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ORIGINAL RESEARCH article

Low-dose ketamine pretreatment and propofol-induced hypotension during general anesthesia: A comparative observational study

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Abstract: Propofol is widely used for induction of general anesthesia but may cause reductions in arterial blood pressure. Ketamine has sympathomimetic properties and may modify this hemodynamic response. This study compared early systolic blood pressure changes after propofol induction with or without low-dose ketamine pretreatment. This prospective, non-randomized comparative observational study included 60 women aged 50 - 80 years with ASA physical status I - III at the National Cancer Institute, Misrata, Libya, between March and December 2025. 30 patients received propofol 2.0 mg/kg with fentanyl 1.0 µg/kg (Group A), and 30 received ketamine 0.3 mg/kg immediately before the same propofol-fentanyl regimen (Group B). Systolic blood pressure (SBP) and heart rate were recorded at baseline and three and six minutes after induction. Co-primary outcomes were SBP reductions greater than 20.0% from baseline at three and six minutes. At three minutes, a systolic blood pressure reduction greater than 20.0% occurred in 22/30 patients (73.3%) in Group A and 5/30 (16.7%) in Group B (Fisher exact p = 0.000020; Holm-adjusted p = 0.000041). At six minutes, rates were 13/30 (43.3%) and 0/30 (0.0%), respectively (p = 0.000046; Holm-adjusted p = 0.000046). Mean systolic blood pressure was higher in Group B at three minutes (129.3 ± 17.5 vs 110.3 ± 14.9 mmHg) and six minutes (131.3 ± 13.8 vs 114.3 ± 11.4 mmHg; both p < 0.001). Heart rate did not differ significantly between groups. Nausea and vomiting were recorded in the same five patients; no hallucinations or agitation were reported. Neither atropine nor ephedrine was administered. Low-dose ketamine pretreatment was associated with a lower frequency of early post-induction systolic blood pressure reduction greater than 20.0%.

Introduction

Propofol is widely used for intravenous induction of general anesthesia because of its rapid onset and predictable recovery profile. However, it can cause reductions in arterial blood pressure through vasodilation, myocardial depression, and attenuation of compensatory cardiovascular responses. The magnitude of the hemodynamic response may be influenced by dose, injection rate, opioid co-administration, intravascular volume, and baseline patient characteristics [1-4].

Ketamine produces dissociative anesthesia and usually has sympathomimetic effects, including increased sympathetic outflow and circulating catecholamine activity [5]. Combining ketamine with propofol has therefore been investigated as a strategy to modify propofol-associated cardiovascular depression. Clinical trials have reported differing hemodynamic responses across ketamine doses, drug combinations, populations, and study protocols [6-11]. This study evaluated the association between low-dose ketamine pretreatment and early systolic hypotension after propofol-based induction in patients aged 50 - 80 years. The co-primary outcomes were the proportions of patients with a systolic blood pressure reduction greater than 20.0% from baseline at three and six minutes after induction.

Materials and methods

Study design and setting: This prospective, non-randomized comparative observational study was conducted at the National Cancer Institute, Misrata, Libya, from March through December 2025. Sixty consecutive eligible patients were included, with 30 patients in each group. Patients were classified according to the induction regimen they received in clinical practice; allocation was not randomized. Reporting was guided by the STROBE recommendations for observational studies [12].

Participants: Participants were women aged 50-80 years with American Society of Anesthesiologists (ASA) physical status I-III who were scheduled to undergo dilatation and curettage (D & C) under general anesthesia during the study period. All 60 patients were planned for the same procedure.

Anesthetic regimens: Group A (n = 30) received propofol 2.0 mg/kg with fentanyl 1.0 µg/kg. Group B (n = 30) received ketamine 0.3 mg/kg immediately before propofol 2.0 mg/kg, with fentanyl 1.0 µg/kg. Face-mask ventilation was used for all operations. The recorded maintenance regimen was sevoflurane 1.5 MAC, and intravenous fluids were administered at 2.0 mL/kg/hr [13].

Atropine 0.5 mg IV was available for bradycardia (heart rate < 50 beats/min), and ephedrine was available for hypotension (systolic blood pressure < 90 mmHg), when clinically indicated. Neither drug was administered to any participant.

Hemodynamic measurements and outcomes: Non-invasive blood pressure was measured using an automated electronic upper-arm cuff. Systolic blood pressure and heart rate were recorded at baseline and at three and six minutes after induction. The co-primary outcomes were a systolic blood pressure reduction greater than 20.0% from baseline at three minutes and at six minutes. A reduction of exactly 20.0% did not meet the outcome definition. Secondary outcomes included mean systolic blood pressure and heart rate at each post-induction time point and recorded nausea, vomiting, hallucinations, and agitation. Diastolic blood pressure was not recorded; mean arterial pressure was therefore not calculated or imputed.

Ethics and consent: The study was approved by the Medical Ethics Committee of the National Cancer Institute, Misrata, Libya. Written informed consent was obtained from all participants before surgery (056-MJ-0023).

Statistical analysis: Continuous variables are summarized as mean ± standard deviation (SD), and categorical variables as number (percentage). Between-group comparisons of continuous variables used Welch's independent-samples t-test; categorical outcomes were compared using Fisher's exact test. The two co-primary outcomes were adjusted for multiplicity using the Holm procedure. Absolute risk differences and 95.0% confidence intervals (CIs) are reported for the primary outcomes. All 60 records were included; no imputation was performed. Statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Given the non-randomized allocation, findings are interpreted as associations rather than causal effects.

Results

Participant characteristics: 60 women were included, with 30 patients in each group. Baseline demographic and clinical characteristics are summarized in **Table 1**. The overall mean age was 65.1 ± 8.8 years (65.5 ± 8.7 in Group A and 64.7 ± 9.1 in Group B; p = 0.717). ASA physical status was I in 25 patients (41.7%), II in 29 (48.3%), and III in 6 (10.0%). The distribution of ASA status did not differ significantly between groups (p = 0.715).

Table 1: Baseline characteristics

Characteristic	Group A (n = 30)	Group B (n = 30)	P - value
Age, years, mean ± SD	65.5 ± 8.7	64.7 ± 9.1	0.717
ASA I, n (%)	11 (36.7)	14 (46.7)	
ASA II, n (%)	16 (53.3)	13 (43.3)	
ASA III, n (%)	03 (10.0)	03 (10.0)	0.715 *
Female, n (%)	30 (100)	30 (100)	

* *Overall comparison of ASA physical status distribution.*

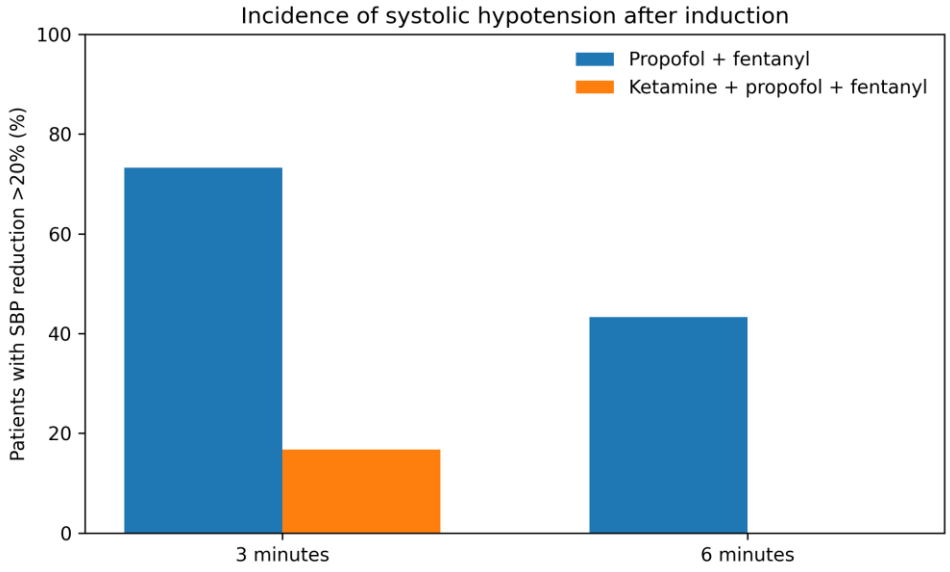
Primary outcomes: The proportions of patients meeting the primary outcome at both assessment points are illustrated in **Figure 1** and summarized in **Table 2**. At three minutes after induction, a systolic blood pressure reduction greater than 20.0% from baseline occurred in 22 patients (73.3%) in Group A and five patients (16.7%) in Group B (Fisher exact p = 0.000020; Holm-adjusted p = 0.000041). The absolute risk difference (Group A minus Group B) was 56.7 percentage points (95% CI 32.1 - 72.3).

At six minutes, the event occurred in 13 patients (43.3%) in Group A and no patients (0.0%) in Group B (Fisher exact p = 0.000046; Holm-adjusted p = 0.000046). The absolute risk difference was 43.3 percentage points (95.0% CI 23.8 - 60.8).

Table 2: Incidence of systolic blood pressure reduction > 20.0% from baseline

Time point	Group A (n = 30)	Group B (n = 30)	Absolute risk difference (95% CI)	Fisher p	Holm p
Three minutes	22 (73.3%)	5 (16.7%)	56.7% (32.1 - 72.3)	0.000020	0.000041
Six minutes	13 (43.3%)	0.0 (0%)	43.3% (23.8 - 60.8)	0.000046	0.000046

Figure 1: Patients with a systolic blood pressure reduction > 20.0% from baseline at three and six minutes after induction



Other hemodynamic measurements: Between-group hemodynamic measurements are presented in **Table 3**. Mean systolic blood pressure was lower in Group A than Group B at three minutes (110.3 ± 14.9 vs 129.3 ± 17.5 mmHg; $p < 0.001$) and at six minutes (114.3 ± 11.4 vs 131.3 ± 13.8 mmHg; $p < 0.001$). Mean heart rate did not differ significantly between groups at three minutes (74.8 ± 11.2 vs 71.4 ± 11.0 beats/min; $p = 0.241$) or six minutes (72.6 ± 12.9 vs 69.3 ± 13.2 beats/min; $p = 0.336$).

Table 3: Hemodynamic measurements after induction

Variable	Group A	Group B	p-value
Baseline SBP (mmHg)	139.1 ± 11.3	138.3 ± 12.4	0.803
SBP at 3 min (mmHg)	110.3 ± 14.9	129.3 ± 17.5	< 0.001
SBP at 6 min (mmHg)	114.3 ± 11.4	131.3 ± 13.8	< 0.001
Baseline HR (beats/min)	74.1 ± 7.5	73.1 ± 7.5	0.632
HR at 3 min (beats/min)	74.8 ± 11.2	71.4 ± 11.0	0.241
HR at 6 min (beats/min)	72.6 ± 12.9	69.3 ± 13.2	0.336

Values are mean ± SD. SBP, systolic blood pressure; HR, heart rate. Welch's t-test.

Adverse events: Recorded adverse events are summarized in **Table 4**. Nausea and vomiting were recorded in two patients (6.7%) in Group A and three patients (10.0%) in Group B (Fisher exact $p = 1.000$). No hallucinations or agitation were recorded. Neither atropine nor ephedrine was administered to any participant.

Table 4: Recorded adverse events

Adverse event	Group A (n = 30)	Group B (n = 30)	P - value
Nausea and vomiting	2 (6.7%)	3 (10.0%)	1.000
Hallucinations	0	0	Not estimable
Agitation	0	0	Not estimable

Nausea and vomiting occurred in the same five patients; these are not ten distinct patients.
Neither atropine nor ephedrine was administered.

Discussion

In this prospective comparative observational cohort of women aged 50 - 80 years, low-dose ketamine administered immediately before propofol was associated with a lower incidence of an SBP reduction greater than 20.0% at three and six minutes after induction. Mean systolic blood pressure was also higher in the ketamine group at both assessment points, whereas heart rate did not differ significantly between groups. These findings do not establish a causal protective effect because treatment allocation was not randomized. The direction of the association is consistent with previous work investigating ketamine-propofol combinations. Furuya and colleagues reported that ketamine administered before propofol attenuated arterial pressure changes [6]. Smischney and colleagues found fewer episodes of a 20.0% systolic blood pressure reduction with ketofol than with propofol alone at five and ten minutes [7, 14]. Hayakawa-Fujii and colleagues examined propofol combined with fentanyl, ketamine, or both, and reported differences in haemodynamic responses among regimens [8]. Goh and colleagues also compared ketamine-propofol, fentanyl-propofol, and propofol-saline before induction [9]. Other randomized studies have investigated ketofol in laparoscopic surgery and in different induction settings [10, 11]. Evidence is not uniform. In patients older than 50 years, Hosseinzadeh and colleagues compared ketamine-propofol with etomidate-propofol and found no significant between-group differences in measured hemodynamic variables [15]. Randomized work in emergency laparotomy has compared different ketamine-propofol ratios [16], while other studies have examined ketofol in patients with left ventricular dysfunction [17]

or propofol-midazolam-ketamine co-induction [18, 19]. A systematic review and meta-analysis of ten randomized trials (722 patients) found a higher pooled systolic pressure with ketamine-propofol at five minutes, but no statistically significant pooled differences in heart rate, diastolic pressure, or mean arterial pressure; the authors noted heterogeneity, risk of bias, and low certainty of evidence [20]. A separate systematic review of low-dose ketamine or opioids combined with propofol for emergency-department procedural sedation found insufficient evidence to establish consistent superiority of one combination [21]. These studies differ from the present study in dose, setting, airway management, and clinical outcomes.

The present study used ketamine 0.3 mg/kg immediately before propofol 2.0 mg/kg, with fentanyl 1.0 µg/kg in both groups. The observed between-group difference was substantial at both assessment points. Nevertheless, non-random allocation leaves the possibility of confounding by clinical selection, baseline risk, provider practice, or unmeasured perioperative factors. The results should therefore be considered hypothesis-generating. Research comparing low-dose ketamine with fentanyl for attenuating the response to laryngoscopy and intubation is relevant to the broader hemodynamic context, but it did not evaluate the same primary question or regimen [22]. Future randomized controlled studies involving larger and more diverse populations, including patients undergoing different surgical procedures, should use prespecified definitions of hypotension, record systolic, diastolic, and mean arterial pressures at standardized time points, document the use of rescue medications, and evaluate clinically meaningful perioperative outcomes beyond short-term blood pressure changes.

Conclusion: Among women aged 50 - 80 years undergoing general anesthesia, low-dose ketamine pretreatment before propofol was associated with a lower incidence of a systolic blood pressure reduction greater than 20.0% at three and six minutes after induction compared with propofol-based induction without ketamine.

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