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"A Comparison Of Two Different Proportions Of Ketofol With Fentanyl-Propofol For Day Care Gynecological Procedures: A Randomized Double-Blind Trial" In Karpagavinayaga Institute of Medical Sciences, Maduranthagam.

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Abstract
Background: *Ketofol is a combination of ketamine and propofol in a single syringe which can be prepared in any desired concentration. Several gynecological procedures like tubal sterilization, dilatation and curettage, cervical polypectomy, fractional curettage are of short duration and just require analgesia and moderate sedation. A study was conducted to compare two different proportions of ketofol, with reference to the duration and level of sedation, quality of analgesia, hemodynamic and respiratory profiles, and to compare all the above effects with the well-tried propofol-fentanyl combination.*
Materials and Methods: *This prospective randomized double-blind study was conducted on 60 adult females scheduled for elective day care gynecological procedures. Patients received a slow bolus injection followed by small aliquots of ketofol containing ketamine: Propofol (1:1) (group A), ketamine: Propofol (1:2) (group B), and fentanyl: Propofol (group C) to a predetermined sedation level using Ramsay Sedation Scale. Vital signs, oxygen saturation, and incidence of any side effects were recorded.*
Results: *Ketofol in groups A and B was comparable in onset of sedation (A: 1.59 ± 0.58 min, B: 1.60 ± 0.72 min), intraoperative sedation scores (A: 5.60 ± 0.5, B: 5.85 ± 0.3), and recovery times (A: 4 ± 1 min, B: 3.5 ± 0.67 min). There was no significant difference in the hemodynamic and respiratory profile of ketofol in groups A, B, and C. Considering the onset of sedation, intraoperative sedation score, and recovery time, group C (fentanyl-propofol) patients were less sedated than their counterparts in ketofol group A and B. Furthermore, considering the verbal rating scale for pain at 15 min postoperatively, group C patients had poor analgesia compared to group A and B.*
Conclusion: *Though ketofol in a ratio of 1:2 provides better sedation level compared to the other groups, both ketofol ratios (1:1 and 1:2) were similar in terms of providing hemodynamic and respiratory stability and producing adverse effects.*
Key words: *Analgesia, fentanyl, ketamine, minilaparotomy, propofol, sedation, day care procedures*

I. Introduction

The recommended anesthetic regimen for day care gynecological procedures is moderate sedation/ analgesia in combination with local anesthesia.[1] Moderate sedation/analgesia with local anesthesia entails less cardio-respiratory depression, lower peak drug blood levels, faster recovery, adequate comfort, less cost, and thus a lower risk of unexpected and life-threatening complications than does deeper sedation or general anesthesia.[1-3] Ketofol, a combination of the drugs ketamine and propofol has good analgesic and sedative properties in addition to a fast onset of action thus making it ideal for short procedures.[4] Ketofol is a combination of ketamine and propofol in a single syringe and can be prepared in any desired concentration.[1] Ketamine and propofol are physically compatible for 1 h at 23°C and have been combined in different proportions for different surgical procedures.[5-9] With this background information, the present study was initiated to compare two different solutions consisting of ketamine and propofol in the concentrations of 1:1 and 1:2 with reference to the duration and level of sedation, quality of analgesia, hemodynamic and respiratory profiles and to compare all the above effects with propofol-fentanyl combination. The primary outcomes of our study included effect of study drug solutions on sedation, hemodynamic parameters, and respiratory parameters and on postoperative pain. The total amount of propofol consumption (mg/kg), surgeon satisfaction score, adverse events were the secondary outcomes.

II. Materials And Methods

A prospective, double-blind, randomized study was conducted in patients who underwent elective female sterilization by tubal sterilization, dilatation and curettage, cervical polypectomy, fractional curettage. The duration of surgery was 20 min. After getting approval by our Institutional Ethics Committee and obtaining written informed consent, 60 female patients between 18 and 40 years with physical status I and II were enrolled for the study.

They were randomly allocated using a computer-generated randomization list into three groups of 20 each. A sample size of 20 patients in each group was calculated so as to have a power of 99% and an α error of 0.05 to detect the expected differences among the three groups with respect to the mean Ramsay sedation score (RSS) with a confidence interval of 95%. Patients were excluded if they were drug abusers, had allergy to egg, hypersensitivity to ketamine or propofol, head injury, psychiatric illness, weight more than 70 kg, if posted for emergency procedure or laparoscopic sterilization, had deep scars on the abdomen with two or more previous lower segment caesarean sections or had any pelvic pathology.

In the OR, room temperature was kept at 23°C. The following parameters were noted before induction, every 5 min during the procedure and postoperatively at 5 min intervals for 20 min-heart rate (HR), noninvasive blood pressure that is, systolic blood pressure (SBP) and diastolic blood pressure (DBP), oxygen saturation (SpO2), and respiratory rate. All the patients were premedicated with injections ranitidine 75 mg, ondansetron 4 mg, midazolam 0.03 mg/kg, and glycopyrrolate 0.2 mg intravenously (IV) before induction. All patients received IV ketorolac 0.5 mg/kg preoperatively. The patients were randomly divided (computer generated) into three groups with 20 patients each: A, B, and C. The study was double-blinded with three different anesthesiologists involved. Patients in groups A and B received ketofol IV in a ratio of (ketamine:propofol) 1:1and 2:1, respectively, in 3 ml aliquots as initial dose until an adequate sedation of RSS 5-6 was achieved. The ketofol for group A was prepared by adding 2 ml of 50 mg/ml ketamine to 10 ml of 10 mg/ml propofol in a single syringe. The ketofol for group B was prepared by adding 1 ml of 50 mg/ml ketamine to 10 ml of 10 mg/ml propofol and 1 ml of 5% dextrose in the same syringe. The patients in group C received 2 ml (50 mcg/ml) of fentanyl mixed with 10 ml of 10 mg/ml propofol mixed in a single syringe in 3 ml aliquots IV as an initial dose and repeated until a RSS of 5-6 was achieved. The surgeons locally infiltrated 10 ml of injection lidocaine (1%) at the surgical site. The time to achieve the required goal of sedation was recorded. A score of 5 or 6 on the RSS was required to begin the procedure.

Adverse events such as apnea, hypotension, bradycardia, hypoxia, myoclonus, seizure, rash, and airway intervention during the procedure and emergence phenomena such as agitation, hallucinations, and vomiting after the procedure were recorded. The duration of surgery, total sedation time, and recovery time were recorded. The duration of procedure was defined as the time from local anesthesia infiltration until the last skin stitch. Those cases exceeding time duration of 20 min or those with an extension of the incision were excluded from the study. The recovery time was defined as the time taken from the administration of the last dose of the study drug to the point when the patient achieved a Modified Aldrete Score of 9-10. The total sedation time was defined as time from the first administration of the drug to the opening of eyes to verbal commands after surgery. The postoperative verbal rating for pain was done using verbal rating scale (VRS) 15 min after the procedure.

In case of failed sedation (defined as failure to achieve the desired level of sedation), the case was converted to general anesthesia and the patients were either mask ventilated, intubated with an endotracheal tube or laryngeal mask airway was inserted.Data were analyzed using Statistical Package of Social Sciences (SPSS) (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.) and presented as mean ± standard deviation. The data were compared using one-way analysis of variance test. *Post-hoc* analysis for multiple comparisons within the groups was performed with Tukey's honestly significant difference method. The Chi-square test was used to compare the adverse events, surgeon satisfaction, and verbal rating for pain between the different groups. A P value < 0.05 was considered significant.

III. Results

Sixty female patients were enrolled for the study. Demographic characteristics such as age, weight, and total procedure time among all the patients were comparable [Table 1]. With respect to the time for sedation, there was no significant difference between patients in group A and B ($P = 0.99$) but there was a significant difference between patients in groups A and C ($P < 0.05$) and patients in groups B and C ($P < 0.05$) [Table 2]. There was a significant difference between patients in groups B and C intra-operatively after 5 min and 15 min of induction ($P = 0.0022$) with respect to the RSS. Furthermore, there was a significant difference in RSS between patients in groups A and C after 5 min of induction [Table 4]. There was no statistically significant difference between patients in groups A and B with respect to recovery time. However, there was a statistically significant difference between patients in groups B and C ($P < 0.0001$) [Tables 2 and 3]. Mean total sedation time was prolonged in patients in group C as compared to groups A and B [Tables 2 and 3]. There was no

statistically significant difference between the three groups at induction, after 15 min of induction, at the end of the procedure and after the procedure with respect to pulse rate.

Characteristics	**Group A (N=20)**	**Group B (N=20)**	**Group C (N=20)**	**P Value**
Age(Yrs)	24.75±1.59	25.20±1.15	25.20±1.24	0.475
Weight(Kgs)	52.95±5.40	53.90±5.11	54.95±5.11	0.483
Duration Of Surgey(Mins)	18.70±2.56	18.35±1.35	19.10±1.52	0.458

Table 1. Demographic Characteristics

GROUPS	**MEAN±SD**		
	Time for sedation	**Recovery time**	**Total sedation time**
A	1.59±0.58	4.00±1.01	21.70±2.97
B	1.60±0.72	3.55±0.67	21.33±2.97
C	2.96±0.69	4.50±0.67	23.55±2.38
p Value	**0.0001***	**0.002***	**0.037***

Table 2. Comparison Of Three Groups With Respect To Time For Sedation, Recovery Time And Total Sedation Time. Analysed By One Way Anova.

Groups	**Recovery time**	**Total sedation time**
Group A vs B	p=0.15	p=0.8784
Group A vs C	p=0.073	p=0.1196
Group B vs C	**p □0.0001***	**p=0.00001***

Table 3: Pairwise Comparisons By Tukey's Multiple *Post-Hoc* Procedures

GROUPS	**5mins after induction**	**15 mins**	**At the end of the procedure**	**15 mins post op**
A	5.25±0.44	5.60±0.50	3.85±0.67	2.00±0.00
B	5.70±0.47	5.85±0.37	3.40±0.50	1.90±0.31
C	5.20±0.41	5.30±0.57	3.20±0.41	1.80±0.41
p	**0.0011***	**0.032***	**0.012***	0.1115
Pairwise comparisons by Tukey's multiple *post-hoc* procedures				
A vs B	**0.0061***	0.2451	**0.0284***	0.5379
A vs C	0.9322	0.1354	**0.0011***	**0.0418***
B vs C	**0.0022***	**0.0022***	0.4736	0.5379

Table 4: Comparison Of The Three Groups (A, B, C) With Respect To Ramsay Sedation Scores

A comparison of the patients in the three groups (A, B, C) with respect to SBP and DBP [Figures 1 and 2] showed that all the three groups were comparable throughout the procedure with respect to the SBP and DBP.

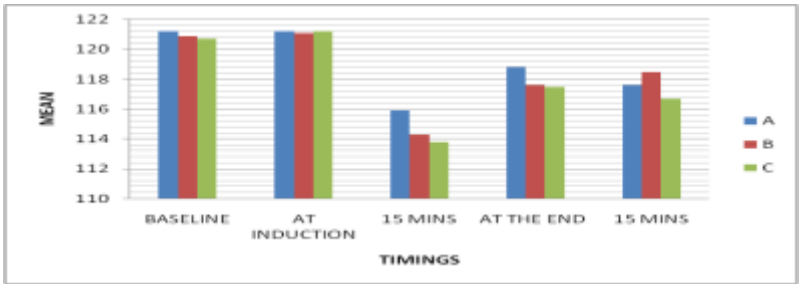

Figure 1: Comparison Of The Three Groups (A, B, C) With Respect To Systolic Blood Pressure: Values Are Expressed As Mmhg.

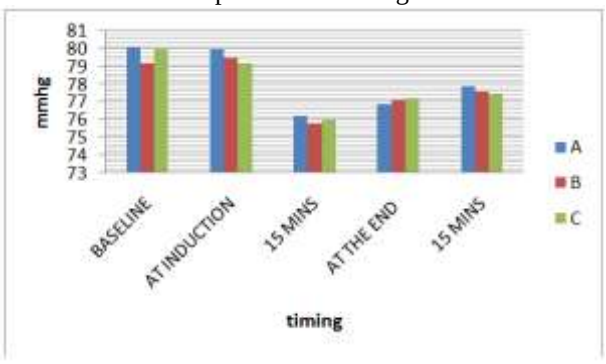

Figure 2: Comparison Of The Three Groups (A, B, C) With Respect To Diastolic Blood Pressure: Values Are Expressed As Mmhg.

All the three groups were comparable with respect to respiratory rate and SpO2 throughout the study. There was a significant difference in VRS for postoperative pain between the patients in the three groups (A, B, C) (P = 0.00001) [Table 5].

Verbal Rating	Group A (%)	Group B (%)	Group C (%)
Score 0	65.00	0.00	20.00
Score 1	35.00	45.00	40.00
Score 2	0.00	55.00	25.00
Score 3	0.00	0.00	15.00
Score 4-10	0.00	0.00	0.00
Total	100.0	100.00	100.00

Table 5: Comparison Of The Three Groups (A, B, C) With Respect To The Verbal Rating Scale For Postoperative Pain

The adverse events that occurred are as shown in [Table 6]. All the three groups were comparable with respect to the surgeon satisfaction score. Groups A and B showed a significant difference in consumption of propofol compared to group C such that propofol consumption was highest in patients in group C and was least in group A [Table 7].

Groups	Adverse Recations	Number Of Patients
A	Increased Secretion	1
	Tongue Fall	1
B	Intraoperative Apnea	1
	Postoperative Shivering	1
C	Restlessness	1
	Tongue Fall	1
	Vomiting	1

Chi-square: 0.2882, p = 0.8861

Table 6: COMPARISON OF ADVERSE EVENTS BETWEEN THE THREE GROUPS (A, B, C)

Groups	Amount Of Propofol Administered(Mg/Kg)
A	1.60±0.30
B	1.74±0.19
C	1.89±0.18
P	**0.0011***
Pairwise Comparisons By Tukey's Multiple *Post-Hoc* Procedures	
A Vs B	P=0.1411
A Vs C	**P=0.0010***
B Vs C	P=0.1241

Numerical data, analyzed by one-way ANOVA

Table 7: Comparison Of The Three Groups (A, B, C) With Respect To Amount Of Propofol Administered (Mg/Kg)

There were three cases of failed sedation in our study. Two of these patients who were from group C needed extra propofol with maintenance on oxygen and nitrous oxide via face mask to maintain required RSS. One from group B (ketofol 1:2) developed apnea and was ventilated with a laryngeal mask airway.

IV. Discussion

The aim of anesthesia in female day care procedures is to reduce the patient's anxiety and her perception and experience of pain to allow performance of a surgical procedure.[10] A number of studies have demonstrated that the combination of ketamine and propofol (ketofol) for sedation is safe and effective. Propofol and ketamine in combination have been found to oppose each other's respiratory and hemodynamic effects.[4,6] The combination appears to reduce each other's side effects and allows for a rapid recovery time.[5]

In the present study on ketofol, ketamine and propofol in the concentrations of 1:1 (ketamine 100 mg and propofol 100 mg) and in the concentrations of 1:2 (ketamine 50 mg and propofol 100 mg) were studied since studies have shown these ratios of ketofol to be effective for sedation and analgesia.[6,9,11,12] There are several studies that have compared ketofol in the two ratios in equal proportions used in our study.[9,12-14] However, these solutions have not been regularly used for tubal ligations. Moreover, there are no studies comparing ketofol in two different ratios for tubal sterilization. In the present study, propofol and fentanyl combination was used as the control group since it is a popular drug combination for procedural sedation and analgesia (PSA). Two earlier studies have compared ketofol with this combination.[6,15]

In the present study, ketofol in groups A and B achieved desired sedation level 5-6 on RSS faster as compared to that in group C (A: 1.59 ± 0.58 min, B: 1.60 ± 0.72 min, C: 2.96 ± 0.69 min). The RSS score was used in the present study as it is simple and easy to use.[16] Sedation scores were higher and better maintained in patients in group B (ketofol 1:2) who received higher amount of propofol intra-operatively compared to the patients in the other two groups (A: 5.60 ± 0.5, B: 5.85 ± 0.3, C: 5.30 ± 0.5). Several authors have recommended ketofol in the concentration of 1:2 as it provides effective sedation with a rapid recovery profile for PSA.[8,17] In contrast, some researchers have preferred a ratio of ketofol 1:1 because the mean propofol dosage and the number of over-sedated patients (sedation score >4) were higher in patients receiving a 1:2 combination.[7,9] In the present study, patients in both the ketofol groups maintained a higher RSS compared to fentanyl-propofol group intra-operatively. Similar results have been reported by Nejati *et al*., Tosun *et al*. who showed that the propofol-ketamine combination was superior to the propofol-fentanyl combination in view of more restlessness in patients given propofol-fentanyl.[18,19] In the present study, the mean total sedation time was comparable in both ketofol groups, and it was prolonged in the fentanyl: Propofol group similar to studies by Abdellatif and Timm *et al*.[12,20] In our study, there was no statistically significant difference between the three groups at induction, after 15 min of induction, at the end of the procedure and after the procedure with respect to HR, SBP, and DBP. There was no episode of hypotension or bradycardia in all the three groups. Many authors have shown similar results in their studies and found improved cardiovascular stability when using different mixtures of ketamine and propofol in comparison to either drug used alone.[21-24] In fact, some researchers of ketofol have reported significantly lower HR and better hemodynamic stability in patients who received ketamine and propofol compared to those who received propofol/fentanyl.[16,19,25] All these can be explained by the fact that propofol in the recommended dose of 2-2.5 mg/kg almost always causes a fall in blood pressure and the extent of this fall depends on the dose and the adjuvant drugs used. The addition of ketamine is thought to counteract the intraoperative cardiorespiratory depression that occurs when propofol is used alone.[12,13,26] There were no cases of oxygen desaturation in the present study. One patient in group B had apnea intra-operatively and SpO2 fell to 92% that required laryngeal mask airway insertion. The laryngeal mask airway was inserted after giving propofol. Nonetheless, some authors have shown that the addition of low dose ketamine to propofol improves ventilation and reduces the risk of respiratory depression, the need for repeat medication administration and apnea. All this may be due to ketamine-induced sympathoadrenal activation.[6,13,15,16]

In the present study, it was noted that the patients receiving ketofol (1:1) had better postoperative analgesia than the other two groups. These results may be due to the analgesic effect of ketamine in the higher ketamine concentration group (1:1). However, researchers like Willman and Andolfatto[7] have showed that patients receiving a 1:1 ketofol infusion experienced significantly higher VRS pain scores. The requirement of propofol was significantly lower in ketofol (1:1) group (mean dose 1.60 ± 0.3 mg/kg) in our study probably because the addition of ketamine decreases the consumption of propofol, thus suggesting synergism between the two drugs. The consumption of propofol was higher in the present study compared to that in studies by some authors.[7,26] This may be explained by the fact that the surgical procedure (minilaparotomy) in the present study was more invasive and hence needed higher degrees of sedation. There was no significant difference in the incidence of observed adverse effects between the patients in the three groups. It is postulated that the sedative and antiemetic effects of propofol may counter-balance the emetic and psychomimetic effects of ketamine.[16,26] Nonetheless, some other authors have reported less adverse effects of ketofol when compared to propofol alone. The possible explanation for this could be that the addition of ketamine to propofol provides an analgesic component and counterbalances the hemodynamic instability that can be caused by propofol alone. Ketamine also decreases the total dose of propofol needed for the same level of sedation. Moreover, propofol decreases the occurrence of postoperative emergence phenomena associated with ketamine use.[7,27] Our three groups did not exhibit any statistically significant difference in terms of surgeon satisfaction scores.

Nevertheless, our study has some limitations viz-the operating surgeon was not the same for all the study cases. Sedation scores using sophisticated monitors like bispectral index and electroencephalography could not be used due to nonavailability.

V. Conclusion

It can be thus concluded that ketofol in a ratio of 1:2 provides better sedation level compared to the other groups (propofol-fentanyl and ketofol 1:1). However, both ketofol ratios (1:1 and 1:2) were similar in terms of providing hemodynamic and respiratory stability and producing adverse effects. Ketofol (1:1 and 1:2) can be used for short surgical procedures like gynecological minilaparotomy, dilatation and curettage, cervical polypectomy, fractional curettage safely and effectively.

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