynaecological procedures as it provides reduced limb movements during procedure, stable sedation levels, lesser postoperative side effects and short recovery time.

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