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Original Article

A PROSPECTIVE STUDY TO COMPARE 1:1 COMBINATION OF KETAMINE AND PROPOFOL (KETOFOL) WITH PROPOFOL ALONE IN DAY CARE PROCEDURES.

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Abstract:
Introduction: Ketamine and propofol are two anaesthetic commonly used for intravenous anaesthesia, in day care procedures, as they have desired characteristics like rapid induction and rapid recovery. Ketamine and propofol combination in 1:1 ratio is termed as ketofol, which has several advantages, due to their opposing physiologic effects. The present study was done to understand, whether ketofol is superior to propofol alone, and to assess their side effects. **Material and methods**: Prospective study, was done in 100 adult patients between, with ASA grade I and II, scheduled for day care surgeries in a hospital. Institutional ethical committee clearance and informed consent from patients were obtained. Patients were divided into two groups of 50 each and were administered total intravenous anaesthesia with ketofol or propofol alone, after premedication: Group A: received ketofol Group B: received Propofol alone. Continuous monitoring of patients in either group was done during induction, intra-op and in post operative recovery room for 1 hour. Induction, Time to loss of eye lash reflex, Time for incision, total drug used, adverse Events, hemodynamic changes, PONV, return of airway reflex, recovery time, VAS Score, recovery scale (using Modified Aldrete Scale) were recorded. Independent sample t test and chi-quare test was used, with $P<0.05$ as statistically significant. **Results: Conclusions:** The combination of propofol and ketamine has several benefits because of hemodynamic stability, lack of respiratory depression, good recovery and potent post-procedural analgesia.

Keywords: Ketofol, Propofol, day care procedures, modified aldrets scale, VAS pain score, Haemodynamic changes.

Introduction:

Ketamine and propofol are two anaesthetic commonly used for intravenous anaesthesia, in day care procedures, as they have desired characteristics like rapid induction and rapid recovery. Ketamine is characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. [1] Hence, best suited for short procedures. However, ketamine causes emesis and recovery agitation, which was not favoured by anesthetists, along with its prolonged recovery time compared to propofol .[2]

Propofol belongs to group of alkylphenols, it exerts its sedative hypnotic effects through interaction with GABA. The opposing physiologic effects of ketamine and propofol suggest the potential for synergy termed as ketofol, which has several advantages. These include [3]

- Hypotension from propofol balanced by sympathomimetic effects of ketamine
- Ketamine causes vomiting, whereas propofol has antiemetic properties,
- Respiratory depression seen in propofol potentially reduced with ketofol due to lower overall dose of propofol given (synergistic effect with ketamine)
- Propofol is not an analgesic but ketamine is an analgesic
- Reduced emergence reactions with addition of propofol to ketamine
- Shorter recovery time than ketamine alone
- When used in combination, the doses of each are reduced due to synergism
- Sedation may be smoother and more predictable with ketofol than with propofol alone.

Advantage of ketofol over propofol alone include deep sedation with lower doses of propofol, thus limiting propofol-associated adverse respiratory effects; the provision of ketamine analgesia without the increased adverse respiratory effects associated with concomitant opioid administration; and the mitigation of propofol-induced hypotension. Other advantages include shorter recovery time, lower incidence of ketamine-associated emesis and recovery agitation. Though there are many articles on ketamine-propofol combination, there is no comprehensive evidence, due to heterogeneity of clinical studies and various study designs.[4-11]

Hence this study was undertaken to assess, whether anesthesia with ketofol is superior to propofol alone, and also to evaluate its side effects.

Material and methods:

A prospective study was done in 100 adult patients, with ASA grade I and II, posted for short surgery. Patient who refused for the procedure and who did not give consent. Patient with a psychiatric history. Patient allergic to Ketamine or Propofol were excluded. After obtaining institutional ethical committee clearance and written informed consent, patients were divided into two groups of 50 each and were given total intravenous anaesthesia (TIVA) with 1:1 combination of ketamine and propofol or propofol alone, after appropriate premedication:

Group A: Patients received Induction by 1:1 combination of ketamine and propofol

Group B: Patients induction by Propofol alone

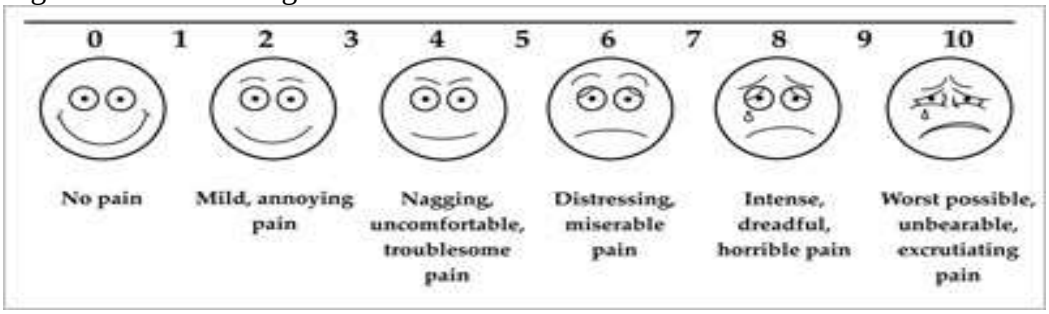
Procedure: Preanaesthetic checkup was done on the night before surgery, patients were explained about the type of surgery, type of anaesthesia. Visual Analogue Scale was shown to the patients to make them familiar to the scale, and their ability to comprehend the scale about their pain perception was confirmed. Patients vitals like pulse, systolic and diastolic blood pressure, and examination of cardio respiratory, CNS and abdominal systems were recorded periodically. Drugs used were Glycopyrrolate 0.004mg/kg, Fentanyl 3mcg/kg, Midazolam 0.03mg/kg for premedication. Ketofol and Propofol as anesthetic agents. Equipments used were monitors for continuous monitoring of vitals.

Anaesthetic technique:
Patients were taken to the operation theatre after confirming NBM status. Following monitors were attached to the patient: Pulse oximeter, Cardioscope (ECG), Blood pressure cuff and BIS strip.
Vitals like Pulse, BP, Respiratory rate were taken and noted. Intravenous cannula 18G was secured on non-dominant hand. Following preloading with ringer's lactate 5-8 ml/kg and premedication with Glycopyrrolate 0.004mg/kg, Fentanyl 3mcg/kg and Midazolam 0.03mg/kg, anaesthesia was induced with:
Group A: By 1:1 combination of ketamine and propofol
Group B: By Propofol alone
Continuous patients monitoring started soon after induction during intraoperative period and in post operative recovery room for 1 hour: Induction, time to loss of eye lash reflex, time for inscision, total drug used, adverse events noticed, hemodynamic changes (Pulse rate/min, Blood pressure – Systolic, Diastolic and Mean, Respiratory rate / min), respond to verbal command, return of airway reflex, recovery time, VAS Score, Recovery scale-Modified Aldrete Scale were recorded. Aldrete Scale is a simple numeric scale for discharge of patient with points of 9 or10 measured at the end of anaesthesia and1hr into the post operative period.[12]

Table 1. Modified Aldrete Scale

Characteristics		Score
Activity	Moves 4 extremities voluntarily o on command	2
	Moves 2 extremities voluntarily o on command	1
	Unable to move any extremities	0
Respiration	Able to deep breathe and cough freely	2
	Dyspnoea or limited breathing	1
	Apnoea	0
Circulation	Able to deep breathe and cough freely	2
	Dyspnoea or limited breathing	1
	Apnoea	0
Conscience	Fully awake	2
	Arousable on calling	1
	Not responding	0
Arterial oxygen	Maintains Sa02 >92% on room air	2
	Maintains Sa02 <90% on room air	1

Figure 1:Visual analogue scale



Statistical analysis**:** Data represented as mean (±SD), frequencies (number of cases) and percentages. Statistical analysis was done using Student t test for independent samples (age, weight, etc.), Mann–Whitney U test (Aldert's score, VAS Score), for comparing categorical data (gender, ASA grade, etc), Chi square test and Fisher's exact test was used instead when the expected frequency is less than 5 P-value < 0.05 was considered statistically significant. All statistical

analysis was done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 21.

Results:

Table 2: Distribution by patient characteristics in Group Ketofol versus Group Propofol

PARAMETERS	Sub- group	Group Ketofol	Group Propofol	P value
Age (years) Mean±SD		28.8±12.14	25.43±7.29	0.198
Sex	Male	14(46.6%)	16(53.4%)	0.7
	Female	34 (48.6%)	36(51.3%)	
Height (cms) Mean±SD		159.8±6.21	161.72±5.22	0.097
Weight (Kg) Mean±SD		50.2±4.58	49.4±3.38	0.445
ASA (n/%)	Grade 1	44(93.6%)	3(6.7%)	1
	Grade 2	49(92.4%)	4(7.6%)	
Time of loss of Consciousness (sec.)		40.8±7.76	49.6±3.5	<0.001

No difference was observed between groups on the basis of age, sex, height, weight, ASA grade and also with respect to duration of surgery (P>0.05). Mean time to loss of consciousness was significantly lower in Ketofol group compared to propofol group (40.8 vs 49.6 sec; p< 0.05).

Table 3: Distribution of Pulse rate in Group Ketofol versus Group Propofol

Pulse rate (per min)	Ketofol (N=50)		Propofol (N=50)		P value
	Mean	SD	Mean	SD	
0 min	78.7	8.956	78.4	5.157	0.631
1 min	75.4	7.147	74.8	5.235	0.819
2 min	73	6.2	72.9	5.341	0.76
3 min	72.23	6.886	71.93	4.362	0.669
4 min	71.9	6.988	71.57	6.055	0.78
5 min	71.07	7.508	70.77	6.218	0.76
10 min	71.33	7.372	71.03	6.631	0.91
15 min	71.1	6.682	70.97	6.955	0.832
20 min	70.27	5.937	69.97	5.129	0.786
25 min	71.3	4.552	71.07	4.464	0.521
30 min	72.3	4.792	72	4.68	0.314

No significant variation was observed in mean pulse rate between the two groups during the course of surgery (p> 0.05).

Table 4: Distribution of Mean arterial pressure in Group Ketofol versus Group Propofol

Mean arterial pressure (mmHg)	Ketofol (N=50)		Propofol (N=50)		P value
	Mean	SD	Mean	SD	
0 min	82.49	4.245	88.38	7.948	< 0.05
1 min	80.38	7.458	79.31	9.694	0.633
2 min	77.15	10.207	76.46	11.047	0.802
3 min	76.91	10.061	73.83	10.853	0.26
4 min	76.05	10.578	72.39	10.146	0.178
5 min	77.26	8.752	71.13	9.936	< 0.05
10 min	77.31	10.001	72.46	8.23	< 0.05
15 min	80.46	7.999	74.14	6.803	< 0.05
20 min	83.22	8.381	75.44	6.916	< 0.05
25 min	82.19	10.43	75.49	6.083	< 0.05
30 min	82.3	6.372	76	6.023	< 0.05

Significantly lower mean arterial blood pressure was observed in the propofol group compared to Ketofol group patients during the major part of surgery ($p< 0.05$).

Table 5: Distribution of modified Aldert's score in Group Ketofol versus Group Propofol

Modified Aldert's score	Ketofol (N=50)		Propofol (N=50)		P value
	Mean	SD	Mean	SD	
0 min	8.57	0.568	7.77	0.43	< 0.05
5 min	9.27	0.521	8.17	0.461	< 0.05
10 min	9.87	0.346	8.67	0.479	< 0.05
15 min	9.91	0.13	8.87	0.346	< 0.05
20 min	9.97	0.07	8.97	0.183	< 0.05
30 min	10	0	9.23	0.43	< 0.05
60 min	10	0	9.67	0.39	< 0.05

Significantly higher Aldert's score was observed in the Ketofol group compared to propofol group ($p< 0.05$).

Table 6: Distribution of VAS score **in Group Ketofol versus Group Propofol**

VAS Score	Ketofol		Propofol		P value
	Mean	SD	Mean	SD	
0 min	0	0	0.03	0.183	0.824
5 min	0.07	0.254	0.1	0.305	0.824
10 min	0.57	0.504	0.2	0.484	< 0.05
15 min	0.6	0.498	0.27	0.583	< 0.05
20 min	0.97	0.183	1.17	0.379	0.196
30 min	1.0	0.263	1.3	0.535	0.085
60 min	1.5	0.63	1.97	0.414	< 0.05

Significantly lower VAS score was observed in the Ketofol group compared to propofol group patients at 10, 15 and 60 minutes of surgery ($p< 0.05$).

Table 7: Distribution of Post operative symptoms in Group Ketofol versus Group Propofol

PARAMETERS	Sub- group	Group Ketofol	Group Propofol	P value
Post operative cough (n/%)	Present	4(8%)	5(10%)	0.317
	Absent	46(92%)	45(90%)	
Post operative nausea/ vomiting (n/%)	Present	3(6%)	5(10%)	0.793
	Absent	47(93.5%)	45(90%)	

No significant difference was observed between groups on the basis of occurrence of post-operative cough and post operative Nausea/ vomiting ($P>0.05$).

Discussion:

A Hospital based comparative study was conducted at a tertiary care hospital with the aim of comparing incidence of adverse events, recovery characteristics and quality of anesthesia with ketofol (1:1 combination of ketamine and propofol) versus propofol alone for short surgical procedures.

In the current study, No significant difference was observed between groups on the basis of baseline parameters like age, weight, ASA grade and also with respect to duration of surgery ($P>0.05$).Similar results were seen in study by Seyou Hailu et al.[13]

In this study Mean time to loss of consciousness was significantly lower in Ketofol group compared to propofol group (40.8 vs 49.6 sec; $p< 0.05$). Similar results were found by Green S et al. in a randomized double-blind study. They found that patients in the ketofol group had a significantly

shorter time until sedation (164 +/− 67 s) when compared to the propofol group (235 +/− 137 s). They conclude that adding ketamine to propofol resulted in faster onset of sedation.[14]

In this study No significant variation was observed in mean pulse rate between the two groups during the course of surgery (p> 0.05). In study by Seyou Hailu et al, There was a significant decrease in mean HR at 25th minute in the ketofol group (80.42 ± 11.800) as compared to propofol (86.68 ± 12.300) with a statistically significant difference of −6.258 (95% CI, −12.382 to -.134), t (60) = −2.044, p = 0.045. In all other levels, there was no significant difference (p > 0.05) between the two groups.[13]

In this study, Significantly lower mean arterial blood pressure was observed in the propofol group compared to Ketofol group patients during the major part of surgery (p< 0.05). In study by Aberra B With the induction of anesthesia, a significant drop in mean arterial blood pressure was observed in propofol group from baseline while in the ketofol group, there was a rise in mean arterial pressure at all measurement times ($P < 0.001$) [15] .Maximum mean blood pressure was 81.5 ± 11.02 mmHg with a ketofol group seen immediately after induction]. In study by Seyoum Hailu et al, There was a significant difference in mean MAP at 5th minute between the ketofol (90.74 ± 11.147) and propofol (81.77 ± 13.223) with a statistically significant difference of 8.968 (95% CI, 2.754 to 15.181), t (60) = 2.887, p = 0.005. [13]

In study by Damor P et al, blood pressure was better maintained in group K as compared to Group P. However, in Group P, fall in SBP and DBP was well within 20% of baseline. And none of the patient had fall in SBP 0.05, However, in Group P, fall in SBP and DBP was well within 20% of baseline. And none of the patient had fall in SBP 0.05, and DBP 0.05. So, none had hypotension and hence did not require any vasopressor treatment. Mean pulse rate was comparable in two groups at all time intervals, P>0.05. [16]

In this study, No significant difference was observed between groups on the basis of occurrence of post-operative cough and post operative Nausea/ vomiting (P>0.05).Study by Seyou Hailu et al In the ketofol group 3 patients (9.7%) developed PONV while only 2 patients (6.5%) in the propofol group developed PONV. There was no statistically significant association between the group of the study and PONV as assessed by Fisher's exact test, p = 1.000.[13]

A negative inotropic effect of propofol may be due to decrease in intracellular calcium availability secondary to inhibition of transsarcolemmal calcium influx. The relaxation of vascular smooth muscle produced by propofol is primarily due to inhibition of sympathetic vasoconstrictor nerve activity.Heart rate remain unchanged inspite of decreased systemic blood pressure during induction with propofol. Propofol may decrease sympathetic nervous system activity to a greater extent than parasympathetic nervous system activity, resulting in predominance of parasympathetic activity. Propofol depresses baroreceptor reflex control of heart rate. The heart rate may increase, decrease or remain unchanged when anesthesia is maintained with propofol. Ketofol, which is the combination of ketamine and propofol stimulates the cardiorespiratory system due to the sympathomimetic effects of ketamine. A direct effect increases cardiac output, arterial blood pressure, heart rate and central venous pressures. Therefore, it is a valuable agent for hypotensive or hypovolemic patients .

In this study Significantly higher Aldert's score was observed in the Ketofol group compared to propofol group (p< 0.05). No significant difference was observed between groups on the basis of occurrence of post-operative cough and nausea/ vomiting (P>0. 05). Akin A et al in their study noted that time to recovery was almost identical in the two groups, and the number of adverse events was not statistically different.[17] These findings led the authors to conclude that the addition of low-dose ketamine to propofol increases the quality of anaesthesia without prolonging recovery or increasing the incidence of adverse events.

Shah A et al compared ketofol with ketamine alone for Paeds-ortho reductions. The Ketofol produced slightly faster recovery, with less vomiting, higher satisfaction scores and similar efficacy.[18] Sing R et al. in a study concluded that the addition of low-dose ketamine to propofol for sedation during spinal anesthesia in pediatric patients provided better quality of sedation and

lowered the risk of respiratory depression because of propofol, without delaying recovery.[1] Contrary to other studies, we observed a faster recovery in ketofol group.
In present study we found ketofol to be both safe and efficacious but larger randomized, prospective studies are needed to further validate our findings.

Conclusions and limitations:

Ketofol is a combination of ketamine and propofol. It is an agent of choice for various procedures. The combinationof propofol and ketamine has several benefits because of hemodynamic stability, lack of respiratory depression, good recovery and potent post-procedural analgesia. Therefore, ketofol should be an ideal combination drug for procedural sedation but larger randomized, prospective studies are needed to further validate our findings.

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