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CLINICAL TRIAL REPORT

Efficacy and Safety of Esketamine–Lidocaine for Anesthesia Induction in Elderly Patients Undergoing Elective Surgery: A Randomized Controlled Trial

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Background: Esketamine, the S-enantiomer of ketamine, has sympathomimetic and analgesic properties. Intravenous lidocaine provides sedative and analgesic adjuvant effects and blunts airway reflexes during anesthesia induction. However, the role of their combination in elderly patients remains unclear. This study aimed to compare the efficacy and safety of esketamine–lidocaine–propofol induction with those of sufentanil–propofol induction in this population.

Methods: In this prospective, double-blind, randomized trial, 116 elderly patients undergoing elective surgery were assigned to receive esketamine (0.5 $mg \cdot kg^{-1}$), lidocaine (1.5 $mg \cdot kg^{-1}$), and propofol (Group E) or sufentanil (0.4 $\mu g \cdot kg^{-1}$) and propofol (Group S) for anesthesia induction. The primary outcomes were the incidence of hypotension and the absolute area under the curve (AUC) of mean arterial pressure (MAP) deviation, measured during anesthesia induction (from the initiation of anesthetic drug administration to 5 minutes after tracheal intubation).

Results: The absolute AUC for Group E was smaller than that for Group S (93.83 [79.74–130.78] mmHg·min vs.147.50 [99.38–-210.62] mmHg·min), with a median difference of −51.09 mmHg·min (95% confidence interval (CI), −84.53– −14.00; $P = 0.005$). The incidence of hypotension in the Group E was lower than Group S (62.1% vs 82.8%), with a relative risk of 0.750 (95% CI, 0.594–0.947; $P = 0.013$). The incidence of coughing ($P < 0.001$) and total phenylephrine dose ($P < 0.001$) were significantly lower in Group E than Group S, whereas BIS values at 2–5 minutes post-intubation were significantly higher ($P < 0.05$). There were no serious adverse events in either group.

Conclusion: Esketamine–lidocaine–propofol improved hemodynamic stability and reduced adverse events compared with sufentanil–propofol, supporting its use for anesthesia induction in elderly patients.

Keywords: esketamine, lidocaine, elderly patients, induction

Introduction

Elderly patients undergoing general anesthesia are highly susceptible to hemodynamic instability during induction due to diminished cardiac reserve, vascular stiffness, and attenuated autonomic reflexes.[1,2] Peri-induction hypotension has been linked to organ hypoperfusion, postoperative complications, and increased mortality, emphasizing the need for strategies that preserve cardiovascular stability in this population.[3]

Propofol in combination with sufentanil remains a widely used induction regimen due to its rapid onset, reliable hypnosis, and attenuation of intubation-induced sympathetic surges.[4] However, this approach is not without drawbacks. Intravenous administration of sufentanil may cause several adverse effects, such as nausea, vomiting, cough, chest tightness, dizziness, and even respiratory depression, with the incidence of cough reported to be as high as 40%.[5] Although these reactions are usually transient, severe cough can increase intracranial, intraocular, and intra-abdominal

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pressures, potentially leading to complications in high-risk patients. Moreover, both propofol and sufentanil exert dose-dependent vasodilatory and negative inotropic effects, which can exacerbate peri-induction hypotension, particularly in elderly patients with impaired autonomic reserve.

Esketamine, the S-enantiomer of ketamine, is a potent N-methyl-D-aspartate (NMDA) receptor antagonist with strong analgesic and sedative properties and a more favorable side-effect profile than racemic ketamine.[6] At subanesthetic doses, it enhances central sympathetic activity and promotes endogenous catecholamine release, counterbalancing anesthetic-induced vasodilation and supporting blood pressure in hypotension-prone populations, such as the elderly or those with shock.[7] Additionally, esketamine induces bronchodilation without provoking histamine release, and its NMDA receptor antagonism, combined with intrinsic analgesic properties, may attenuate stress responses and reduce opioid-associated adverse events, including induction-related coughing.[8,9] Intravenous lidocaine, a versatile local anesthetic, has similarly been shown to reduce anesthetic requirements and suppress airway reflexes, further contributing to a smoother induction process and enhanced hemodynamic stability.[10–12] Prior clinical evidence suggests that lidocaine–ketamine combinations confer favorable hemodynamic profiles, even in high-risk populations such as patients with septic shock undergoing rapid sequence induction.[13]

Thus, the present randomized controlled trial was designed to compare the effects of two induction regimens esketamine–lidocaine–propofol versus sufentanil–propofol on hemodynamic stability during the induction period (from induction onset to 5 minutes after intubation) in elderly patients undergoing elective non-cardiac surgery. We hypothesized that the esketamine–lidocaine regimen would reduce the incidence of post-induction hypotension, provide more stable hemodynamic control, and thereby improve perioperative outcomes compared with the conventional sufentanil–propofol protocol.

Materials and Methods

This study was a prospective, single-center, double-blind, randomized controlled clinical trial conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Jiangxi Provincial People's Hospital (The First Affiliated Hospital of Nanchang Medical College), Nanchang, China (Chairperson: Professor Xu Renxu) on 13 December 2024 (Approval No. Kekuai 2024(89)). The trial was prospectively registered with the Chinese Clinical Trial Registry (ChiCTR2400094676) on 16 December 2024 (www.chictr.org.cn). All participants provided written informed consent prior to enrollment, allowing for the use of their clinical and personal data, including any potentially identifiable information, for research and publication purposes. The study followed the CONSORT reporting guidelines.

In the trial registration, the induction dose of propofol was initially specified as 2.0 $mg \cdot kg^{-1}$. Prior to patient enrollment, this was amended to 1.5 $mg \cdot kg^{-1}$ based on pilot study findings to reduce the risk of hypotension while maintaining adequate anesthetic depth. This modification was implemented before randomization and blinding, and did not impact trial integrity. Details regarding this protocol amendment are provided in Supplementary File 1.

Study Design and Patient Selection

From January to May 2025, a total of 120 patients aged 60 to 80 years who were scheduled for elective non-cardiac surgery under general anesthesia were recruited at Jiangxi Provincial People's Hospital (The First Affiliated Hospital of Nanchang Medical College).

Eligible patients met the following inclusion criteria: (1) ASA physical status II–III; (2) body mass index (BMI) between 18.5 and 25 $kg\ m^{-2}$; (3) fasting for at least 8 hours and abstaining from fluids for 2 hours prior to anesthesia. Exclusion criteria included: (1) known allergy to any of the induction agents; (2) severe hepatic dysfunction (Child–Pugh class C) or renal insufficiency as defined by Kidney Disease Improving Global Outcomes guidelines; (3) grade 3 hypertension, defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥ 110 mmHg; (4) elevated intracranial or intraocular pressure; (5) history of myocardial infarction within the past 6 months or severe heart failure, classified as New York Heart Association (NYHA) class III–IV or a left ventricular ejection fraction <50%; (6) psychiatric or neurological disorders, including Alzheimer's disease, stroke, traumatic brain injury, intracerebral hemorrhage, or intracranial mass lesions; (7) long-term use of sedatives or antidepressants; (8) inability to communicate or cooperate; and (9) current participation in another clinical trial. There were no specific eligibility criteria for study sites or for individuals delivering the intervention.

Randomization and Blinding

Eligible patients were randomly assigned in a 1:1 ratio to either the esketamine–lidocaine group (Group E) or the sufentanil group (Group S). The random allocation sequence was generated by an independent statistician, who was not involved in patient recruitment, data collection, or analysis, using the Random Number Generator function in SPSS Statistics software (version 27.0; IBM Corp., Armonk, NY, USA). A fixed random seed was set to ensure reproducibility. Allocation concealment was maintained with sequentially numbered, opaque, sealed envelopes, which were opened immediately before anesthesia induction by an anesthesiologist not involved in outcome assessment.

This was a double-blind study. Both patients and outcome assessors were blinded to group allocation. To maintain blinding, all study drugs were prepared in identical 10 mL syringes by a nurse anesthetist who was not involved in the subsequent clinical management or data analysis. The syringes were labeled with only the patient's study number.

The anesthesiologists who administered the anesthesia were not involved in data collection or outcome evaluation. All hemodynamic data and clinical outcomes were assessed by independent investigators who were blinded to group assignment throughout the perioperative period.

Procedure and Interventions

On the day of surgery, diuretics and angiotensin receptor blockers (ARBs) / angiotensin-converting enzyme inhibitors (ACEIs) were withheld, and maintenance fluids were administered in the ward to reduce perioperative hypotension. No regional anesthesia, sedative premedication, or analgesics were given before induction. Preoperative pain was assessed using the visual analog scale (VAS), and all patients had scores < 2 to ensure baseline comfort and physiological comparability. In the operating room, following a positive Allen's test by an experienced anesthesiologist, radial artery cannulation was performed under local anesthesia for continuous invasive blood pressure monitoring. Patients were instructed to remain relaxed to minimize anxiety, and 100% oxygen was delivered via a face mask at 8 $L \cdot min^{-1}$. Once calm and cooperative, baseline mean arterial pressure (MAP; averaged over three readings), heart rate (HR), and bispectral index (BIS) values were recorded.

Anesthesia induction was performed as follows. In both groups, remimazolam (0.2 $mg \cdot kg^{-1}$; Nhwa Pharmaceutical Co., Ltd., Lianyungang, Jiangsu, China) was administered first. In Group E, remimazolam was followed by intravenous lidocaine (1.5 $mg \cdot kg^{-1}$; Qidu Pharmaceutical Co., Ltd., Zibo, Shandong, China) and then esketamine (0.5 $mg \cdot kg^{-1}$; Nhwa Pharmaceutical Co., Ltd., Nanjing, Jiangsu, China). In Group S, remimazolam was followed by an equivalent volume of 0.9% saline and then sufentanil (0.4 $\mu g \cdot kg^{-1}$; Renfu Pharmaceutical Group Co., Ltd., Yichang, Hubei, China). The sequence of these three agents in each group (remimazolam plus either lidocaine and esketamine, or saline and sufentanil) was completed within 2 minutes. All study drugs —esketamine, lidocaine, sufentanil, and 0.9% saline — were each prepared separately as 10 mL solutions and loaded into identical syringes to ensure blinding.

Following the administration of the above agents, all patients received intravenous propofol (1.5mg kg^{-1}; manufactured by Guorui Pharmaceutical Co., Ltd., Chengdu, Sichuan, China) and rocuronium (0.6 mg kg^{-1}; manufactured by Tonghui Pharmaceutical Co., Ltd., emeishan, Sichuan, China) over 1 minute. After the onset of apnea, manual ventilation was performed using 8 L min^{-1} of 100% oxygen for 3 minutes to increase oxygen reserve. Tracheal intubation was performed by an experienced attending anesthesiologist within 30 seconds.

Post-intubation, mechanical ventilation was initiated with a tidal volume of 8 mL kg^{-1} and a respiratory rate of 12–16 breaths min^{-1}. Ventilation parameters were adjusted as necessary to maintain end-tidal CO_2 between 35–45 mmHg. Five minutes after intubation, total intravenous anesthesia was maintained using target-controlled infusion of propofol and remifentanil. Rocuronium was administered intermittently to maintain adequate muscle relaxation as required. The BIS value was maintained between 40 and 60 throughout the surgical procedure.

MAP, HR, and BIS values were recorded at the following time points: before induction (baseline, T_0), immediately after administration of induction agents (T_1), immediately before intubation (T_2), immediately after intubation (T_3), and at 1-, 2-, 3-, 4-, and 5-minutes post-intubation (T_4 -T_8). Arterial blood gas samples were collected at T_0 and before skin incision to assess changes in blood glucose and lactate levels. The incidence of adverse events, including coughing, hypertension (MAP > 110 mmHg or > 20% above baseline), and tachycardia (HR >100 bpm or >20% above baseline), was recorded during the induction period.

Outcome Measures

The primary outcomes were the absolute AUC of the deviation between MAP and baseline during the induction period (from drug administration to 5 minutes post-intubation) and the incidence of hypotension, defined as MAP reduction >20% from baseline or MAP < 65 mmHg sustained for ≥1 minute. Both elevations and reductions in MAP were included in the AUC calculation to reflect overall hemodynamic fluctuation (the absolute AUC). The absolute AUC for MAP deviation from baseline was estimated using the trapezoidal rule based on MAP values recorded at discrete time points (T_1–T_8). The resulting absolute AUC was expressed in units of mmHg·min.

The secondary outcomes included bispectral index (BIS) values during induction; blood glucose and lactate levels measured at two time points (before induction and prior to skin incision); the number of patients requiring additional boluses of propofol; the cumulative dose of phenylephrine administered; the amplitude of MAP and HR fluctuations during induction; and the incidence of adverse events, including coughing, hypertension, and tachycardia.

Crisis Management

During tracheal intubation, if BIS value exceeded 60, a rescue dose of propofol (0.5 mg kg^{-1}) was administered to deepen sedation. Hypotension was defined as MAP reduction > 20% from baseline or MAP < 65 mmHg sustained for ≥ 1 minute. In such cases, intravenous phenylephrine (40 μg) was administered and repeated as necessary. Hypertension was defined as MAP > 110 mmHg or a > 20% increase from baseline, and treated with urapidil (5 mg) or esmolol (10 mg). Bradycardia (HR < 50 beats min^{-1}) was treated with atropine (0.5 mg), while tachycardia (HR > 100 beats min^{-1}) was managed with esmolol (10 mg). No interim analyses or stopping guidelines were specified.

Statistical Analysis

Based on preliminary data from our pilot study conducted using a propofol induction dose of 1.5 mg·kg^{-1}, the incidence of hypotension during anesthesia induction was approximately 40% in Group E and 70% in Group S. Assuming a two-sided α level of 0.05 and a power (1−β) of 80%, and accounting for an estimated 20% dropout rate, each group would require 53 patients. Consequently, a total of 120 patients (60 per group) were required for this study.

The sample size was primarily determined based on the expected difference in the incidence of hypotension, which was considered the clinically dominant endpoint. The AUC of MAP deviation was included as an additional co-primary outcome to provide quantitative support for the assessment of hemodynamic stability.

To assess baseline comparability between groups, absolute standardized differences (ASD) were calculated for key baseline variables, including sex, age, height, weight, body mass index (BMI), ASA physical status, comorbidities, and surgical type. Differences greater than $1.96 \times \sqrt{\frac{1}{N1} + \frac{1}{N2}}$ (N1, Number of participants in group 1; N2, Number of participants in group 2) were considered imbalanced.[14,15] Calculated differences > 0.365 were considered imbalanced in this trial.

Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed with the Shapiro–Wilk test. Data with a normal distribution were expressed as mean ± SD and compared using independent-samples t-tests, with mean differences and 95% confidence intervals (CIs) reported. Non-normally distributed data were summarized as median (interquartile range [IQR]) and analyzed using the Mann–Whitney *U*-test, with median differences and 95% CIs calculated when applicable. Categorical variables were presented as counts (percentages) and compared using the chi-square test or Fisher's exact test, with relative risks (RRs) and 95% CIs provided.

All statistical tests were two-sided, with a nominal significance level of $P < 0.05$. For primary outcomes, statistical significance was determined using a Bonferroni-adjusted threshold of $P < 0.025$ (0.05/2) to account for two co-primary endpoints. For secondary outcomes, to control for potential type I error due to multiple testing, Bonferroni correction was applied, with an adjusted significance threshold of $P < 0.0063$ (0.05/8).

An exploratory, post hoc subgroup analysis was conducted in patients with a history of hypertension to evaluate between-group differences in the incidence of intra-induction hypotension, hypertension, and tachycardia. Baseline balance within this subgroup was assessed using absolute standardized differences (ASDs), with values > 0.588 considered indicative of potential imbalance in this subgroup analysis. Given three subgroup comparisons, a Bonferroni-adjusted significance threshold of $P < 0.017$ (0.05/3) was applied. These subgroup results are considered hypothesis-generating.

Results

The trial was completed as planned without early termination. A total of 120 elderly patients were screened for eligibility between January and May 2025. Of these, two patients were excluded due to surgery cancellation and another two declined to participate. The remaining 116 patients were enrolled in the clinical study and randomly divided into two groups: the esketamine–lidocaine group (Group E, n =58), or the sufentanil group (Group S, n =58) (Figure 1). Interventions and comparators were administered intravenously by experienced anesthesiologists in the operating room according to the study protocol. All patients received standard perioperative care in accordance with institutional protocols. This included preoxygenation with 100% oxygen and mechanical ventilation following intubation. No additional sedatives, analgesics, or vasoactive drugs were administered during the 5-minute induction observation period unless clinically indicated. Hemodynamic management, including phenylephrine use, was recorded and standardized between groups. No other concomitant medications were systematically administered during the induction phase. Similar baseline characteristics were observed in the randomized patients and all ASDs were < 0.365 (Table 1). Anesthesia was successfully induced in all patients.

Primary Outcomes

The absolute area under the curve (AUC) representing the deviation of mean arterial pressure (MAP) from baseline and the incidence of intra-induction hypotension are shown in Figure 2. Compared with Group S, Group E exhibited a smaller absolute AUC of MAP deviation during anesthesia induction, along with a lower incidence of intra-induction hypotension.

Secondary Outcomes

No serious adverse events occurred in either group. Group E demonstrated a lower incidence of coughing and required a smaller cumulative dose of phenylephrine during induction compared with Group S (Table 2 and Supplementary Figure S1). Other secondary outcomes—including the need for additional propofol, incidences of hypertension and tachycardia and blood glucose and lactate levels at two measurement time points—did not differ significantly between groups after accounting for

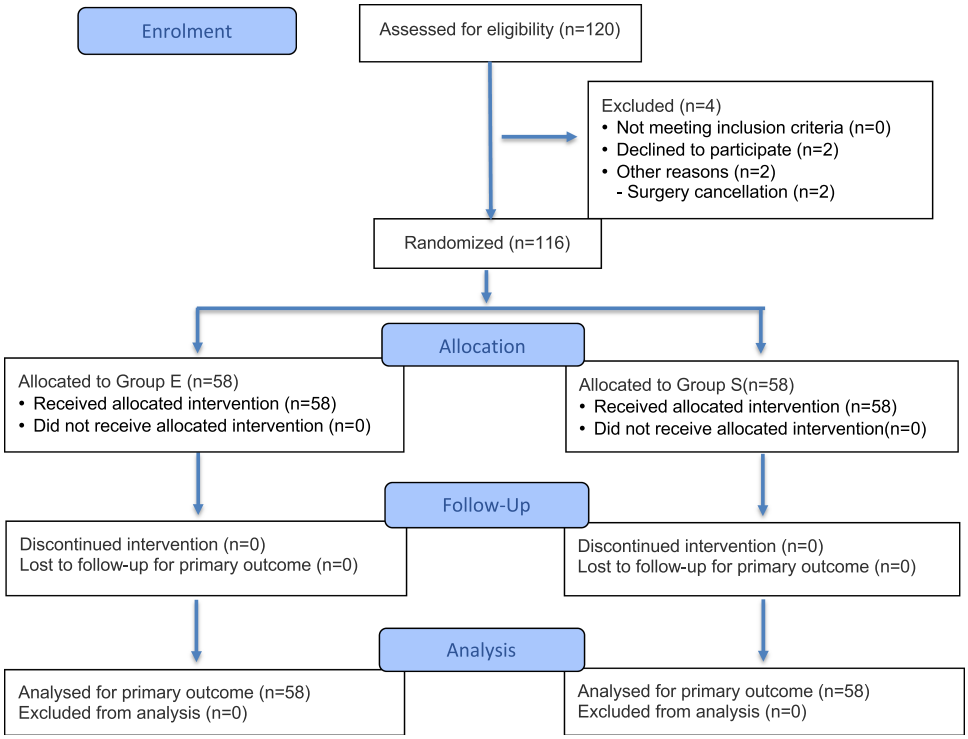

Figure 1 CONSORT flow chart of the trial.

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Table 1 Patient Demographics and Baseline Values

	Group E (*n*=58)	Group S (*n*=58)	ASD
Age (yr)	68.1 ± 5.3	69.2 ± 5.0	0.213
Gender n (%)			
Male	38 (65.5)	31 (53.4)	0.248
Female	20 (34.5)	27 (46.6)	
Height (cm)	161.5 ± 7.2	160.3 ± 8.4	0.153
Weight (kg)	58.6 ± 5.0	57.3 ± 7.8	0.199
BMI (kg m^{-2})	22.5 ± 2.0	22.2 ± 1.9	0.154
ASA n (%)			
II	50 (86.2)	48 (82.8)	0.095
III	8 (13.8)	10 (17.2)	
Combined diseases n (%)			
Hypertension	25 (43.1)	20 (34.5)	0.178
Diabetes	5 (8.6)	6 (10.3)	0.059
Hypertension& diabetes	4 (6.9)	6 (10.3)	0.123
Surgery type n (%)			
Abdominal surgery	30 (51.7)	32 (55.2)	0.069
Urologic surgery	19 (32.8)	19 (32.8)	< 0.001
Otolaryngologic surgery	6 (10.3)	5 (8.6)	0.059
Breast surgery	3 (5.2)	2 (3.4)	0.085

Notes: Data are presented as mean ± SD or number (%). Absolute standardized difference (ASD) is the absolute difference in group means divided by the pooled standard deviation. Calculated differences > 0.365 were considered imbalanced in this table.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; ASD, Absolute standardized difference.

multiple comparisons. With respect to hemodynamic variability, MAP differences from baseline (T0) were significant at T_1, T_2, T_3, T_6, T_7, and T_8, while HR differences were significant at T_4 and T_5 (Table 3). Group E exhibited higher BIS values than Group S from 2 to 5 minutes post-intubation (T_5–T_8) (Table 4 and Supplementary Figure S1).

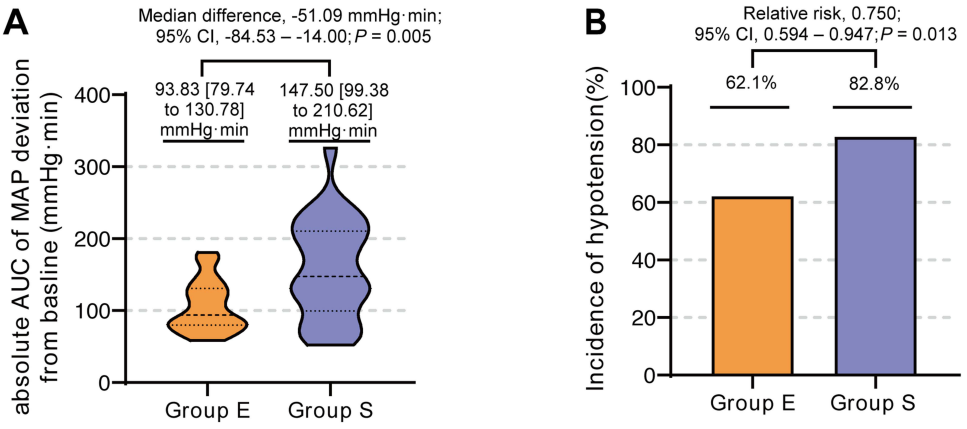

Figure 2 Primary outcomes. Comparison of the change in the absolute AUC of MAP deviation from baseline (**A**) and incidence of hypotension (**B**) between the two groups. *P* values <0.025 indicates statistical significance (Bonferroni correction). (**A**) the absolute AUC of the deviation between MAP and baseline during the induction period (from drug administration to 5 minutes post-intubation). Both elevations and reductions in MAP were included in the AUC calculation to reflect overall hemodynamic fluctuation (the absolute AUC). The absolute AUC for MAP deviation from baseline was estimated using the trapezoidal rule based on MAP values recorded at discrete time points (T_1–T_8). The resulting absolute AUC was expressed in units of mmHg·min. Violin plots show medians (thick dashed Line) and the 25th and 75th percentiles (thin dotted line). The absolute AUC for Group E was smaller than that for Group S, with a median difference of −51.09 mmHg·min (*P* = 0.005). (**B**) the incidence of hypotension, defined as MAP reduction > 20% from baseline or MAP < 65 mmHg sustained for ≥1 minute. The incidence of hypotension in the Group E was lower than Group S, with a relative risk of 0.750 (*P* = 0.013).
Abbreviations: AUC, area under the curve; CI, confidence intervals; MAP, mean arterial pressure.

Table 2 Secondary Outcomes

	Group E (*n*=58)	Group S (*n*=58)	Median Difference (95% CI) or RR (95% CI)	[a]*P*
Additional propofol n (%)	0 (0)	0 (0)	–	–
Adverse events n (%)				
Coughing	3 (5.2)	18 (31.0)	0.167 (0.052–0.535)	< 0.001
Hypertension	10 (17.2)	4 (6.9)	2.500 (0.831–7.517)	0.087
Tachycardia	12 (20.7)	7 (12.1)	1.714 (0.727–4.044)	0.210
Pre-induction				
Blood glucose (mmol L^{-1})	5.20 [4.60 to 5.93]	5.30 [4.58 to 6.15]	0.000 (−0.700–0.500)	0.869
Lactate (mmol L^{-1})	1.18 [0.89 to 1.58]	1.05 [0.84 to 1.33]	0.070 (−0.120–0.340)	0.405
Pre-incision				
Blood glucose (mmol L^{-1})	5.15 [4.60 to 5.60]	5.00 [4.53 to 5.75]	0.200 (−0.300–0.700)	0.509
Lactate (mmol L^{-1})	1.01 [0.78 to 1.51]	0.87 [0.70 to 1.10]	0.120 (−0.030–0.320)	0.124
Total dose of phenylephrine (μg)	40.00 [0.00 to 85.00]	100.00 [57.50 to 150.00]	−60.00(−80.00 – −40.00)	< 0.001

Notes: Data are presented as median [IQR] or numbers (%). For continuous variables with non-normal distributions, differences between groups were estimated using the Hodges–Lehmann method and expressed as median difference with 95% CI; For categorical outcomes, RR and 95% CI were calculated to assess between-group differences in incidence rates. [a]$P < 0.0063$ indicates statistical significance (Bonferroni correction).
Abbreviations: AUC, area under the curve; CI, confidence interval; RR, relative risk.

Table 3 Comparison of Changes in Vital Signs Over Different Time Periods

	Group E (*n*=58)	Group S (*n*=58)	Mean or Median Difference (95% CI)	[a]*P*
ΔMAP (mmHg)				
T_1-T_0	12.65 ± 7.68	20.23 ± 10.15	−7.58 (−12.59 – −2.56)	0.004
T_2-T_0	10.00 [6.00 to 12.00]	28.00 [22.00 to 33.00]	−15.50 (−21.00 – −8.00)	0.001
T_3-T_0	12.50 [4.00 to 20.00]	20.00 [11.75 to 32.00]	−7.00 (−14.00–0.00)	0.032
T_4-T_0	25.50 ± 16.04	18.08 ± 12.46	7.42 (−0.59–15.43)	0.069
T_5-T_0	18.12 ± 11.86	23.08 ± 13.22	−4.96 (−11.96–2.03)	0.160
T_6-T_0	13.73 ± 8.56	22.81 ± 14.92	−9.08 (−15.89 – −2.26)	0.010
T_7-T_0	14.15 ± 8.30	26.27 ± 12.95	−12.11 (−18.20 – −6.03)	< 0.001
T_8-T_0	11.27 ± 7.01	24.00 ± 12.02	−12.73 (−18.25 – −7.21)	< 0.001
ΔHR (bpm)				
T_1-T_0	9.00 [4.00 to 13.00]	13.50 [6.75 to 20.50]	−3.00 (−8.00–1.00)	0.097
T_2-T_0	7.00 [2.00 to 16.00]	5.00 [2.00 to 8.25]	2.00 (−1.00–6.00)	0.226
T_3-T_0	11.50 [3.75 to 22.00]	10.50 [7.00 to 20.00]	0.00 (−6.00–5.00)	0.956
T_4-T_0	20.00 [9.75 to 30.75]	6.00 [2.75 to 12.50]	10.00 (5.00–17.00)	0.001
T_5-T_0	10.50 [5.75 to 22.75]	6.00 [3.75 to 11.00]	4.00 (0.00–9.00)	0.045
T_6-T_0	7.00 [3.00 to 16.00]	8.50 [6.00 to 16.00]	−1.00 (−4.00–4.00)	0.693
T_7-T_0	9.50 [1.75 to 17.00]	11.00 [6.75 to 16.00]	−2.00 (−6.00–2.00)	0.279
T_8-T_0	7.50 [3.00 to 13.50]	13.00 [7.00 to 15.25]	−3.00 (−8.00–1.00)	0.092

Notes: Data are presented as mean ± SD or median [IQR]. Δ values indicate absolute changes from baseline (T_0). Continuous variables with normal distribution are reported as mean differences (95% CI); For continuous variables with non-normal distributions, differences between groups were estimated using the Hodges–Lehmann method and expressed as median difference with 95% CI; [a]$P < 0.05$ indicates statistical significance.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; T_0 (Baseline), Before induction of anesthesia; T_1, Immediately after induction drug administration; T_2, Before tracheal intubation; T_3, Immediately after intubation completion; T_4, 1minute post-intubation; T_5, 2 minutes post-intubation; T_6, 3 minutes post-intubation; T_7, 4 minutes post-intubation; T_8, 5 minutes post-intubation.

Exploratory Subgroup Analysis

An exploratory analysis was performed in patients with a history of hypertension (Group S, *n* =25; Group E, *n* =20). Baseline demographic and clinical characteristics were comparable between groups (Supplementary Table S1). Within

Table 4 Comparison of BIS Values Across Time Points

Time Point	Group E (*n*=58)	Group S (*n*=58)	Mean Difference (95% CI)	[a]*P*
T_0	93.42 ± 2.35	93.65 ± 2.28	−0.23 (−1.52–1.06)	0.721
T_1	64.00 ± 14.85	57.42 ± 15.29	6.58 (−1.82–14.97)	0.122
T_2	27.73 ± 3.54	27.42 ± 1.98	0.31 (−1.30–1.91)	0.700
T_3	30.96 ± 3.27	31.27 ± 2.03	−0.31 (−1.82–1.21)	0.686
T_4	35.46 ± 5.01	34.46 ± 3.29	1.00 (−1.37–3.37)	0.399
T_5	47.31 ± 9.05	40.88 ± 8.17	6.42 (1.62–11.22)	0.010
T_6	54.04 ± 8.60	44.27 ± 11.10	9.77 (4.24–15.30)	0.001
T_7	57.35 ± 7.95	44.50 ± 11.29	12.85 (7.41–18.28)	< 0.001
T_8	60.88 ± 6.28	48.27 ± 11.50	12.61 (7.42–17.81)	< 0.001

Notes: Data are presented as mean ± SD. Continuous variables with normal distribution are reported as mean differences (95% CI). [a]*P* <0.05 indicates statistical significance.

Abbreviations: BIS, Bispectral Index; T_0 (Baseline), Before induction of anesthesia; T_1, Immediately after induction drug administration; T_2, Before tracheal intubation; T_3, Immediately after intubation completion; T_4, 1minute post-intubation; T_5, 2 minutes post-intubation; T_6, 3 minutes post-intubation; T_7, 4 minutes post-intubation; T_8, 5 minutes post-intubation; CI, confidence interval.

this subgroup, the incidence of intra-induction hypotension appeared lower in Group E compared with Group S (55.0% vs 88.0%; RR, 0.625; 95% CI, 0.410–0.953). Incidences of intra-induction hypertension and tachycardia showed no significant differences between groups (all *P*-values for interaction > 0.017; Supplementary Table S2).

Discussion

In this randomized controlled trial, induction with an esketamine–lidocaine–propofol regimen significantly reduced both the incidence and severity of post-induction hypotension compared with a conventional sufentanil–propofol protocol, while maintaining a favorable safety profile decreasing both the frequency of coughing and the requirement for phenylephrine. These findings suggest that an opioid-free, multimodal induction strategy may offer clinical advantages in elderly patients who are susceptible to peri-induction hemodynamic instability.

From a pharmacological perspective, esketamine and lidocaine exert complementary actions that underlie the rationale of this induction strategy. Esketamine, through its sympathomimetic activity, counteracts the vasodilatory and negative inotropic effects of propofol, thereby supporting blood pressure stability during induction. Lidocaine primarily acts by blocking voltage-gated sodium channels on sensory neurons, which attenuates airway reflexes and reduces cough responses triggered by opioids or tracheal instrumentation. In addition, lidocaine provides mild analgesic and anti-inflammatory effects and mitigates sympathetic activation associated with laryngoscopy. The synergistic pharmacodynamic profile of these two agents thus contributes to both hemodynamic stability and smoother airway management in elderly patients.

Our empirical results are consistent with these pharmacologic expectations. The incidence of hypotension was lower (62.1% vs 82.8%), with a comparable ~20% relative reduction to that reported by Zhang,[16] despite our higher rates due to remimazolam co-administration and a stricter definition of hypotension (sustained ≥1 min MAP reduction >20% or MAP < 65 mm Hg). Notably, patients receiving esketamine required significantly less phenylephrine, supporting the interpretation that esketamine's sympathomimetic properties contributed materially to improved hemodynamic stability rather than the benefit being secondary to increased vasopressor use.

A transient, mild increase in heart rate was observed approximately 2 minutes after intubation in the esketamine group, which aligns with esketamine's expected sympathetic effect. Importantly, this tachycardic response was short-lived and was not accompanied by sustained hypertension or clinically significant arrhythmias in our cohort, suggesting acceptable cardiovascular tolerability at the 0.5 $mg \cdot kg^{-1}$ induction dose when administered with appropriate monitoring. Nevertheless, clinicians should exercise caution in patients with severe ischemic heart disease or markedly reduced myocardial reserve, since even modest increases in heart rate may increase myocardial oxygen demand.

Cough is a common adverse event during anesthesia induction, typically arising from increased airway sensitivity, mechanical irritation, or drug-induced modulation of respiratory reflexes.[17] Reducing cough not only facilitates smoother induction but may also lessen intubation-related complications—such as laryngeal trauma, hemodynamic fluctuations,

and transient intracranial pressure surges—which is particularly important in elderly patients with limited cardiovascular and cerebrovascular reserve. Previous studies have demonstrated that pretreatment with esketamine or Lidocaine effectively suppresses opioid-induced coughing.[18,19] For example, low-dose esketamine reduced the incidence of sufentanil-induced cough from 34.7% to 6.0% in one randomized trial.[20] In our study, cough occurred in 31% of patients receiving sufentanil–propofol but in only 5.2% of those receiving esketamine–lidocaine–propofol—a sixfold reduction (RR 0.167, 95% CI 0.052–0.535). This pronounced reduction plausibly reflects lidocaine's primary antitussive action augmented by esketamine's bronchodilatory/antitussive properties, producing a less reactive airway during induction.

Although BIS values were elevated in the esketamine group during the 2–5 minutes following intubation, no clinical signs of inadequate sedation were observed, no supplemental propofol was required, and no instances of intraoperative awareness were reported during postoperative follow-up. These findings—consistent with previous reports describing the dissociative properties of NMDA antagonists and their potential to decouple BIS readings from true hypnotic depth—underscore the importance of interpreting BIS alongside clinical and hemodynamic indicators rather than as a standalone metric in esketamine-based regimens.[21,22]

In a prespecified exploratory analysis of patients with preexisting hypertension, the esketamine–lidocaine regimen was associated with a 37.5% relative reduction in intra-induction hypotension compared with sufentanil–propofol (55.0% vs 88.0%; RR 0.625, 95% CI 0.410–0.953). Incidences of hypertension and tachycardia did not differ significantly between groups. While these results suggest potential utility of esketamine–lidocaine in this high-risk cohort, they should be interpreted cautiously given the exploratory nature and limited statistical power.

Although esketamine possesses favorable analgesic and sedative properties, its adverse effects are clearly dose-dependent. At higher doses, the risks of dissociation, hallucinations, and hemodynamic excitation (elevated blood pressure and heart rate) increase.[23] Previous studies have shown that a single intravenous dose of 0.5 $mg \cdot kg^{-1}$ esketamine for anesthesia induction is well tolerated, with a low incidence of psychotomimetic symptoms and serious cardiovascular events.[24] Given that the present study focused on hemodynamic stability and safety during induction with the esketamine–lidocaine regimen in elderly patients, psychiatric manifestations were not designated as primary or secondary endpoints. Nevertheless, all participants were closely monitored in the post-anesthesia care unit and during postoperative follow-up, and no hallucinations, agitation, or dissociative symptoms were observed. This may be attributable to the moderate esketamine dose (0.5 $mg \cdot kg^{-1}$) used and the concurrent administration of remimazolam, which provides sedative and anxiolytic effects that may mitigate esketamine-related psychotropic reactions.[25] Lidocaine, one of the most widely used anesthetic agents, is traditionally applied for local or regional anesthesia. Although intravenous lidocaine administration has shown perioperative benefits in certain clinical studies, concerns regarding potential systemic toxicity have limited its broader use. At appropriate doses ($\leq$ 1.5 $mg \cdot kg^{-1}$), intravenous lidocaine appears to be safe and potentially beneficial in the perioperative setting;[26] however, excessive or cumulative dosing, as well as impaired hepatic or renal clearance, may markedly increase the risk of central nervous system and cardiovascular toxicity, necessitating careful monitoring.

Despite these promising findings, our study has several limitations. First, it was a single-center trial with a relatively small sample size, which may limit generalizability of the results. However, the use of rigorous randomization, double-blinding, and balanced baseline characteristics helped ensure internal validity. Second, although the sample size estimation was primarily based on the incidence of hypotension, post hoc analyses confirmed that the achieved cohort size provided sufficient statistical power for both co-primary endpoints, thereby supporting the robustness and reliability of the findings. Third, postoperative outcomes such as cognitive function, delirium incidence, and broader recovery profiles were not systematically assessed. Although no psychotropic symptoms (eg, agitation, hallucination, or emergence delirium) were observed during recovery or follow-up, future studies should incorporate standardized neuropsychiatric assessments to comprehensively evaluate the neurobehavioral safety of esketamine. Fourth, the two-arm design of this trial does not allow for separation of the independent effects of esketamine and lidocaine; factorial or multi-arm studies are needed to further clarify their individual and synergistic contributions. Finally, BIS monitoring may underestimate hypnotic depth in the presence of NMDA antagonists; thus, concurrent clinical and hemodynamic evaluation remains essential. Future multicenter studies with larger sample sizes and mechanistic investigations are warranted to validate these findings and explore the underlying pharmacodynamic interactions of this regimen.

Conclusion

Compared with sufentanil, the esketamine-lidocaine combination significantly reduces the incidence of hypotension during anesthesia induction in elderly patients undergoing elective surgery and provides more stable hemodynamic control. Additionally, it lowers the occurrence of induction-related coughing. These findings suggest that esketamine-lidocaine is a safe and effective regimen for anesthesia induction in the elderly population.

Abbreviations

AUC, area under the curve; CI, confidence interval; RR, relative risk; ASA, American Society of Anesthesiologists; BMI, body mass index; ASD, Absolute standardized difference; MAP, mean arterial pressure; HR, heart rate; T_0, Before induction of anesthesia; T_1, Immediately after induction drug administration; T_2, Before tracheal intubation; T_3, Immediately after intubation completion; T_4, 1minute post-intubation; T_5, 2 minutes post-intubation; T_6, 3 minutes post-intubation; T_7, 4 minutes post-intubation; T_8, 5 minutes post-intubation; BIS, Bispectral Index; CI, confidence interval; RR, relative risk.

Data Sharing Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Informed Consent

This prospective clinical trial was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Jiangxi Provincial People's Hospital (The First Affiliated Hospital of Nanchang Medical College) [reference No. Kekuai 2024(89); December 13, 2024], and registered at https://www.chictr.org.cn (ChiCTR2400094676).

Consent for Publication

All authors have approved the manuscript and given their consent for submission and publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no financial competing interests.

References

1. Pereira EM, Moraes VR, Gaya da Costa M, et al. Remimazolam vs. propofol for general anaesthesia in elderly patients: a meta-analysis with trial sequential analysis. *Eur J Anaesthesiol*. 2024;41(10):738–748. doi:10.1097/EJA.0000000000002042
2. Yang R, Wolfson M, Lewis MC. Unique aspects of the elderly surgical population: an anesthesiologist's perspective. *Geriatr Orthop Surg Rehabil*. 2011;2(2):56–64. doi:10.1177/2151458510394606

3. Huang S, Liao Z, Chen A, Wang J, Xu X, Zhang L. Effect of carotid corrected flow time combined with perioperative fluid therapy on preventing hypotension after general anesthesia induction in elderly patients: a prospective cohort study. *Int J Surg*. 2024;110(2):799–809. doi:10.1097/JS9.0000000000000863
4. Gu QL, Xue FL, Zheng ZL, et al. Nongenetic and genetic predictors of haemodynamic instability induced by propofol and opioids: a retrospective clinical study. *Br J Clin Pharmacol*. 2023;89(1):209–221. doi:10.1111/bcp.15480
5. Xu Q, Zou X, Wu J, Duan G, Lan H, Wang L. Low-dose alfentanil inhibits sufentanil-induced cough during anesthesia induction: a prospective, randomized, double-blind study. *Drug Des Devel Ther*. 2024;18:1603–1612. doi:10.2147/DDDT.S464823
6. Mion G, Himmelseher S. Esketamine: less drowsiness, more analgesia. *Anesth Analg*. 2024;139(1):78–91. doi:10.1213/ANE.0000000000006851
7. Li J, Wang Z, Wang A, Wang Z. Clinical effects of low-dose esketamine for anaesthesia induction in the elderly: a randomized controlled trial. *J Clin Pharm Ther*. 2022;47(6):759–766. doi:10.1111/jcpt.13604
8. Wang J, Huang J, Yang S, et al. Pharmacokinetics and safety of esketamine in chinese patients undergoing painless gastroscopy in comparison with ketamine: a randomized, open-label clinical study. *Drug Des Devel Ther*. 2019;13:4135–4144. doi:10.2147/DDDT.S224553
9. Eberl S, Koers L, van Hooft J, et al. The effectiveness of a low-dose esketamine versus an alfentanil adjunct to propofol sedation during endoscopic retrograde cholangiopancreatography: a randomised controlled multicentre trial. *Eur J Anaesthesiol*. 2020;37(5):394–401. doi:10.1097/EJA.0000000000001134
10. Lovett-Carter D, Kendall MC, Park J, Ibrahim-Hamdan A, Crepet S, De Oliveira G. The effect of systemic lidocaine on post-operative opioid consumption in ambulatory surgical patients: a meta-analysis of randomized controlled trials. *Perioper Med*. 2021;10(1):11. doi:10.1186/s13741-021-00181-9
11. Taiym D, Cowan M, Nakamura B, Azad H, Strohl A, Barber E. Effect of continuous post-operative lidocaine infusion in an enhanced recovery program on opioid use following gynecologic oncology surgery. *J Gynecol Oncol*. 2023;34(5):e61. doi:10.3802/jgo.2023.34.e61
12. Yang F, Wang J, Zhang H, et al. Effect of intravenous lidocaine infusion on propofol dose and perioperative pain during moderate sedation-analgesia for hysteroscopy: a randomized controlled trial. *Drug Des Devel Ther*. 2024;18:5873–5880. doi:10.2147/DDDT.S484486
13. Fathy S, Hasanin A, Mostafa M, et al. The benefit of adding lidocaine to ketamine during rapid sequence endotracheal intubation in patients with septic shock: a randomised controlled trial. *Anaesth Crit Care Pain Med*. 2021;40(1):100731. doi:10.1016/j.accpm.2020.06.017
14. Xiao YY, Zou HD, Qin XN, Zhu R, Dai RP. A comparison of remimazolam versus propofol on blood pressure changes during therapeutic endoscopic retrograde cholangiopancreatography: a randomized controlled trial. *Anesth Analg*. 2025;141(1):90–99. doi:10.1213/ANE.0000000000007309
15. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083–3107. doi:10.1002/sim.3697
16. Zhang Y, Zhou Q, Chen R, et al. Effect of esketamine on postinduction hypotension in elderly patients undergoing elective noncardiac surgery: a secondary analysis of a randomized clinical trial. *Sci Rep*. 2025;15(1):18843. doi:10.1038/s41598-025-03297-w
17. Ji H, Zhang F, Yang M, et al. A comparison of the effects of sevoflurane, propofol, and propofol combined with butorphanol in suppressing sufentanil-induced cough-a randomized controlled trial. *Drug Des Devel Ther*. 2025;19:1347–1355. doi:10.2147/DDDT.S492641
18. Qian J, Peng Y, Mao Y, et al. Inhibitory effect of low-dose esketamine on cough induced by sufentanil during the induction of anesthesia and postoperative impact on mental health status: a prospective, single-center, randomized controlled trial. *BMC Anesthesiol*. 2024;24(1):471. doi:10.1186/s12871-024-02864-4
19. Hu Y, Du MC, Zhu GH, Long X, Jiang JJ, Gong Y. 50% efficacy dose of intravenous lidocaine in supressing sufentanil-induced cough in children: a randomised controlled trial. *BMC Anesthesiol*. 2024;24(1):149. doi:10.1186/s12871-024-02541-6
20. Zhou X, Guo C, Liu B, Guan Y, Wang S, Ji J. Prevention of sufentanil-induced cough during induction of general anesthesia by low-dose esketamine. *BMC Anesthesiol*. 2025;25(1):14. doi:10.1186/s12871-024-02852-8
21. Ma J, Wang F, Wang J, et al. The effect of low-dose esketamine on postoperative neurocognitive dysfunction in elderly patients undergoing general anesthesia for gastrointestinal tumors: a randomized controlled trial. *Drug Des Devel Ther*. 2023;17:1945–1957. doi:10.2147/DDDT.S406568
22. Linassi F, Troyas C, Kreuzer M, et al. Effect of ketamine on the bispectral index, spectral edge frequency, and surgical pleth index during propofol-remifentanil anesthesia: an observational prospective trial. *Anesth Analg*. 2024;140(6):1276–1285. doi:10.1213/ANE.0000000000007255
23. Kritzer MD, Pae CU, Masand PS. Key considerations for the use of ketamine and esketamine for the treatment of depression: focusing on administration, safety, and tolerability. *Expert Opin Drug Saf*. 2022;21(6):725–732. doi:10.1080/14740338.2022.2069749
24. Luo T, Deng Z, Ren Q, Mu F, Zhang Y, Wang H. Effects of esketamine on postoperative negative emotions and early cognitive disorders in patients undergoing non-cardiac thoracic surgery: a randomized controlled trial. *J Clin Anesth*. 2024;95:111447. doi:10.1016/j.jclinane.2024.111447
25. Yu X, Xu X, Wang J, Wang Z, Zhang Y. Effects of remimazolam tosilate combined with esketamine on anesthetic efficacy and psychiatric symptoms in patients undergoing ambulatory surgery: a randomized controlled study. *Drug Des Devel Ther*. 2025;19:4527–4535. doi:10.2147/DDDT.S519732
26. Lee IW, Schraag S. The use of intravenous lidocaine in perioperative medicine: anaesthetic, analgesic and immune-modulatory aspects. *J Clin Med*. 2022;11(12):3543. doi:10.3390/jcm11123543