Pharmaceutical Sciences Asia

Pharm Sci Asia 2025; 52(4), 541-560

DOI:10.29090/psa.2025.04.25.5178

Research Article

Comparative impact of ketofol vs propofol on postoperative cognitive, functional and pain outcomes in surgical patients

Daisy Priya Pugazhenthi[1], Abul Yasar. M[1], Dhanuja Ravichandran[1], Maheshwari Paramasivam[1*], Karthickeyan Krishnan[1], Shanmugasundaram Palani[2]

[1] Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai – 600117, Tamil Nadu, India

[2] Dean, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Pallavaram, Chennai – 600117, Tamil Nadu, India

ABSTRACT

Postoperative cognitive dysfunction is an emerging condition associated with surgery under general anesthesia, especially in elderly patients, with major detrimental health effects. To optimize anesthetic drug use, the study aimed to evaluate the effects of ketofol (ketamine-propofol combination) on postoperative cognition, pain, and functional recovery in comparison with propofol. In this prospective, observational, and comparative study, 52 patients were enrolled and divided into two groups based on the anesthetic agent employed for induction: either ketofol (Group KP) or propofol (Group P). Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) preoperatively and at 2, 24 and 48 hours post-surgery. Functional recovery was examined using the Modified Aldrete Score (MAS), and pain levels were recorded at the same time intervals using the Visual Analog Scale (VAS). Hemodynamics were also monitored during the procedure. Data were initially analyzed using the Mann-Whitney U Test and student's t-test; subsequently, Linear Mixed Models (LMM) were employed to adjust for potential covariates. MoCA scores at 24 and 48 hours were significantly higher in the ketofol group ($p = 0.001$ *and* $p = 0.002$), but MMSE scores showed no statistical difference. Pain scores were significantly lower in the ketofol group at 2, 24, and 48 hours ($p = 0.010$, $p = 0.001$, *and* $p = 0.0001$). However, LMM did not confirm these findings as statistically significant. Ketofol demonstrated better hemodynamic stability, especially in terms of systolic and diastolic blood pressure and SpO_2 readings. Although Ketofol was associated with better postoperative cognitive preservation, pain control, and hemodynamic stability compared to propofol in the unadjusted analyses, adjusted models indicated that these differences could be influenced by confounders such as age and gender, necessitating further investigation into its clinical use.

Keywords:
Cognitive dysfunction; Ketofol; Propofol; Pain; Postoperative; Recovery of function

1. INTRODUCTION

Postoperative cognitive dysfunction or decline (POCD) is one of the emerging clinical conditions in which there is a decline in the patient's cognitive abilities following a surgical procedure, and it can only be assessed through proper neuropsychological tests that compare baseline scores with postoperative scores. POCD is not yet a formal psychiatric diagnosis but is referred to as a cognitive decline that occurs in the first few days after surgery and may last for months to even years[2]. In more recent days, further research and systematic reviews have suggested POCD to be a serious public health problem, affecting not only older patients but also younger adults. The prevalence rates of POCD have been mentioned to range from 36.6% in

***Corresponding author:**
* Maheshwari Paramasivam Email: meswari.sps@vistas.ac.in

Pharmaceutical Sciences Asia © 2024 by
Faculty of Pharmacy, Mahidol University, Thailand is licensed under CC BY-NC-ND 4.0. To view a copy of this license, visit https:// www.creativecommons.org/licenses/by-nc-nd/4.0/

young adults to 42.4% in older people[3]. It is estimated that approximately 50% of the elderly around the world undergo at least one surgery in their lifetime, and around a quarter of the elderly population facing major surgery have an identifiable cognitive decrease, with 50% of these patients experiencing permanent cognitive damage[4]. Two main factors identified to have a temporal relationship with the development of POCD are surgery and anesthesia; however, causality cannot be guaranteed and has not been confirmed. Surgery and anesthesia are said to be causes of cognitive impairment post-operatively because of the inflammatory pathways triggered during the process, such as the release of pro-inflammatory cytokines into the bloodstream, possibly leading to neuroinflammation[5]. Several mechanisms have been elucidated to explain the pathogenesis of POCD, including cerebral inflammation, neuronal apoptosis, and synaptic plasticity[2,6-7] among other abnormalities. The diagnosis involves tests like the Mini-Mental State Examination (MMSE) and Abbreviated Mental Test (AMT) which are widely used on a global scale but lack the sensitivity and specificity required to address minute changes in the various cognitive domains[8]. The gold standard for assessing cognitive impairment would include the Montreal Cognitive Assessment Tool (MoCA), Addenbrooke's Cognitive Exam (ACE-III), and the Quick MCI Screen (Qmci)[8]. As of now, there is no specific treatment for POCD, and the worsening of the clinical condition is prevented by providing patients with symptomatic relief[9]. Improvement in patient care outcomes can be achieved through the cautious use of anesthetic agents and other drugs and the reduction of postoperative complications resulting from efficient cooperation among healthcare team members[7].

The anesthetic agents used during the intraoperative period influence patient outcomes even months after the surgery is completed. The choice of anesthetic drug and regimen impacts the patient's hemodynamic stability, as well as their inflammatory and neuropsychological responses. Propofol is a commonly used fast-acting intravenous anesthetic drug for induction and maintenance of anesthesia[10-11]. However, the use of propofol does have its own adverse effects, like dose-dependent respiratory depression, pain at the local site of injection, hypotension, and mild transient apnea[12-13]. Propofol also lacks an analgesic feature. Ketamine, on the other hand, is a dissociative anesthetic that provides profound analgesia and amnesia. It stimulates the activity of the sympathetic nervous system, resulting in increased heart rate, blood pressure, and doesn't cause any cardiovascular or respiratory depression[10,14].

Ketofol is a combination of the two anesthetic agents, propofol and ketamine. Recently, the research investigations regarding this mixture have increased, and more evidence is being gathered about the true effectiveness and safety of ketofol. Ketofol seems to be a promising drug combination as it neutralizes the opposing effects of the two drugs, thereby producing better hemodynamic stability and minimal adverse effects[10,12-13]. Ketofol also tends to have a positive impact on post-operative cognitive function and pain. Ketofol's influence on cognition has not yet been fully elucidated, and there have been very few studies conducted on the aspect of cognitive function. Despite the fact that ketofol has shown promising results in maintaining hemodynamic stability and providing better sedation, limited clinical studies have directly evaluated the effects of ketofol vs. propofol on early postoperative cognitive decline, creating a gap in evidence-based anesthetic decision making. There still remains a lack of knowledge on whether ketofol offers neurocognitive advantages in comparison to propofol, highlighting the need for further studies exploring the cognitive endpoints.

With this background, the objectives of the study are to i) differentiate the influence of ketofol vs propofol in postoperative cognitive function, to analyze which anesthetic agent results in a reduced cognitive impairment and ii) monitor and evaluate the functional recovery in patients anesthetized with ketofol vs propofol, as well as to assess and compare pain levels post-operatively between the two groups. The primary outcomes of interest of the study were postoperative cognitive function and pain. We hypothesized that patients receiving ketofol will exhibit less postoperative cognitive decline, better pain control, and a faster functional recovery compared to those receiving propofol alone.

2. MATERIALS AND METHODS

2.1. Study site and patient recruitment

This prospective, single-blinded, observational cohort study was carried out between November 2024 and May 2025 at ESI Hospital, Ayanavaram, Chennai, after receiving approval from the institutional ethics committee (IEC Number: ECR/288/Indt/TN/2018/RR-21/151, Date of Approval: 15/11/2024). The entire procedure and patient monitoring were carried out under the guidance and supervision of the chief anesthesiologist and anesthetic specialists of the respective study site. Written informed consent was obtained from all the participants prior to conducting the study. Fifty-two patients aged 18-70 years, belonging to the American Society of Anesthesiologists (ASA) physical grades I and II, with no previous cognitive disorders or impairment, were included in the study. Patients with a history of previous cognitive disorders or diseases, those allergic to the components of propofol and ketofol or having known contraindications to either drug, pregnant women more

than 20 weeks, and patients with underlying severe renal or hepatic diseases or dysfunction were excluded from the study. After obtaining informed consent, patients were then allocated to either the propofol or ketofol group based on the anesthesiologist's clinical judgment and the pharmacist's review, taking into account factors such as hemodynamic stability, comorbidities, contraindications, and past medication history. It is a single-blinded study, as the patients were unaware of the anesthetic drug administered to them.

2.2. Sample size calculation

The sample size was calculated using a Cohen's d of 0.8, as a conservative estimate, along with a significance level, α (alpha) = 0.05 and 80% power. A priori power analysis was conducted with G*Power 3.1.9.7 version software to yield a sample size of 52 participants. This estimate was used to guide patient recruitment and ensure adequate power within the practical constraints of the study.

2.3. Study instruments and data collection

A manual patient data collection form was designed to gather and record the important details on various study variables, including the participant demographics, like age, gender, body mass index (BMI), ASA class, past medical and medication history, surgical and anesthesia-related details, hemodynamic parameters, pre-operative and post-operative cognitive and pain assessment scores, the use of pain medications during their course of stay, and additional observations like adverse effects. Two questionnaires and two scales were employed in the study: the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE), the Visual Analog Scale (VAS), and the Modified Aldrete Score (MAS), respectively. The MMSE and MoCA are both validated tools to assess cognitive function. The MMSE consists of 11 questions testing five areas of cognitive function: orientation, registration, attention and calculation, recall, and language, while MoCA is a more sensitive screening tool for identifying mild cognitive impairment, exploring visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation. A decline in scores is usually indicative of cognitive impairment. To monitor postoperative pain and functional recovery, VAS and MAS were used to measure pain levels and determine the patient's readiness for discharge from the post-anesthesia care unit (PACU), respectively. Before the surgery was performed, the MMSE, MoCA, and VAS were administered to the patients, and the baseline scores were recorded. The patient's vitals, including blood pressure (BP), heart rate (HR), respiratory rate (RR), and oxygen saturation (SpO_2), were also measured before the surgery. The entire process of patient participation has been depicted in Figure 1.

2.4. Drug intervention and anesthetic procedure

Once the patient arrived in the operating room, intravenous access was established through a Venflon to administer the pre-medications, which included glycopyrrolate (0.2 mg), ondansetron (4 mg), dexamethasone (8 mg), and fentanyl (100 mcg). Midazolam (1 mg) is another pre-medication that was used mostly for patients allocated to the ketofol group. Inj. Loxicard (2%) was also administered to avoid the pain at the local site of injection. Three lead electrocardiography, pulse oximetry, and a non-invasive blood pressure cuff were used to monitor BP, HR, RR, and SpO_2, with the readings displayed on the multi-parameter monitor screen. Prior to sedation, oxygen supplementation was initiated at 100% oxygen at a rate of 10 L/min for approximately 3 minutes. Then, the patients were induced with either an intravenous bolus of propofol (2 mg/kg) or ketofol, prepared by mixing 1 mL (50 mg) of ketamine and 10 mL (100 mg) of propofol in a 12 mL syringe (1:2 ratio of ketamine to propofol). Standard solutions of ketamine (50 mg/mL) and propofol (10 mg/mL) were used for the preparation of ketofol. The administered volume was titrated, based on clinical judgment, to achieve an adequate depth of anesthesia induction equivalent to a 2 mg/kg propofol dose. If skeletal muscle relaxation was required during the surgical procedure, then a 5 mg dose of atracurium was administered every 25 minutes during surgery (a total dose of 25-30 mg). The patient was either intubated with an endotracheal tube or, in case of short procedural sedation, a laryngeal mask airway (LMA) was employed. Maintenance of anesthesia was done with inhalational sevoflurane up to 2 %. After the patient is under the influence of GA, the surgical procedure is performed, and upon skin closure or completion, the patient is aroused from the sedated state. During the surgical procedure, the patient's BP, HR, RR, and SpO_2 were monitored immediately after induction, after intubation and extubation, and at various time intervals. After spontaneous respiratory efforts, the patient is reversed with an inj. neostigmine 2.5 mg plus glycopyrrolate 0.4 mg (if atracurium was administered). Once the patient opens their eyes and responds to verbal commands, they are then extubated and transferred to the post-anesthesia care unit (PACU) for further management.

2.5. Postoperative assessments

MoCA, MMSE, and VAS were administered at 2 hours, 24 hours, and 48 hours post-operatively. The baseline cognitive and pain scores were compared with

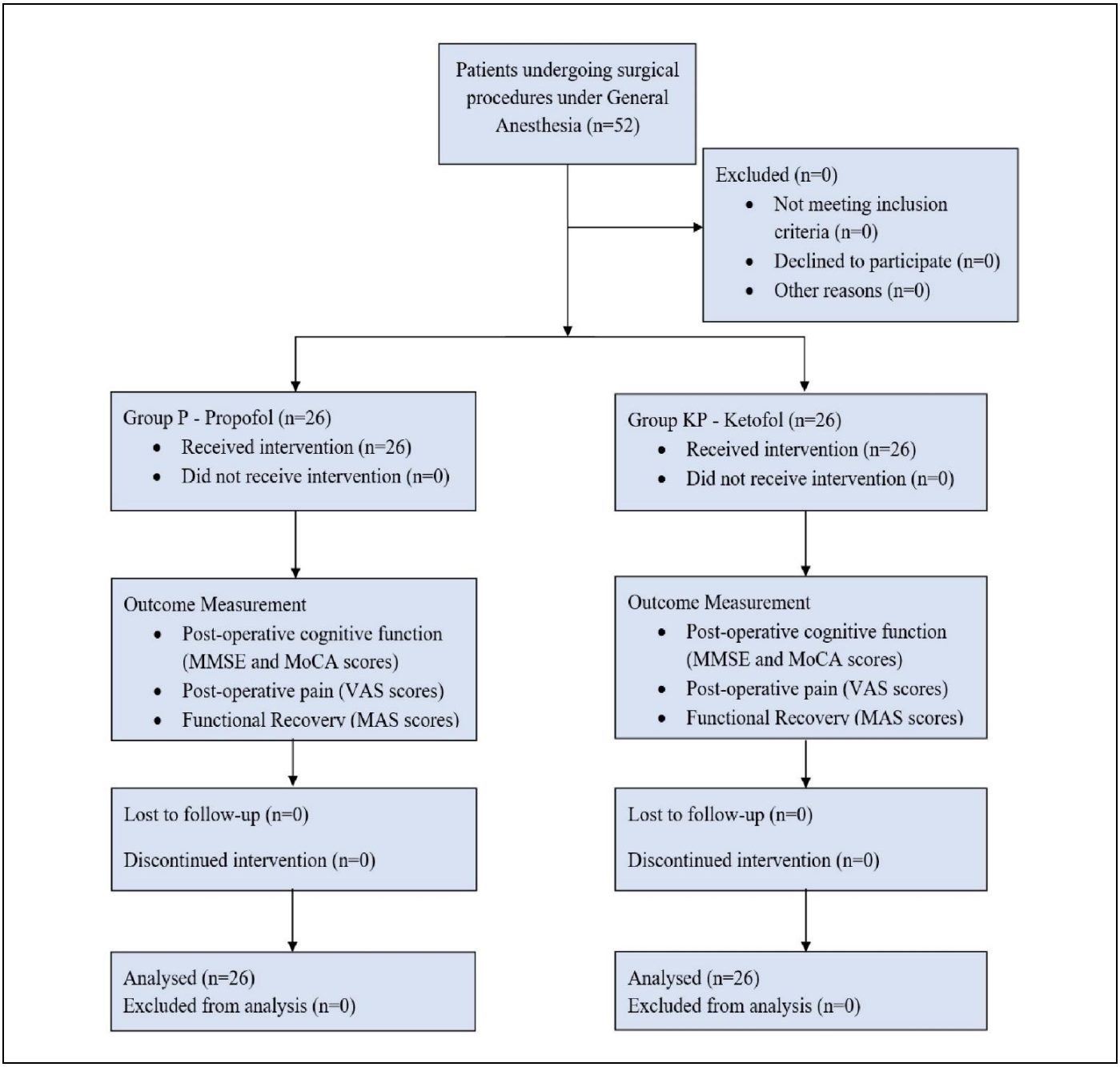

Figure 1. Flowchart of the Patient Participation

the post-operative scores, and interpretations were made. While assessing the pain levels, the patient's drug chart was reviewed to check what pain medications were prescribed. The difference in the need for pain medications was noted between the two groups. The pain medications that were usually prescribed to reduce post-operative pain included inj. paracetamol (1 g) or inj. Tramadol IM (50 mg) and/or inj. Pentazocine (30 mg). MAS was used to evaluate the patient's functional recovery at 2, 24, and 48 hours, and the anesthetic agent that resulted in a faster recovery was observed. The patients were monitored up to 48 hours post-surgery to record any incidences of adverse effects that may be due to the immediate effects of the anesthetic drugs.

2.6. Statistical analysis

All data entry and analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Version 26.0) for Windows. The test of normality was used to determine whether the data was normally distributed or not. Parametric and nonparametric quantitative data were compared using the Student's t-test and the Mann-Whitney U Test, respectively, as part of the initial descriptive and inferential analyses. P-value < 0.05 was taken as statistically significant. Bonferroni correction was also applied to adjust for multiple comparisons. Furthermore, to appropriately account for within-

subject correlation and adjust for potential confounders (e.g., age and gender), the Linear Mixed Model (LMM) was thereafter employed. LMM helped in preserving the longitudinal data structure while considering time as a repeated measure and estimating fixed effects across groups and time intervals with improved precision.

3. RESULTS AND DISCUSSION

A total of 52 surgical patients were enrolled in the study, with 26 patients allocated to the ketofol group and the remaining 26 patients allocated to the propofol group. There were 19 females (73.07%) and 7 males (26.92%) in the propofol group, whereas in the ketofol group, there were 24 (92.30%) females and only 2 (7.69%) males. The majority of the patients in both groups were middle-aged. The baseline demographic data, including age, gender, BMI, and ASA class, were found to be comparable, indicating no significant difference ($p > 0.05$) between the two groups, as depicted in Table 1.

To determine whether the data were normally distributed or not, the test of normality was performed, as shown in Table 2. Almost all the data for the MMSE and MoCA were found to be non-normal; therefore, non-parametric tests were employed for further analysis of the data. The data distribution was found to be non-normal due to the smaller sample size, which can cause samples to deviate from normality, especially when the outcomes are skewed, ordinal, or bounded. The cognitive assessment scores, such as the MoCA and MMSE, are bounded, whereas the VAS scores are both skewed and ordinal. Recognizing the non-normality in data distribution, the Mann-Whitney U Test (with Bonferroni correction) was performed to provide more valid results and interpretation of the data, especially for the smaller sample size involved in the study. Even after the correction was applied, the results for MMSE, MoCA, VAS, and MAS maintained their statistical reliability. Furthermore, the LMM was performed to account for the repeated-measures design and to adjust for any potential covariates over time, providing a more effective and precise estimation of both the intra- and the inter-group variability.

3.1. Postoperative cognitive function

Table 3 depicts the comparison of the MMSE scores between the groups, both preoperatively and at 2, 24, and 48 hours postoperatively. There was no statistically significant difference in the MMSE scores between Group P and KP at any of these intervals. Before surgery, the mean rank of MMSE scores was 28.58 in the propofol group and 24.42 in the ketofol group ($p = 0.30$). At 2 hours postoperatively, the mean ranks were 25.65 and 27.35 for the propofol and ketofol groups,

Table 1. Comparison of Baseline Demographic Data

Demographics	Group P (n = 26)	Group KP (n = 26)	P value
Age, yr	40.50 ± 15.690	39.12 ± 7.399	0.686
Gender (M:F)	7:19	2:24	0.067
BMI, kg/m^2	24.958 ± 5.2432	23.238 ± 2.4479	0.136
ASA Class (I:II)	8:18	8:18	1.00

Data presented as mean ± SD. P value > 0.05: not significant. ASA = American Society of Anesthesiology; P = propofol; KP = ketofol (ketamine-propofol)

Table 2. Test of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	P value	Statistic	df	Sig.
MMSE pre	0.237	52	<0.001	0.787	52	<0.001
MOCA pre	0.227	52	<0.001	0.837	52	<0.001
MMSE 2h	0.104	52	0.200*	0.977	52	0.391*
MMSE 24h	0.198	52	<0.001	0.781	52	<0.001
MMSE 48h	0.274	52	<0.001	0.634	52	<0.001
MOCA 2h	0.176	52	<0.001	0.795	52	<0.001
MOCA 24h	0.149	52	0.005	0.894	52	<0.001
MOCA 48h	0.224	52	<0.001	0.783	52	<0.001

p<0.001- highly significant, p<0.01- very significant, *Not significant. a. Lilliefors Significance Correction

Table 3. Comparison of MMSE scores between Group P and KP

Parameter	Timeline	Group	N	Mean Rank	Sum of Ranks	P value	Significance after Bonferroni Correction
MMSE	Pre-op	P	26	28.58	743.00	0.30	Already non-significant
		KP	26	24.42	635.00		
	2 hours	P	26	25.65	667.00	0.68	Already non-significant
		KP	26	27.35	711.00		
	24 hours	P	26	25.48	662.50	0.62	Already non-significant
		KP	26	27.52	715.50		
	48 hours	P	26	27.33	710.50	0.68	Already non-significant
		KP	26	25.67	667.50		

p>0.05- Not significant. Data analyzed using Mann Whitney U Test. Bonferroni correction was applied - Adjusted threshold: 0.05/3 = 0.0167.

respectively (*p = 0.68*). Likewise, no significant differences were observed at 24 hours (*p = 0.62*) and 48 hours (*p = 0.68*) following surgery. Although the differences were not statistically significant, there was a slight decline in the MMSE scores in Group P at 2 hours and 24 hours after surgery, but the MMSE scores in Group KP had no further decline from baseline. In fact, a "learning effect" occurred in Group KP, with slight improvements in MMSE scores at the various assessed time points after surgery when compared to baseline. Furthermore, a separate LMM (Tables 4A and 4B) was fitted to examine the impact of group, age, gender, and their interactions. Consistent with our unadjusted findings, the LMM showed no significant main effect of group on MMSE scores (*F = 1.25, p = 0.267*). However, the model identified age as a significant predictor (*F* = 7.53, *p* = 0.008), and also found a significant interaction between age and group (*F* = 5.54, *p* = 0.022). This suggests that MMSE scores differed not only with age but also that the relationship between age and cognitive performance varied across groups. In contrast, gender showed no significant main effects, and none of the higher-order interactions involving gender reached statistical significance. These results imply that age-related cognitive changes are more pronounced in MMSE performance and may be modulated by group differences.

Table 4A. LMM Type I Tests of Fixed Effects for MMSE

Type I Tests of Fixed Effects[a]				
Source	**Numerator df**	**Denominator df**	**F**	**Sig.**
Intercept	1	64.307	8318.889	<.001
Age	1	64.307	7.527	.008
Gender	1	64.307	1.743	.191
Group	1	64.307	1.254	.267
Age * Gender	1	64.307	.806	.373
Age * Group	1	64.307	5.544	.022
Gender * Group	1	64.307	.558	.458
Age * Gender * Group	1	64.307	1.240	.270

a. Dependent Variable: MMSE.

Table 4B. LMM Estimates of Fixed Effects for MMSE

Estimates of Fixed Effects[a]							
Parameter	**Estimate**	**Std. Error**	**df**	**t**	**Sig.**	**95% Confidence Interval**	
						Lower Bound	**Upper Bound**
Intercept	-1.350	25.795	64.307	-.052	.958	-52.877	50.176
Age	.765	.576	64.307	1.327	.189	-.386	1.916
Gender	12.964	13.359	64.307	.970	.335	-13.722	39.649
Group	18.518	14.319	64.307	1.293	.201	-10.085	47.121
Age * Gender	-.344	.300	64.307	-1.145	.256	-.944	.256
Age * Group	-.526	.329	64.307	-1.599	.115	-1.183	.131
Gender * Group	-7.024	7.759	64.307	-.905	.369	-22.523	8.474
Age * Gender * Group	.201	.180	64.307	1.113	.270	-.159	.561

a. Dependent Variable: MMSE.

Table 5. Comparison of MoCA scores between Group P and KP

Parameter	Timeline	Group	N	Mean Rank	Sum of Ranks	P value	Significance after Bonferroni Correction
MoCA	Pre-op	P	26	30.37	789.50	0.41	Baseline not corrected
		KP	26	22.63	588.50		
	2 hours	P	26	25.29	657.50	0.061	Already insignificant
		KP	26	27.71	720.50		
	24 hours	P	26	17.62	458.00	0.001**	Significant
		KP	26	35.38	920.00		
	48 hours	P	26	20.63	536.50	0.002**	Significant
		KP	26	32.37	841.50		

**p<0.01-very significant. Bonferroni correction was applied - Adjusted threshold: 0.05/3 = 0.0167.

On the other hand, when comparing the MoCA scores between Group P and KP, significant differences were found at 24 hours and 48 hours postoperatively (Table 5). Preoperatively, no significant differences were found between the two groups, with mean ranks of 30.37 and 22.63 in Group P and KP, respectively ($p = 0.41$). At 2 hours postoperatively, the differences were closer to attaining significance but didn't reach the threshold, with mean ranks of 25.29 in Group P and 27.71 in Group KP ($p = 0.061$). However, at 24 hours postoperatively, the mean rank of Group KP was 35.38, much higher than the mean rank of Group P, 17.62 ($p = 0.001$), indicating a very significant difference. Similarly, the mean rank of Group KP, 32.37, was significantly higher than that of Group P, 20.63 ($p = 0.002$), at 48 hours postoperatively. A graphical representation of the MoCA scores is presented in Figures 2A and 2B, highlighting that the MoCA scores in Group P declined gradually over time,

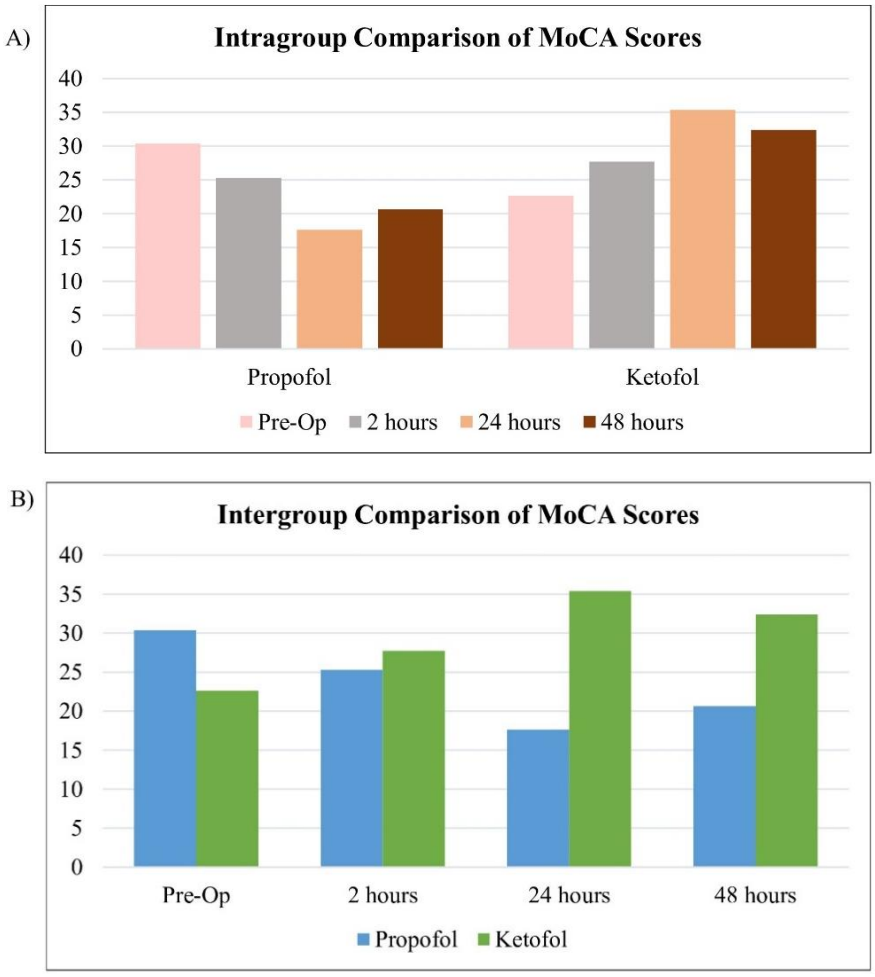

Figure 2. Intra- and Intergroup Comparison of MoCA Scores Between Group P and KP
A) Intragroup Comparison of MoCA Scores Between Group P and KP preoperatively, and at 2, 24 and 48 hours postoperatively.
B) Intergroup Comparison of MoCA Scores Between Group P and KP at the corresponding time intervals.

and patients in Group KP had better cognitive scores at 2, 24, and 48 hours after surgery. These results suggest a potential cognitive benefit with ketofol anesthesia in the early postoperative phase. In order to provide a more robust analysis, LMM was performed, and the results are shown in Tables 6A and 6B. The model showed a statistically significant fixed effect of group ($F = 11.33$, $p < 0.001$), indicating that cognitive performance as measured by MoCA varied between the groups. However, the estimates of fixed effects for group, age, gender, and their interactions were not individually significant, suggesting that while the group factor contributes to variability in MoCA scores at the model level, the effect sizes were small and confidence intervals were wide. This is most probably due to model complexity or overfitting. No significant main effects or interactions were observed for age or gender. This indicates that group differences are the primary source of variation in MoCA performance. Thus, group membership had a notable but small effect on MoCA scores, with minimal influence from age or gender in this model.

To the best of our knowledge, this is one of the first studies to make a direct comparison between ketofol and propofol, using both the MoCA and MMSE to evaluate postoperative cognition in the South Indian population. Although there are a few studies investigating the esketamine-propofol combination, which found that it resulted in higher MoCA scores[15-16], our study is unique as it involves ketamine directly and tries to demonstrate ketofol's effects on cognition. Previous research conducted by Jia et al[17], comparing the efficacy of MMSE and MoCA assessments in terms of mild cognitive impairment, had shown that MMSE is more likely to have a ceiling effect in patients with mild cognitive impairment (MCI), and those patients with normal MMSE scores may tend to exhibit declines when assessed using MoCA. Thus, MoCA is considere a more sensitive and specific assessment for detecting even minute differences in cognition. We used a combination of two cognitive assessments to better understand changes in cognition and improve the accuracy of detecting true differences. However, the MoCA test was more reliable than the MMSE in identifying the mild differences. Our analysis suggests that the use of propofol may lead to mild cognitive changes compared to ketofol, and thus, ketofol appears to result in better cognitive performance. Li et al[18] performed a randomized trial investigating the effects of different rates of propofol injection on cognitive functioning and found that lowering the rate of injection may not decrease the incidence of early POCD

Table 6A. LMM Type I Tests of Fixed Effects for MoCA

Type I Tests of Fixed Effects[a]				
Source	**Numerator df**	**Denominator df**	**F**	**Sig.**
Intercept	1	147.302	17675.175	<.001
Group	1	147.302	11.333	<.001
Gender	1	147.302	.052	.821
Age	1	147.302	.566	.453
Group * Gender	1	147.302	.057	.811
Group * Age	1	147.302	3.265	.073
Gender * Age	1	147.302	.441	.508
Group * Gender * Age	1	147.302	.323	.570

a. Dependent Variable: MoCA.

Table 6B. LMM Estimates of Fixed Effects for MoCA

Estimates of Fixed Effects[a]							
Parameter	**Estimate**	**Std. Error**	**df**	**t**	**Sig.**	**95% Confidence Interval**	
						Lower Bound	**Upper Bound**
Intercept	24.392	7.894	147.302	3.090	.002	8.791	39.992
Group	-.079	6.469	147.302	-.012	.990	-12.863	12.705
Gender	-2.091	4.564	147.302	-.458	.648	-11.110	6.928
Age	.007	.196	147.302	.036	.971	-.380	.394
Group * Gender	2.440	3.676	147.302	.664	.508	-4.823	9.704
Group * Age	.017	.164	147.302	.106	.916	-.307	.341
Gender * Age	.039	.112	147.302	.343	.732	-.183	.260
Group * Gender * Age	-.053	.092	147.302	-.569	.570	-.235	.130

a. Dependent Variable: MoCA.

in surgical patients. Therefore, propofol does cause a certain level of cognitive impairment in patients, especially during the immediate postoperative phase. On the other hand, intravenous infusion of ketamine has been found to prevent the development of POCD and improve cognitive functioning in several studies[19-22]. Ketofol's impact on cognition was assessed using a different test called the Confusion Assessment Method (CAM) in two different studies, where Tekletsadik et al[23] found a 46.25% incidence of postoperative delirium (POD), that is, 6 out of the 15 patients induced with ketofol had POD, which was not statistically significant. The other study indicated that the incidence of POD was lower in the ketofol group than in the placebo group[24]. Interestingly, our findings contrast with those of Tian et al[12], who reported that the patients who received the combination performed poorer in different cognitive tasks, like one-card learning and one-back memory, compared to those who received propofol alone. This discrepancy could be due to differences in patient populations, surgical type, the anesthetic dosing protocols, and the fact that the study used the CogState battery. The CogState assesses specific domains like psychomotor function and attention[25], which may be more sensitive to minute changes in cognition. In contrast, our study employed the MMSE and MoCA, which are broader tools for detecting cognitive changes and tend to provide overall cognitive trends rather than domain-specific deficits. Our study found that ketofol was associated with better cognitive scores at 24 and 48 hours postoperatively, hinting at the possible neuroprotective effect of ketamine through NMDA receptor blockade[6]. This preliminary observation was partially supported by LMM, suggesting a significant main effect of group on MoCA scores as per the F test, but the estimates of fixed effects implied that age, gender, and group did not contribute significantly to the variation. Alternatively, LMM was consistent with the fact that there was no major difference in MMSE scores between the two groups. These divergent results underscore the need for further investigation into the impact of ketofol on cognition across diverse clinical settings, and future studies involving MMSE should also pay close attention to its interaction with patients' age to determine the true influence.

3.2. Postoperative pain

Postoperative pain was evaluated using the visual analog scale (VAS) preoperatively and at 2, 24, and 48 hours postoperatively. No significant difference was observed in the baseline pain scores between the two groups ($p = 0.097$). In contrast, patients who received ketofol reported lower pain scores at all postoperative time intervals assessed, and all of these differences were statistically significant, as depicted in Table 7. The mean rank pain score was significantly lower in the ketofol group than in the propofol group (21.17 vs 31.83, $p = 0.010$) at 2 hours after surgery. The difference became more prominent at 24 hours (19.77 vs 33.23, $p = 0.001$) and 48 hours (19.25 vs 33.75, $p = 0.0001$) postoperatively. Figures 3A and 3B illustrate that Group P had higher pain scores throughout the various study time points compared to Group KP. These results strongly emphasize the analgesic effects of ketofol, which tends to provide much better postoperative analgesia compared to propofol. On the contrary, when the data were further analyzed using LMM to account for repeated measures and covariates (Tables 8A and 8B), the main effect of the anesthetic group on pain scores were no longer statistically significant ($F = 0.614$, $p = 0.437$), indicating that overall pain intensity did not differ meaningfully between the two groups. Similarly, age ($p = 0.422$) and gender ($p = 0.394$) did not have significant main effects. However, a significant interaction between group and gender was identified ($F = 4.585$, $p = 0.038$), suggesting that the influence of anesthetic type on pain perception may vary between male and female patients. These findings imply that while the anesthetic choice may not directly alter pain scores for the overall population, gender-specific differences in response to anesthesia should be considered in postoperative pain management.

Table 7. Comparison of VAS scores between Group P and KP

Parameter	Timeline	Group	N	Mean Rank	Sum of Ranks	P value	Significance after Bonferroni Correction
Pain score	Pre-op	P	26	23.08	600.00	0.097	Baseline not corrected
		KP	26	29.92	778.00		
	2 hours	P	26	31.83	827.50	0.010*	Significant
		KP	26	21.17	550.50		
	24 hours	P	26	33.23	864.00	0.001**	Significant
		KP	26	19.77	514.00		
	48 hours	P	26	33.75	877.50	0.0001***	Significant
		KP	26	19.25	500.50		

*p<0.05-significant, **p<0.01-very significant, ***p<0.001-highly significant. Bonferroni correction was applied – Adjusted threshold: 0.05/3 = 0.0167.

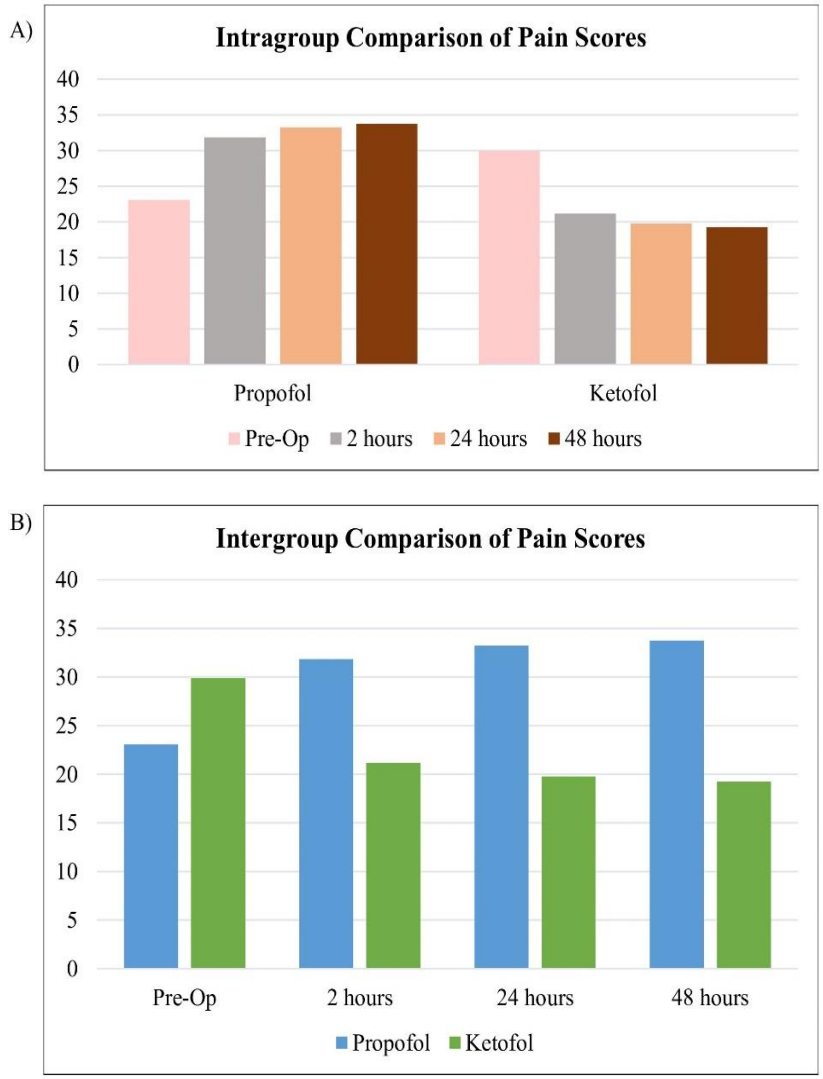

Figure 3. Intra- and Intergroup Comparison of Pain Scores Between Group P and KP
A) Intragroup Comparison of Pain Scores Between Group P and KP preoperatively, and at 2, 24 and 48 hours postoperatively.
B) Intergroup Comparison of Pain Scores Between Group P and KP at the corresponding time intervals.

Table 8A. LMM Type I Tests for Fixed Effects for VAS

Type I Tests of Fixed Effects[a]				
Source	**Numerator df**	**Denominator df**	**F**	**Sig.**
Intercept	1	44.013	121.601	<.001
Age	1	44.013	.656	.422
Gender	1	44.013	.740	.394
Group	1	44.013	.614	.437
Age * Gender	1	44.013	1.038	.314
Age * Group	1	44.013	.902	.348
Gender * Group	1	44.013	4.585	.038
Age * Gender * Group	1	44.013	.801	.376
a. Dependent Variable: Pain.				

3.2.1 Pain medication consumption

Table 9 and Figure 4 illustrate that out of 26 patients who received Ketofol, only 14 (53.84%) patients required pain medications, and the remaining 12 patients (46.15%) didn't consume any pain medications. On the other hand, out of the 26 patients who received propofol, a total of 24 (92.30%) patients required pain medications, and only 2 patients (7.69%) didn't need any analgesics. Therefore, ketofol seems to

Table 8B. LMM Estimates of Fixed Effects for VAS

Estimates of Fixed Effects[a]							
Parameter	**Estimate**	**Std. Error**	**df**	**t**	**Sig.**	**95% Confidence Interval**	
						Lower Bound	**Upper Bound**
Intercept	-9.820	8.072	44.013	-1.217	.230	-26.087	6.448
Age	.188	.200	44.013	.941	.352	-.215	.592
Gender	8.288	4.667	44.013	1.776	.083	-1.116	17.693
Group	7.986	6.615	44.013	1.207	.234	-5.345	21.316
Age * Gender	-.140	.115	44.013	-1.217	.230	-.371	.091
Age * Group	-.095	.168	44.013	-.565	.575	-.432	.243
Gender * Group	-5.804	3.758	44.013	-1.544	.130	-13.378	1.770
Age * Gender * Group	.085	.095	44.013	.895	.376	-.106	.275

a. Dependent Variable: Pain.

Table 9. Consumption of Pain Medications Between Group P and KP

S. No	**Drug Group**	**No. of patients given pain medications**		**Percentage (%) of consumption**	
		Yes	**No**	**Yes**	**No**
1	Propofol	24	2	92.30%	7.69%
2	Ketofol	14	12	53.84%	46.15%

reduce the extra pain medications that a patient may require during the course of their hospitalization.

Postoperative pain control is crucial for faster patient recovery and improved patient care outcomes, and our study demonstrated that ketofol was associated with more effective analgesia than propofol alone. While investigating the need for analgesics and VAS scores between Group P and KP patients, the scores differed significantly at the 2-hour to 48-hour time intervals. The initial statistical analysis highlights that ketofol reduces postoperative pain drastically compared to propofol. The group of patients who were administered ketofol had lower VAS scores postoperatively, underscoring the nature of ketofol as an effective analgesic. Nevertheless, the discrepancy in results due to the use of adjusted models like LMM highlights the importance of the effects exerted by confounding variables in research. The LMM found a significant interaction between gender and group, indicating that gender may alter the analgesic effect as well as the pain perception, leading to an overall impact on the pain scores for each group. Many research studies have shown that the administration of the bolus or infusion of ketamine has been highly efficacious in reducing post-operative pain[26-28]. In a study, Brinck et al[29] found that perioperative ketamine reduced the opioid consumption of patients undergoing various surgeries

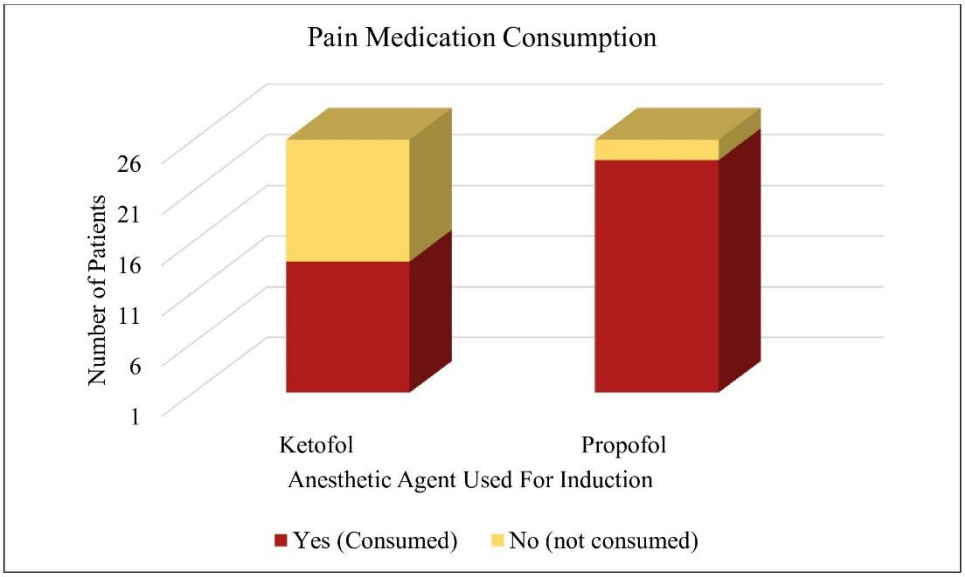

Figure 4. Comparison of Pain Medication Consumption Between Group P and KP

and decreased the VAS scores when compared to those receiving a placebo or another analgesic. Due to the addition of ketamine to propofol, the analgesic effect is more evident, and thus, ketofol can be a potential drug choice in dealing with patients undergoing painful surgeries or procedures while avoiding the side effects of ketamine alone. Our study correlates with a similar study conducted to compare the effects of ketofol and propofol in uterine cervical dilation and curettage, which concluded that adding ketamine as an adjuvant to propofol improved the efficacy of the anesthetic technique, and painkillers weren't required in the ketofol group[30]. Furthermore, due to the lack of analgesia with the use of propofol, the patients in Group P required analgesics like tramadol, Phenergan, and paracetamol to relieve and control post-operative pain. Thus, our findings were consistent with other studies that suggested ketofol decreases pain intensity and morphine or other pain medication consumption in surgical patients[11,13,31]. Even though the group effect was not statistically significant after adjustment, the trend observed in the Mann-Whitney U Test still remains clinically relevant, especially in the early post-surgical phase. There is a chance that Ketofol may provide better subjective analgesia, particularly in certain subgroups such as females, but a more stratified exploration is required to prove this inference.

3.3. Functional recovery and hemodynamic stability

Functional recovery was assessed using the Modified Aldrete Score (MAS), and no statistically significant difference was found between the two groups (Table 10), suggesting the anesthetic choice didn't have a major impact on functional recovery. Both anesthetic drugs showed comparable recovery status in terms of the five aspects examined in MAS: oxygen saturation, respiration, circulation, activity, and level of consciousness. This finding was similar to that of Akcaalan et al[32], who reported no difference in postoperative MAS between ketofol and propofol for shoulder surgery at any of the assessed time points. Extended analysis, as depicted in Tables 11A and 11B, showed that the main effect of anesthetic group approached statistical significance (F = 3.617, p = 0.063), suggesting a potential trend toward better recovery profiles in group KP, though not definitive. Neither age (p = 0.186), gender (p = 0.453), nor their interactions showed statistically significant effects. These findings suggest that, within the first 48 hours postoperatively, recovery as measured by Aldrete score was largely similar across anesthetic groups, although a non-significant trend warrants further exploration in larger samples or with more sensitive functional recovery measures.

Table 10. Comparison of MAS between Group P and KP

.	Timeline	Group	N	Mean Rank	Sum of Ranks	P value
Modified Aldrete	2 hours	P	26	25.12	653.00	0.47
		KP	26	27.88	725.00	
	24 hours	P	26	28.02	728.50	0.43
		KP	26	24.98	649.50	
	48 hours	P	26	25.00	650.00	0.27
		KP	26	28.00	728.00	

p>0.05-Not significant. Bonferroni correction was not applied as all p – values were clearly non- significant.

Table 11A. LMM Type I Tests of Fixed Effects for MAS

Type I Tests of Fixed Effects[a]				
Source	**Numerator df**	**Denominator df**	**F**	**Sig.**
Intercept	1	47.272	26750.403	<.001
Age	1	47.272	1.799	.186
Gender	1	47.272	.573	.453
Group	1	47.272	3.617	.063
Age * Gender	1	47.272	.075	.785
Age * Group	1	47.272	.085	.772
Gender * Group	1	47.272	.697	.408
Age * Gender * Group	1	47.272	.603	.441

a. Dependent Variable: Aldrete.

Table 11B. LMM Estimates of Fixed Effects for MAS

Estimates of Fixed Effects[a]							
Parameter	**Estimate**	**Std. Error**	**df**	**t**	**Sig.**	**95% Confidence Interval**	
						Lower Bound	**Upper Bound**
Intercept	9.894	2.232	47.272	4.432	<.001	5.404	14.383
Age	-.054	.055	47.272	-.977	.334	-.165	.057
Gender	-.569	1.290	47.272	-.441	.661	-3.165	2.027
Group	-.726	1.829	47.272	-.397	.693	-4.405	2.953
Age * Gender	.025	.032	47.272	.801	.427	-.038	.089
Age * Group	.039	.046	47.272	.848	.401	-.054	.132
Gender * Group	.480	1.039	47.272	.462	.646	-1.610	2.570
Age * Gender * Group	-.020	.026	47.272	-.777	.441	-.073	.032

a. Dependent Variable: Aldrete.

3.3.1 Systolic and diastolic blood pressure measurements

Table 12 and Figure 5 illustrate the differences in systolic blood pressure (SBP) between Group P and KP. While no significant difference was observed at 5 minutes ($p = 0.119$), the ketofol group consistently maintained higher SBP readings than the propofol group between 10 and 30 minutes, with statistically significant differences noted at 10 minutes ($p = 0.002$), 15 minutes ($p = 0.001$), 20 minutes ($p = 0.001$), 25 minutes ($p = 0.003$), and 30 minutes ($p = 0.009$). After the Bonferroni correction, the difference at 30 minutes was no longer statistically significant. Likewise, at 40 ($p = 0.16$), 50 ($p = 0.14$), and 60 minutes ($p = 0.57$), no significant difference was found. The changes in diastolic blood pressure (DBP) are shown in Table 13, with Figure 6 illustrating the fluctuations in DBP. A statistically significant difference was observed at 5 ($p = 0.001$), 10 ($p = 0.001$), 15 ($p = 0.001$), 20 ($p = 0.015$), 25 ($p = 0.018$), and 30 minutes ($p = 0.010$). However, Bonferroni correction rendered the differences at 20, 25, and 30 minutes non-significant. Nonetheless, there was a significant drop in both the systolic and diastolic blood pressure in patients who received propofol as opposed to those who received ketofol, indicating ketofol provides better hemodynamic stability in terms of maintaining stable blood pressure. The SBP and DBP readings for the patients in Group P and KP were compared to determine whether our study results would align with and confirm or refute the statements made in previous research studies. In general, the previously conducted research on the hemodynamic parameters had concluded that ketofol had better hemodynamic stability than propofol. Like our study, Sabertanha et al[33] and Gupta et al[34] have also reported higher mean SBP and DBP values with the use of ketofol than with propofol. In another example, Hailu et al[35] conducted a double-blinded, randomized controlled trial,

Table 12. Differences in Systolic Blood Pressure (SBP) between Group P and KP

Parameter	**Timeline**	**Group**	**Mean**	**SD**	**Std Error**	**P value**	**Significance after Bonferroni Correction**
SBP	5	P	108.0385	17.67367	3.46609	0.119	Already non-significant
		KP	114.1154	8.30097	1.62795		
	10	P	104.4231	14.20753	2.78633	0.002**	Significant
		KP	115.4231	8.87772	1.74106		
	15	P	103.2308	13.03321	2.55602	0.001**	Significant
		KP	117.0000	8.95321	1.75587		
	20	P	103.1154	13.69475	2.68576	0.001**	Significant
		KP	117.2800	8.70594	1.74119		
	25	P	106.5000	15.21381	2.98367	0.003**	Significant
		KP	118.1739	9.50910	1.98278		
	30	P	109.4615	17.53221	3.43835	0.009**	Non-significant after correction
		KP	120.3636	7.27386	1.55079		
	40	P	114.0000	18.33248	3.59530	0.16	Already non-significant
		KP	119.6364	5.01944	1.07015		
	50	P	116.5769	13.85113	2.71643	0.14	Already non-significant
		KP	121.3810	5.92854	1.29371		
	60	P	121.3462	12.68682	2.48809	0.57	Already non-significant
		KP	123.0000	4.01314	.89736		

**p<0.01-very significant. Data analyzed using Student's t-test. Bonferroni correction was applied – Adjusted threshold: 0.05/9 = 0.0056.

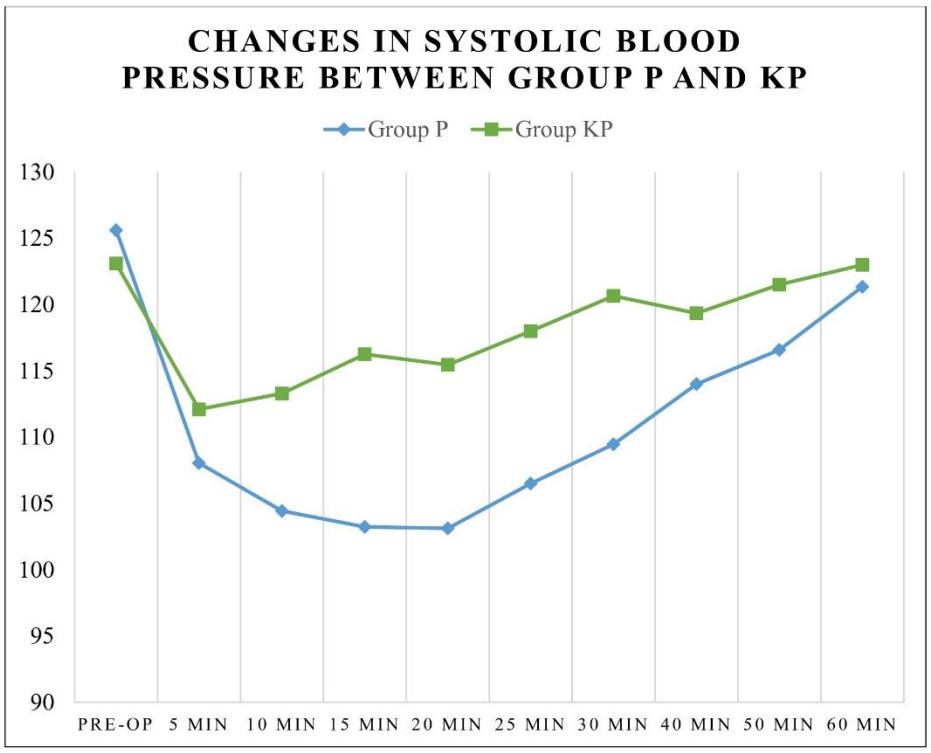

Figure 5. Changes in Systolic Blood Pressure (SBP) Between Group P and KP

concluding that ketofol had a higher mean SBP than propofol, and statistically significant differences in hemodynamic parameters were achieved during the first 30 minutes intraoperatively. Likewise, our study also found a statistically significant difference in systolic blood pressure (SBP) and diastolic blood pressure (DBP) between the two groups. Ketofol had only mild fluctuations in SBP and DBP, whereas propofol resulted in a significant drop in blood pressure, especially after induction, which slowly returned to the normal range. These findings correlate with the fact that ketamine's sympathomimetic effects neutralize propofol's hypotensive effects, resulting in more stable hemodynamics.

Table 13. Differences in Diastolic Blood Pressure (DBP) between Group P and KP

Parameter	Timeline	Group	Mean	SD	Std Error	P value	Significance after Bonferroni Correction
DBP	5	P	68.5385	9.41161	1.84577	0.001**	Significant
		KP	76.0385	5.48803	1.07629		
	10	P	67.1538	8.83942	1.73355	0.001**	Significant
		KP	75.2692	6.53947	1.28249		
	15	P	67.6154	8.70897	1.70797	0.001**	Significant
		KP	76.5000	6.86003	1.34536		
	20	P	68.8846	10.90441	2.13853	0.015*	Non-significant after correction
		KP	75.3600	6.86707	1.37341		
	25	P	70.6923	10.35285	2.03036	0.018*	Non-significant after correction
		KP	76.8261	6.43606	1.34201		
	30	P	70.5000	10.63673	2.08603	0.010*	Non-significant after correction
		KP	77.3182	5.84226	1.24557		
	40	P	73.1538	8.96523	1.75823	0.235	Already non-significant
		KP	75.7727	5.27286	1.12418		
	50	P	75.6538	9.80181	1.92229	0.59	Already non-significant
		KP	77.0000	6.92820	1.51186		
	60	P	77.5769	9.61737	1.88612	0.82	Already non-significant
		KP	78.1000	4.11544	.92024		

*p<0.05-significant, **p<0.01-very significant. Bonferroni correction was applied – Adjusted threshold: 0.05/9 = 0.0056.

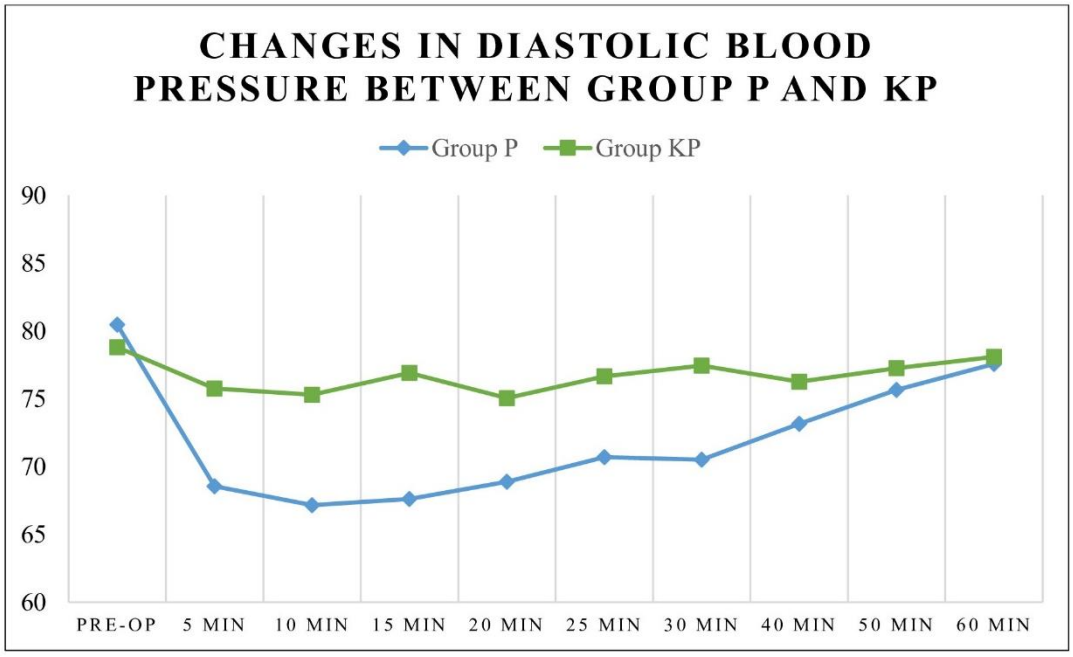

Figure 6. Changes in Diastolic Blood Pressure (DBP) Between Group P and KP

3.3.2 Changes in heart rate and respiratory parameters

Table 14 and Figure 7 show that there were no significant differences in HR between the two groups. Despite the pharmacological differences between these two agents, the data analysis reveals that neither of the drugs had a dominant effect on sympathetic stimulation, affecting heart rate drastically. It is essential to note that the figure still displays increased fluctuations in heart rate in Group P patients at various time intervals, and when compared to ketofol, it exhibits more pronounced peaks and drops. Therefore, the heart rate in Group KP patients seems to be more stable with minor fluctuations. Previous studies have also reported no significant difference in heart rate between the groups[34,36-37]. Although a higher mean HR was expected with ketofol due to its sympathomimetic effects, as mentioned in other studies[14,33], the observed heart rate was more balanced, probably due to the synergism of the opposing cardiovascular effects of the two different drugs[38].

Table 14. Differences in Heart Rate (HR) between Group P and KP

Parameter	Timeline	Group	Mean	SD	Std Error	P value
Heart Rate	5	P	84.0000	11.00545	2.15835	0.61
		KP	85.3846	8.24173	1.61634	
	10	P	82.9615	10.36718	2.03317	0.29
		KP	85.8846	9.50927	1.86492	
	15	P	83.1538	12.17437	2.38759	0.23
		KP	86.5769	7.91542	1.55234	
	20	P	81.5385	10.35463	2.03071	0.18
		KP	85.3200	9.72420	1.94484	
	25	P	83.9615	9.97389	1.95604	0.57
		KP	85.3913	7.52414	1.56889	
	30	P	85.6538	11.65484	2.28570	0.61
		KP	84.2273	6.28628	1.34024	
	40	P	88.0000	12.42578	2.43690	0.55
		KP	86.2273	7.26985	1.54994	
	50	P	86.5385	13.13082	2.57517	0.64
		KP	85.0000	8.15475	1.77951	
	60	P	77.46	21.159	4.150	0.07
		KP	86.70	8.597	1.922	

p>0.05-Not significant. Bonferroni correction was not applied as all p – values were clearly non-significant.

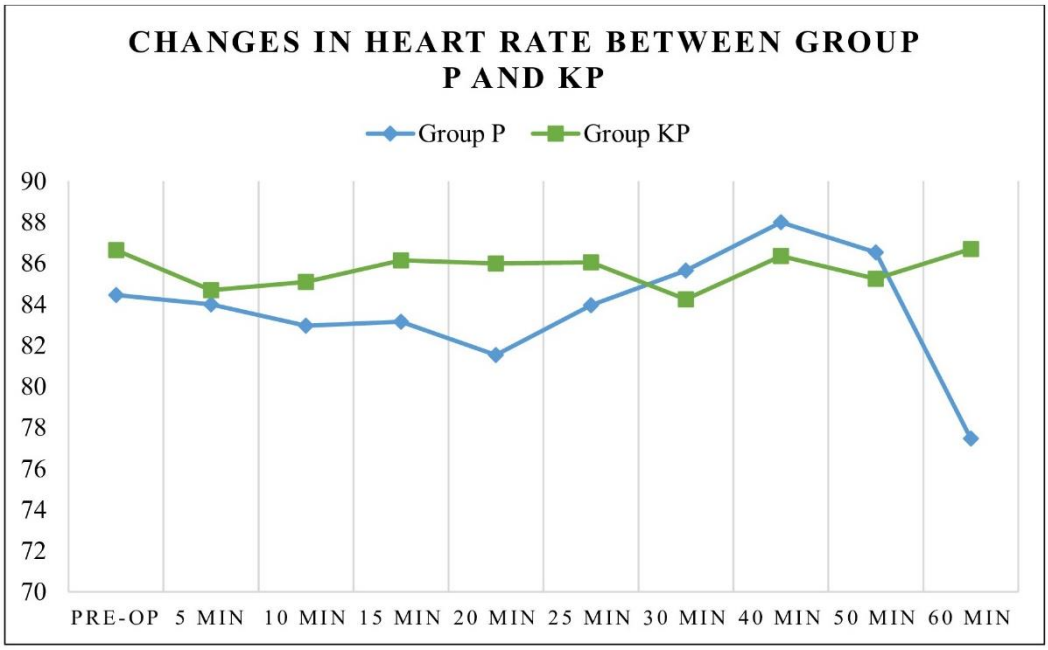

Figure 7. Changes in Heart Rate Between Group P and KP

Oxygen saturation levels were monitored at very crucial intraoperative phases: at induction, intubation, and extubation, besides the pre-and postoperative assessments. As shown in Table 15, ketofol resulted in a higher SpO_2 level than propofol at intubation (mean rank: 31.08 > 21.92, $p = 0.002$) and in the immediate postoperative phase (mean rank: 29.02 > 23.98, $p = 0.043$). However, the postoperative SpO_2 lost significance after the Bonferroni correction. Nevertheless, the remaining data and Figure 8 demonstrate that both anesthetic agents maintained adequate SpO_2 levels throughout the procedure, with no significant differences noted before surgery, at induction, or extubation. Interestingly, the ketofol group consistently showed slightly higher SpO_2 values at each time point compared to the propofol group. A noticeable dip in SpO_2 was observed in the propofol group during intubation, whereas the ketofol group maintained more stable values. These findings imply that ketofol provides better oxygen saturation and preserves respiratory function, particularly at intubation. Table 16 shows that there was no statistically significant difference between the respiratory rates of the two groups. Despite not being statistically significant, the respiratory rate still showed mild variations, particularly preoperatively and at induction, with Group KP remaining relatively more stable compared to Group P. Akcaalan et al[32] reported lower SpO_2 levels in the ketofol group compared to propofol, which differs from our study. The difference could be accountable to the prior use of a peripheral nerve block before induction, with regional anesthesia possibly altering the presentation of respiratory depression in the patient when general anesthesia is administered. On the contrary, a study conducted by Canpolat et al[39] compared the safety of

Table 15. Differences in SpO_2 Between Group P and KP

Parameter	Timeline	Group	N	Mean Rank	Sum of Ranks	P value	Significance after Bonferroni Correction
SpO2	Pre-op	P	26	23.65	615.00	0.058	Baseline not corrected
		KP	26	29.35	763.00		
	Induction	P	26	25.54	664.00	0.53	Already non-significant
		KP	26	27.46	714.00		
	Intubation	P	26	21.92	570.00	0.002**	Significant
		KP	26	31.08	808.00		
	Extubation	P	26	25.46	662.00	0.50	Already non-significant
		KP	26	27.54	716.00		
	Post-op	P	26	23.98	623.50	0.043*	Non-significant after correction
		KP	26	29.02	754.50		

*p<0.05-significant, **p<0.01-very significant. Bonferroni correction was applied – Adjusted threshold: 0.05/4 = 0.0125.

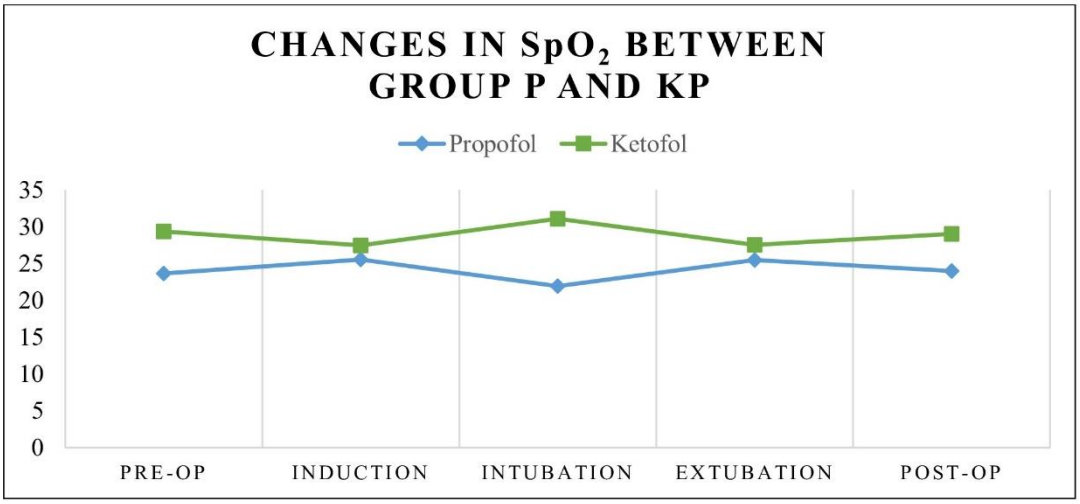

Figure 8. Changes in SpO_2 Between Group P and KP

propofol, ketamine, and ketofol for pediatric procedural sedation and found no significant difference between the groups in terms of SpO_2 and RR, which is similar to our findings. Since the groups differed significantly in terms of SpO_2 levels but not RR, this finding suggests that ketofol may be a better choice in maintaining oxygenation, an essential feature during any surgery, without requiring additional respiratory support. Ketamine is known to preserve the airway reflexes[40], and thus ketofol seems to lead to better SpO_2 levels despite RR remaining similar between the groups. The difference may be because of the fact that propofol leads to increased respiratory depression[39], which would have been counteracted by the addition of ketamine.

3.4. Limitations

The main limitation of our study was the small sample size of 52 participants, which may reduce the statistical power and the generalizability of the results. The study should include a larger number of patients to truly understand the effects of propofol and ketofol on postoperative cognitive function, functional recovery, and pain, as well as how these effects impact participants of varying characteristics. Although an LMM was used in the final analysis, the sample size was initially calculated based on a simple model to ensure the study's feasibility. Thus, a larger sample size, calculated with more advanced model assumptions, will be better at enhancing the external validity. Future studies should focus on more appropriate sample size estimation based on advanced modeling techniques. Another limitation is that this study was conducted at a single site, and the anesthetic techniques, postoperative care plans, and surgical protocols typically vary depending on the particular hospital. If a multi-center study were conducted, it would yield a broader application of the findings. Further research should be undertaken to explore the long-term effects of ketofol and propofol on postoperative cognitive function and functional recovery, as our study only assessed the short-term effects. There may be cases of delayed cognitive impairment, which could not have been identified by this study, as the patients were only followed till 48 hours after surgery. As our study was observational in nature, the randomization process was not followed,

Table 16. Differences in Respiratory Rate between Group P and KP

Parameter	Timeline	Group	N	Mean Rank	Sum of Ranks	P value
Respiratory rate	Pre-op	P	26	30.44	791.50	0.054
		KP	26	22.56	586.50	
	Induction	P	26	23.81	619.00	0.18
		KP	26	29.19	759.00	
	Intubation	P	26	24.31	632.00	0.28
		KP	26	28.69	746.00	
	Extubation	P	26	24.15	628.00	0.25
		KP	26	28.85	750.00	
	Post-op	P	26	25.21	655.50	0.52
		KP	26	27.79	722.50	

$p>0.05$-Not significant. Bonferroni correction was not applied as all p - values were clearly non-significant.

and thus, it is more susceptible to selection bias. The anesthesiologist's preference and clinical judgement involved in patient allocation can confound the relationship between the anesthetic agent and the measured outcomes. Moreover, there was a notable imbalance in the sex ratio between the groups, with more females than males in each group (Group P – 7:19, Group KP – 2:24). In our analysis, gender appeared to only affect post-operative pain scores, but mostly it had no significant impact on the other measured parameters, implying a limited confounding effect. Even though we controlled for gender in our statistical analysis, upcoming research should focus on more balanced cohorts to determine the true influence of sex on these outcomes. Furthermore, the level of education has an impact on cognitive functioning, and although we did not formally record the exact years of education of each patient, it was observed that some participants we assessed had difficulty comprehending how to perform the cognitive test, resulting in lower MoCA or MMSE scores. These lower scores could be unrelated to true cognitive impairment, introducing potential measurement bias. However, we identified those individuals with education levels $\leq 12^{th}$ grade and applied the standard MoCA correction by adding 1 point to their total score, improving the accuracy of the scores to prevent underestimation of cognitive function in such individuals. Additionally, both tools were originally developed and validated in older patient populations and their psychometric properties may vary when employed in middle-aged patients such as those in our cohort (mean age of 40 years). Even though both groups were comparable in terms of age and education levels, these factors may limit the generalizability and interpretability of our research findings. Certain findings shifted from significance to non-significance with the use of LMM and Bonferroni correction due to their conservative approach. This highlights the importance of adjusting for covariates and accounting for multiple comparisons. Although we tried to reduce bias by adjusting for potential covariates like age and gender, and conducting a more advanced statistical approach like LMM, residual confounding cannot be entirely eliminated. This limitation should be considered while interpreting the findings of our study. Hence, randomized clinical studies should be carried out in the future to confirm these findings and avoid any possible bias due to participant selection, gender distribution, and educational background.

4. CONCLUSION

The study demonstrated that although the MMSE scores, MAS, HR, and RR were unaffected by the anesthetic choice, significant differences were initially noted in high-order cognitive performance assessed with MoCA, pain levels using VAS scores, and hemodynamic stability (SBP, DBP, and SpO_2). Although LMM resulted in certain findings becoming non-significant, ketofol still seems to have a better performance when compared to propofol. Our findings lead to the conclusion that ketofol may be a better anesthetic choice for reducing postoperative cognitive impairment, improving hemodynamic stability, particularly in terms of blood pressure and oxygenation, and relieving postoperative pain, especially in female patients, since pain perception was influenced by gender differences. However, its effects on cognition warrant further clinical investigations due to varying results obtained with different cognitive assessments. The differing outcomes found between MMSE and MoCA highlight that it is better to utilize the test with greater sensitivity, and even different combinations of sensitive neuropsychological tests, along with advanced statistical testing, can be used to truly evaluate postoperative cognitive function. The combination of ketamine-propofol, as ketofol, seems to have more advantages than propofol alone for general anesthesia in surgical procedures. Given the slightly favorable outcomes associated with ketofol in this study, the evidence suggests considering the development of a commercially available ketofol formulation, which would reduce preparation errors and save time in emergencies. The observed benefits in pain control and cognitive preservation, combined with stable hemodynamics, suggest that a standardized product could streamline anesthetic practices while improving patient outcomes. Despite some limitations, our research contributes to the growing body of evidence suggesting that ketofol may be a more suitable anesthetic choice than propofol in terms of postoperative cognition, pain, and hemodynamic stability.

5. ACKNOWLEDGEMENTS

The authors would like to thank Dr. K. Kalpana, Resident Medical Officer and Chief Anesthesiologist, ESI Hospital, Ayanavaram, for her unwavering belief in our ability to complete the project successfully. We want to extend our sincere thanks to the other anesthesiologists, OT nurses, and staff for providing us with the opportunity to work with them and for mentoring us in all aspects of the research. We would also like to thank the entire faculty of the Department of Pharmacy Practice, Vels Institute of Science, Technology, and Advanced Studies, for their constant support.

Author contribution

D.P. – conceptualization, designing of methodology, data entry and analysis, writing – original draft preparation. A.M. and D.R. – Data collection, draft

editing. M.P. provided overall supervision and made corrections. K.K. and S.P. reviewed the final manuscript and provided their academic insights.

Funding
None to declare

Conflict of interest
None to declare

Ethics approval
The study was approved (Approval No. ECR/288/Indt/TN/2018/RR-21/151) by the Institutional Ethics Committee (IEC) affiliated with Vels Institute of Science, Technology, and Advanced Studies (VISTAS), Chennai, India.

Article info:
Received June 5, 2025
Received in revised form July 31, 2025
Accepted August 21, 2025

REFERENCES

1. Berger M, Nadler JW, Browndyke J, Terrando N, Ponnusamy V, Cohen HJ, et al. Postoperative Cognitive Dysfunction. Anesthesiol. Clin. 2015;33(3):517–50.
2. Brodier EA, Cibelli M. Postoperative cognitive dysfunction in clinical practice. BJA Educ. 2021;21(2):75–82.
3. Varpaei HA, Farhadi K, Mohammadi M, Khafaee Pour Khamseh A, Mokhtari T. Postoperative cognitive dysfunction: a concept analysis. Aging Clin Exp Res. 2024;36(1):133.
4. Kotekar N, Shenkar A, Nagaraj R. Postoperative cognitive dysfunction - current preventive strategies. Clin Interv Aging. 2018;13:2267–73.
5. Evered LA, Silbert BS. Postoperative Cognitive Dysfunction and Noncardiac Surgery. Anesth Analg. 2018;127(2):496–505.
6. Wang K, Wang Y, Zhang T, Chang B, Fu D, Chen X. The Role of Intravenous Anesthetics for Neuro: Protection or Toxicity? Neurosci Bull. 2025;41(1):107–30.
7. Zhao Q, Wan H, Pan H, Xu Y. Postoperative cognitive dysfunction—current research progress. Front Behav Neurosci. 2024;18:1328790.
8. Evered L, Silbert B, Scott DA, Zetterberg H, Blennow K. Association of changes in plasma neurofilament light and tau levels with anesthesia and surgery: Results from the CAPACITY and ARCADIAN studies. JAMA neurol. 2018;75(5):542.
9. Saxena S, Uchida Y, Maze M. Restoring order to postoperative neurocognitive disorders. JAMA neurol. 2018;75(5):535.
10. Karki SB, Rajbanshi LK, Arjyal B, Khanal K. Comparison of anesthetic properties of ketofol (ketamine with propofol) and propofol in minor surgical procedures. Birat J Health Sci. 2018;2(3):287–91.
11. Işık Y, Kurdoğlu Z, Göktaş U, Kati İ, Sözen D. Comparison of propofol and Ketofol in minor gynecologic interventions. J Clin Trials Exp Investig 2015;6(3).
12. Tian L, Luan H, Zhu P, Zhang Z, Bao H. A randomized controlled trial for measuring effects on cognitive functions of adding ketamine to propofol during sedation for colonoscopy. Medicine. 2020;99(36):e21859.
13. Nashibi M, Mottaghi K, Faraji M, Delavari A, Taghipour H, Amiri M. Comparison of analgesic and sedative effects of ketamine-propofol (ketofol) and fentanyl-midazolam (fentazolam) combinations in outpatient orthopedic procedures. Trauma Mon. 2017;22(5): e100102. V.
14. Yadav R, Thapa AS, Sah R, Upadhyay HP. Anesthetic properties of propofol and ketofol (ketamine with propofol): A comparative study. J. Chitwan Med. Coll. 2022;12(4):21–4.
15. Tu W, Yuan H, Zhang S, Lu F, Yin L, Chen C, et al. Influence of anesthetic induction of propofol combined with esketamine on perioperative stress and inflammatory responses and postoperative cognition of elderly surgical patients. Am J Transl Res. 2021;13(3):1701–9.
16. Zhao L, Li Z, Jin B, Hou N, Yang H. Safety and efficacy of low-dose esketamine in laparoscopic cholecystectomy: a prospective, double-blind randomized controlled trial. BMC Anesthesiol. 2024;24(1):47.
17. Jia X, Wang Z, Huang F, Su C, Du W, Jiang H, et al. A comparison of the mini-mental state examination (MMSE) with the montreal cognitive assessment (MoCA) for mild cognitive impairment screening in chinese middle-aged and older population: a cross-sectional study. BMC Psychiatry. 2021;21(1):485.
18. Li T, Han W, Yang X, Wang Y, Peng L, He L, et al. Effects of different injection rates of propofol on postoperative cognition in elderly patients undergoing laparoscopic inguinal hernia repair. Drug Des Devel Ther. 2023;17:1741–52.
19. Oriby ME, Elrashidy AA, Elsharkawy A, Ahmed SA. Effects of ketamine or dexmedetomidine on postoperative cognitive dysfunction after cataract surgery: A randomized controlled trial. Indian J Anaesth. 2023;67(2):186–93.
20. Chen MH, Li CT, Lin WC, Hong CJ, Tu PC, Bai YM, et al. Cognitive function of patients with treatment-resistant depression after a single low dose of ketamine infusion. J Affect Disord. 2018;241:1–7.
21. Stippl A, Scheidegger M, Aust S, Herrera A, Bajbouj M, Gärtner M, et al. Ketamine specifically reduces cognitive symptoms in depressed patients: An investigation of associated neural activation patterns. J Psychiatr Res. 2021;136:402–8.
22. Rascón-Martínez DM, Fresán-Orellana A, Ocharán-Hernández ME, Genis-Zarate JH, Castellanos-Olivares A. The effects of ketamine on cognitive function in elderly patients undergoing ophthalmic surgery: A pilot study. Anesth Analg. 2016;122(4):969–75.
23. Tekletsadik YA, Workineh SA, Gesso AS, Hirbo HS. Postoperative delirium among elderly elective orthopedic patients in addis ababa ethiopia: a multicenter longitudinal study. BMC Anesthesiol. 2024;24(1):343.
24. Abd Ellatif SE, Mowafy SMS, Shahin MA. Ketofol versus Dexmedetomidine for preventing postoperative delirium in elderly patients undergoing intestinal obstruction surgeries: a randomized controlled study. BMC Anesthesiol. 2024;24(1):1.
25. Borrat X, Ubre M, Risco R, Gambús PL, Pedroso A, Iglesias A, et al. Computerized tests to evaluate recovery of cognitive function after deep sedation with propofol and remifentanil for colonoscopy. J Clin Monit Comput. 2019;33(1):107–13.
26. Li Z, Chen Y. Ketamine reduces pain and opioid consumption after total knee arthroplasty: A meta-analysis of randomized controlled studies. Int J Surg. 2019;70:70–83.
27. Ma X, Yan J, Jiang H. Application of ketamine in pain management and the underlying mechanism. Pain Res Manag. 2023;2023:1–11.
28. Schwenk ES, Mariano ER. Designing the ideal perioperative pain management plan starts with multimodal analgesia. Korean J Anesthesiol. 2018;71(5):345–52.
29. Brinck E, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018;12(12):CD012033.

30. Abdelhalim Taha Hegazy A. Comparative study between Ketofol versus propofol anesthesia for uterine cervical dilation and currettage. AMJ. 2016;45(2):287–96.
31. Jaafarpour M, Vasigh A, Khajavikhan J, Khani A. Effect of ketofol on pain and complication after caesarean delivery under spinal anaesthesia: A randomized double-blind clinical trial. J Clin Diagn Res. 2017;11(3):UC04-UC07.
32. Akcaalan Y, Sahap M, Gulec H, Horasanli E, Ugurlu M, Akcaalan S. Comparison of propofol and ketofol for sedation in patients undergoing shoulder surgery with interscalene and suprascapular nerve blocks. Anaesth pain intensive care. 2022;26(1):102–9.
33. Sabertanha A, Shakhsemampour B, Ekrami M, Allahyari E. Comparison of infusion of propofol and ketamine-propofol mixture (ketofol) as anesthetic maintenance agents on blood pressure of patients undergoing orthopedic leg surgeries. Anesth Pain Med. 2019; 9(6):e96998.
34. Gupta M, Damor P, Naithani U, Verma R, Yadav A. Comparison of ketofol versus propofol for procedural sedation and analgesia in cervical cancer brachytherapy: A prospective, randomized double blind study. IJCA. 2021;8(1):55–61.
35. Hailu S, Getachew H, Hailu S, Abebe T, Seifu A, Regassa T, et al. Effectiveness of ketofol versus propofol induction on hemodynamic profiles in adult elective surgical patients: A randomized controlled trial. Int. J. Surg. Open. 2021;37:100392
36. Singh SA, Prakash K, Sharma S, Dhakate G, Bhatia V. Comparison of propofol alone and in combination with ketamine or fentanyl for sedation in endoscopic ultrasonography. Korean J Anesthesiol. 2018;71(1):43.
37. Colak Y, Ozgul U, Aslan D, Cumurcu H, Colak C, Durmus M. The effects of sedation with propofol and propofol-ketamin combination on postoperative cognitive function in elderly patients undergoing spinal anesthesia. Ann Med Res. 2021;28(6):1201.
38. Jalili S, Esmaeeili A, Kamali K, Rashtchi V. Comparison of effects of propofol and ketofol (Ketamine-Propofol mixture) on emergence agitation in children undergoing tonsillectomy. Afr H Sci. 2019;19(1):1736.
39. Canpolat DG, Yıldırım MD, Aksu R, Kutuk N, Alkan A, Cantekin K. Intravenous ketamine, propofol and propofol-ketamine combination used for pediatric dental sedation: A randomized clinical study. Pak J Med Sci. 2016;32(3):682-7.
40. Bhardwaj A, Panda N, Chauhan R, Bloria S, Bharti N, Bhagat H, et al. Comparison of ketofol (combination of ketamine and propofol) and propofol anesthesia in aneurysmal clipping surgery: A prospective randomized control trial. Asian J Neurosurg. 2020;15(03):608–13.