

Efficacy and Hemodynamic Safety of Low-dose Propofol plus High-dose Alfentanil in Rapid Sequence Induction: A Prospective Non-randomized Interventional Study

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Abstract

Objective

To compare hemodynamic changes and adverse events across four induction regimens and assess whether low-dose propofol (1 mg/kg) plus high-dose alfentanil (50 µg/kg) provides superior stability without compromising intubating conditions.

Methods

This prospective, non-randomized interventional study with four parallel groups enrolled 172 ASA I-II adults (18–60 years) for elective surgery. Four treatment groups (n = 43 each) received propofol 1 mg/kg with alfentanil 50 µg/kg (Group A), or propofol 2 mg/kg with alfentanil 30 µg/kg (Group B), propofol 2 mg/kg with alfentanil 50 µg/kg (Group D), or propofol 2 mg/kg with sufentanil 0.5 µg/kg (Group C), all with rocuronium 0.6 mg/kg. Primary outcomes were hypotension (MAP < 60 mmHg for ≥ 2 min), substantial HR decline (≥ 20% from baseline) and inadequate blunting of intubation response (HR at T2 > baseline×1.2 with MAP ≥ baseline×0.85, or MAP > baseline×1.2). Secondary outcomes included intubating conditions (Steyn scale) and adverse events. Linear mixed models(LMM) and Firth penalized logistic regression were used, adjusting for age, sex, BMI, and baseline values.

Results

Intubating conditions were uniformly excellent (99.4% optimal). Hypotension was lowest in Group A (16.3%) and highest in Group D (55.8%). Inadequate blunting was most frequent in Group C (46.5%), whereas Group A (4.7%) and Group D (0%) had lower rates than Group B (9.3%). Group D was independently associated with hypotension (OR = 8.00, 95% CI: 2.80-25.56, P < 0.001) and HR decline ≥ 20% (OR = 3.40, 95% CI: 1.24–10.08, P = 0.017). Each additional year of age was associated with an increased hypotension risk (OR = 1.12, 95% CI: 1.07–1.19, P < 0.001). Female sex was associated with lower odds of inadequate blunting (OR = 0.18, 95% CI: 0.05–0.56, P = 0.002) but higher odds of HR decline (OR = 5.74, 95% CI: 2.34–15.66, P < 0.001).

Conclusion

Low-dose propofol plus high-dose alfentanil provided the lowest hypotension, effective blunting, and non-inferior intubation, supporting a hypnotic-sparing strategy; age and sex influence the safety, warranting individualized dosing.

Trial registration:

Introduction

Tracheal intubation causes sympathetic responses, such as hypertension and tachycardia, and it can lead to myocardial ischemia in susceptible individuals. According to Grillo et al. [1], hypotension occurs in 26% of cases during rapid sequence intubation for anesthetic induction. Therefore, the search for a solution to balance hemodynamic stability with favorable intubating conditions remains an essential aspect of anesthetic management during intubation.

Propofol is commonly used for anesthesia. However, typical propofol doses (2.0-2.5 mg/kg) can result in hypotension caused by decreased systemic vascular resistance and myocardial depression [2, 3]. Therefore, it has considerable clinical value to minimize the dose of propofol while ensuring adequate intubation conditions.

Propofol combined with opioids may synergistically inhibit the stress response in the body. Among opioids, alfentanil has unique pharmacokinetic characteristics: its equilibration half-time ($t_{1/2ke0}$) is only 1.0 to 1.5 minutes, and the concentration at the site of action peaks within 90 seconds—almost the same time as propofol's peak effect [4, 5]. This time coincidence of propofol and alfentanil makes the two suitable for rapid sequence induction.

It has been confirmed that there is a good synergistic effect between propofol and alfentanil. Vuyk et al. [6] demonstrated a highly nonlinear interaction: when the concentration of propofol increased from 2 µg/mL to 10 µg/mL, the EC₅₀ of alfentanil decreased from 209 ng/mL to 16 ng/mL. Liou et al. (2023), using pharmacodynamic response surface models, confirmed that the synergistic interaction between propofol and alfentanil surpassed that of other drug combinations, with ROC AUCs of 0.83 in the modeling group, 0.96 in the ERCP validation group, and 0.93 in the bronchoscopy validation group [7]. Pharmacodynamic modeling further indicates that alfentanil can reduce propofol requirements by 30–50% [8]. Moreover, a bidirectional pharmacokinetic interaction exists: propofol inhibits alfentanil metabolism, while alfentanil mildly elevates propofol plasma concentrations [9, 10]. These findings support dose reduction of propofol when combined with higher doses of alfentanil.

Even with this evidence, clinical propofol-alfentanil induction protocols are still highly variable, with propofol doses ranging from 1.5 to 2.5 mg/kg and alfentanil doses ranging from 10 to 50 µg/kg [11, 12]. In clinical practice, the most favorable balance between stress reduction and hemodynamic stability has not been established so far, and age and sex effects are often ignored. Increasing age reduces the liver's ability to clear drugs and weakens baroreceptor reflexes, with the clearance of alfentanil being particularly affected, as it is primarily metabolized by CYP3A4 [13]. Meanwhile, women require a lower dose of alfentanil to achieve the same effect [14, 15].

We carried out a prospective, non-randomized interventional study to examine the actual hemodynamic profiles of four popular induction regimens, focusing more on whether the fast-onset opioid regimen

(alfentanil) used during the intubation window gives better results than the slow-onset regimen (sufentanil), which requires prolongation.

Materials and Methods

1. Study Design

This research was a single-center, prospective, non-randomized interventional project with four treatment groups. All patients who participated in the study received one of the four fixed induction regimens that are normally used in our department. Each induction regimen was assigned by the anesthesia team on duty based on the department's rotation schedule. This schedule was generated independently and wasn't based on patient characteristics. In our department, each team always sticks to its established induction protocol in daily clinical practice (Groups A–D correspond to Teams A–D). So, the shift schedule determines which team is on duty, and the team determines which protocol the patient receives. During the study, all eligible patients undergoing planned surgeries were included, with no selection based on the assigned protocol.

It is important to highlight that the different sequences of induction did not occur by chance but were rather carefully devised with the aim of matching the peak of each of the opioids being administered. Alfentanil has a very fast blood-brain equilibration half-time ($t_{1/2ke0} \approx 1.0\text{--}1.5\text{ min}$) and peaks almost at the same time as propofol, thus groups A, B, and D were assigned to the rapid intubation sequence (propofol → alfentanil → rocuronium → intubation after 1 min). Sufentanil is different since it takes longer to equilibrate. Group C used a waiting time of 4 minutes after the administration of sufentanil in order for the effect concentration at intubation to peak. After that, propofol and rocuronium were administered, and intubation was performed a minute later.

Given that this is a non-randomized interventional design, the trial was retrospectively registered on ClinicalTrials.gov ([NCT07730918]) on July 23, 2026, which was completed prior to the data analysis. Besides, the Medical Ethics Committee of Zhangjiagang Aoyang Hospital reviewed and approved the study protocol (Approval No. 2025-018) on July 24, 2025. The study was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice. All participating patients signed written informed consent, and all patient data were anonymized prior to analysis.

2. Study Population

Patients scheduled for elective surgery at our hospital from August 2025 to May 2026, with ASA physical status I-II, aged 18–60 years, and BMI of 18–30 kg/m² were consecutively included. Exclusion criteria included hypertension, diabetes, cardiopulmonary dysfunction, difficult airway, history of anesthesia drug allergy, long-term use of sedatives or analgesics, and obvious preoperative hypovolemia, or painful stimuli.

The types of surgeries mainly involve some minor general procedures in gynecology, otolaryngology, and general surgery. These surgeries do not involve major vascular operations or significant changes in blood volume, so they basically do not severely affect the preoperative baseline hemodynamic state.

3. Treatment Groups and Induction Orders

As described above, patients were categorized by their anesthesia team's routine protocol into four treatment groups (n = 43 each):

- **Group A:** Propofol 1 mg/kg + Alfentanil 50 µg/kg
- **Group B:** Propofol 2 mg/kg + Alfentanil 30 µg/kg
- **Group C:** Propofol 2 mg/kg + Sufentanil 0.5 µg/kg
- **Group D:** Propofol 2 mg/kg + Alfentanil 50 µg/kg

In all groups, rocuronium at a dose of 0.6 mg/kg was administered as the neuromuscular blocker. There were differences in induction procedures among the groups: in Groups A, B, and D, propofol was administered first, followed by an alfentanil injection (over 10 seconds), then rocuronium, while intubation was performed 1 minute after the administration of rocuronium. In Group C, sufentanil was injected over 30 seconds, followed by mask ventilation with oxygen for 4 minutes, then propofol and rocuronium, with intubation performed 1 minute later. These distinct induction sequences reflect the clinical practice of each team to align with the peak effect times of the respective opioids, rather than protocol-mandated variations for research purposes. Groups were enrolled concurrently during the study period.

4. Anesthesia and Monitoring

After arriving in the operating room, the patient was first given 8 mL/kg of lactated Ringer's solution, and radial artery cannulation was done to monitor blood pressure in real time. Intubation of the trachea was done with the help of a video laryngoscope, and the intubation time was ≤ 30 seconds. During the 5-minute observation period after intubation, no surgical procedures were performed, and no additional anesthesia or vasoactive drugs were used unless urgent intervention was needed. Among 172 cases, only one patient (0.6%, Group B) required such intervention ($\text{MAP} \leq 40$ mmHg lasting > 1 minute) and received 100 µg of phenylephrine; no other patients needed drug treatment during the observation period.

Data collection: A trained research nurse recorded systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) at T0 (pre-induction baseline), T1 (immediately before intubation), T2 (the first hemodynamic peak after intubation), T3 (1 min after intubation), T4 (3 min after intubation), and T5 (5 min after intubation). Measurements were taken within ± 2 seconds of the stopwatch prompt. If there were large fluctuations in blood pressure or heart rate after T2, these were not counted as part of the T2 definition, as they were attributed to drug metabolism or circulation redistribution.

Given the inherent limitations of BIS during rapid sequence induction—including signal lag and electromyographic interference during laryngoscopy—we did not use BIS as the primary tool for assessing awareness risk. The final assessment of awareness was uniformly performed using the modified Brice questionnaire interview at 24 hours postoperatively [16].

5. Outcome Measures

Primary outcomes (binary endpoints subjected to multivariable logistic regression):

- ☒ Post-induction hypotension, defined as MAP < 60 mmHg for at least 2 consecutive time points during T1–T5; if MAP < 50 mmHg occurred at any time point, it was separately recorded as severe hypotension.
- ☒ Substantial heart rate (HR) decline, defined as a maximum decrease $\geq 20\%$ from the baseline (T0) value.
- ☒ Inadequate blunting of intubation response, defined as meeting either of the following criteria at T2: (a) $HR > T0 \times 1.2$ and $MAP \geq T0 \times 0.85$ (i.e., MAP decline < 15%), excluding reflex tachycardia secondary to hypotension; or (b) $MAP > T0 \times 1.2$.

Secondary outcomes (descriptive endpoints, not subjected to multivariate modeling):

- ☒ Intubating conditions assessed by the Steyn modified Helbo-Hansen score [17] (range 5–20, with 5 representing optimal conditions).
- ☒ Use of vasoactive agents (e.g., atropine, urapidil) during the observation period (T1–T5).
- ☒ Other adverse events, including hypertensive response to intubation ($SBP \text{ at } T2 > T0 \times 1.3$), body movement, coughing, lacrimation, and vagal reflexes, reported descriptively.

Definitions of hemodynamic parameters (used for adjudication of the above primary outcomes):

The definitions for post-induction hypotension, substantial HR decline, and inadequate blunting are as already specified under **Primary outcomes**. The hypertensive response to intubation is defined as $SBP \text{ at } T2 > T0 \times 1.3$, and is reported as a secondary descriptive event.

6. Sample Size Calculation

Sample size was calculated using G*Power 3.1 software based on a chi-square test for the primary outcome (hypotension incidence) across the four groups. With a medium effect size ($w = 0.30$), a two-sided significance level ($\alpha = 0.05$), and a power ($1-\beta$) of 0.80, the calculation yielded a required sample size of 38 patients per group. Accounting for a 10% dropout rate, we ultimately enrolled 43 patients per group, totaling 172 patients.

7. Statistical Analysis

Statistical analyses were performed using SPSS 32.0 and R 4.6.0 software. Categorical variables were expressed as counts (percentages) and compared using the chi-square test. Continuous variables were presented as mean $\pm$ standard deviation (SD).

Baseline comparisons

Continuous variables (age, BMI, and T0 SBP, DBP, MAP, HR) across the four groups were compared using one-way analysis of variance (ANOVA); sex distribution was compared using the chi-square test.

Primary analysis

Repeated hemodynamic measures (SBP, DBP, MAP, HR) were analyzed using linear mixed-effects models (LMM), with group, time, and their interaction as fixed effects, and age, sex, BMI, and the respective T0 baseline value as covariates. Multiple comparisons were adjusted using the Bonferroni correction. Model residuals were assessed for normality using Q-Q plots, skewness, and kurtosis.

Binary outcome variables (inadequate blunting of intubation response, hypotension, and HR decline $\geq$ 20%) were analyzed using Firth penalized logistic regression to account for zero events and sparse data bias in some outcomes. All variables had complete data with no missing values. A P-value < 0.05 was considered statistically significant. Given that the prevalence and sample size of patients with baseline bradycardia (HR < 60 bpm) could not be predetermined at the study design stage, a post hoc subgroup analysis was conducted in this subset solely for exploratory hypothesis generation; the findings are inherently underpowered and require cautious interpretation.

8. Blinding

Intubating condition scores were assessed by an anesthesia nurse who was blinded to the induction protocol received. Hemodynamic data were collected by the research nurse operating the stopwatch, who was not involved in the clinical management or subsequent data analysis.

Results

Baseline Characteristics

The four treatment groups (n = 43 each) were comparable with respect to sex distribution, age, BMI, and pre-induction (T0) SBP, DBP, MAP, and HR, with no statistically significant differences (all P > 0.05) (Table 1).

Table 1
Baseline characteristics of the four treatment groups

Variable	Group A (n = 43)	Group B (n = 43)	Group C (n = 43)	Group D (n = 43)	P-value
Sex (M/F)	19/24	23/20	18/25	20/23	0.727
Age (years)	37.12 ± 10.12	39.09 ± 11.22	36.91 ± 9.20	38.44 ± 7.69	0.675
BMI (kg/m ²)	23.20 ± 2.38	24.07 ± 2.81	23.87 ± 2.68	23.51 ± 2.71	0.434
Baseline SBP (mmHg)	135.23 ± 12.18	136.72 ± 7.49	134.86 ± 10.39	137.16 ± 10.62	0.678
Baseline DBP (mmHg)	70.63 ± 6.97	72.12 ± 6.37	71.09 ± 5.39	73.09 ± 6.60	0.281
Baseline MAP (mmHg)	92.16 ± 7.96	93.65 ± 5.98	92.35 ± 6.32	94.45 ± 7.04	0.359
Baseline HR (bpm)	70.16 ± 12.02	71.56 ± 8.22	69.93 ± 10.77	70.33 ± 11.22	0.896

Data are presented as mean ± SD or n. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; BMI, body mass index.

Hemodynamic Changes

The linear mixed-effects model revealed significant main effects of group, time, and their interaction on SBP, DBP, MAP, and HR (all $P < 0.001$). The temporal trends of these variables across the four groups are illustrated in Fig. 1. At T2, all four parameters in Group C were significantly higher than those in Groups A, B, and D (all $P < 0.001$). At T4 and T5, blood pressure in Group D remained at the lowest levels. At T5, the recovery of SBP and MAP in Group A was significantly faster than in the other three groups ($P < 0.001$); Group A also exhibited significantly higher DBP, SBP, and MAP than Group B ($P = 0.004$, < 0.001 , and 0.001 , respectively), whereas HR did not differ between the two groups at any time point ($P > 0.05$). Detailed pairwise comparison P-values at each time point are presented in Fig. 2. The residuals of the linear mixed-effects model were tested for normality using Q-Q plots as well as skewness and kurtosis. The absolute values of skewness for the residuals of the SBP, DBP, MAP, and HR models were all < 1 , and the absolute values of kurtosis were all < 3 . The Q-Q plots showed that the points were basically distributed along the diagonal line, which conforms to the normal distribution assumption.

Intubating Conditions

Intubating condition scores did not differ significantly among the four groups, with 99.4% (171/172) of cases achieving the optimal score of 5.

Table 2
Adverse events and intubation-related responses

Category	Event	Group A (n = 43)	Group B (n = 43)	Group C (n = 43)	Group D (n = 43)
Intubation stress	Inadequate blunting of intubation response	2 (4.65%)	4 (9.30%)	20 (46.51%)	0
Circulatory events	Hypotension	7 (16.28%)	16 (37.21%)	8 (18.60%)	24 (55.81%)
	Severe hypotension (MAP < 50 mmHg)	0	1 (2.33%)	0	4 (9.30%)
	Hypertension	0	0	1 (2.33%)	0
	HR decline ≥ 20% from baseline	8 (18.60%)	10 (23.26%)	2 (4.65%)	17 (39.53%)
	Vagal reflex	1 (2.33%)	0	2 (4.65%)	0
Intubation-related signs	Body movement	0	0	1 (2.33%)	0
	Lacrimation	0	1 (2.33%)	1 (2.33%)	0
Rescue interventions	Vasoactive drug use (T1-T5)	0	1 (2.33%)	0	0

Data are presented as n (%). MAP, mean arterial pressure; HR, heart rate.

The 24-hour postoperative modified Brice questionnaire interview revealed no explicit recall of intubation or intraoperative events in any of the 172 patients, including all 43 patients in Group A.

Multivariable Regression Analysis

Table 3
Univariate distribution of binary outcomes across groups

Group	Inadequate blunting of intubation response	Hypotension	HR decline ≥ 20%	Baseline HR < 60 bpm (T0)
Group A	2 (4.65%)	7 (16.28%)	8 (18.60%)	10 (23.26%)
Group B	4 (9.30%)	16 (37.21%)	10 (23.26%)	5 (11.63%)
Group C	20 (46.51%)	8 (18.60%)	2 (4.65%)	7 (16.28%)
Group D	0	24 (55.81%)	17 (39.53%)	8 (18.60%)

Given the presence of zero events and sparse-data bias in some outcomes, all binary endpoints (inadequate blunting of intubation response, hypotension, and HR decline $\geq 20\%$) were analyzed using Firth penalized logistic regression, with Group A as the reference. Results are presented in Fig. 3.

- **Inadequate blunting of intubation response:** Group C (sufentanil group) was identified as an independent risk factor (OR = 20.44, 95% CI: 5.32–118.17, $P < 0.001$), whereas female sex was protective (OR = 0.18, 95% CI: 0.05–0.56, $P = 0.002$). Groups B and D, age, and BMI were not significantly associated with this outcome (all $P > 0.05$).
- **Hypotension:** Group D (conventional propofol + high-dose alfentanil) (OR = 8.00, 95% CI: 2.80–25.56, $P < 0.001$) and increasing age (OR = 1.12 per year, 95% CI: 1.07–1.19, $P < 0.001$) were independent risk factors for post-induction hypotension.
- **Substantial HR decline ($\geq 20\%$):** Group D (OR = 3.40, 95% CI: 1.24–10.08, $P = 0.017$) and female sex (OR = 5.74, 95% CI: 2.34–15.66, $P < 0.001$) were independent risk factors, whereas Group C (OR = 0.22, 95% CI: 0.04–0.89, $P = 0.033$) and increasing age (OR = 0.95 per year, 95% CI: 0.90–0.99, $P = 0.022$) were protective. In this post hoc exploratory subgroup confined to patients with baseline bradycardia (HR < 60 bpm, $n = 30$), the protective effect of baseline bradycardia against substantial HR decline remained significant (OR = 0.18, 95% CI: 0.02–0.81, $P = 0.022$). Among the 30 patients, only one (in Group D) developed HR decline $\geq 20\%$ (1/30, 3.33%), and no events occurred in Group A; however, given the small sample size and post hoc nature, this finding should not be overinterpreted as a definitive safety guarantee.

Discussion

Despite the non-randomized allocation and the inherent collinearity between teams and regimens, the observed differences are unlikely to be attributable solely to operator-related factors. The most compelling internal evidence comes from the comparison between Groups A and D, which shared identical induction sequences and the same alfentanil dose (50 $\mu\text{g/kg}$), differing only in propofol dosage (1 mg/kg vs. 2 mg/kg). The markedly higher hypotension rate in Group D (55.8%) compared with Group A (16.3%), with an adjusted OR of 8.00, cannot be plausibly explained by subtle inter-operator variations; the pharmacological dose-response relationship is the most parsimonious explanation. Furthermore, the objective nature of the primary outcomes (MAP and HR measured via invasive arterial monitoring) and the well-balanced baseline characteristics across groups further support the reliability of the between-group comparisons.

Based on these findings, we identified three major implications for clinical practice. First, the low-dose propofol (1 mg/kg) plus high-dose alfentanil (50 $\mu\text{g/kg}$) regimen (Group A) was associated with the most favorable hemodynamic profile, with the lowest hypotension rate (16.3%) and the fastest post-intubation blood pressure recovery, while maintaining adequate intubating conditions. Second, age and sex emerged as independent modulators of induction safety—each 1-year increase in age was associated with a 12% increase in hypotension risk, and while female sex was protective against inadequate blunting of intubation response (OR = 0.18), it was associated with a markedly elevated risk of

bradycardia (OR = 5.74). Third, the conventional "propofol (2 mg/kg) + high-dose alfentanil (50 µg/kg)" combination (Group D) paradoxically emerged as the most hazardous in terms of hypotension (OR = 8.00), a finding likely attributable to synergistic pharmacokinetic-pharmacodynamic interactions.

Mechanisms underlying the advantage of low-dose propofol plus high-dose alfentanil

The advantage of Group A can be attributed to the well-established synergistic interaction between propofol and alfentanil [6]. Group A (half-dose propofol, alfentanil 50 µg/kg) achieved suppression of intubation stress comparable to that of Group D (full-dose propofol), yet the hypotension rate was only one-third that of Group D—a finding consistent with this synergy. Mechanistically, propofol inhibits alfentanil metabolism, while alfentanil mildly elevates propofol plasma concentrations [9, 10]. In Group D, the combination of full-dose propofol and high-dose alfentanil resulted in excessively high effect site concentrations of both agents, which may have contributed to profound cardiovascular depression. The reduced propofol dose in Group A appeared to reveal the beneficial synergy without precipitating excessive hypotension.

Comparison with previous studies

Miller et al. (1993) proposed that alfentanil 30 µg/kg with propofol 2 mg/kg represented an optimal dose [12]. Our Group B replicated this regimen and observed a hypotension rate of 37.2%—acceptable but suboptimal. In contrast, Group A reduced hypotension to 16.3% with a similar stress attenuation profile (inadequate blunting rate 4.65% vs. 9.30%). This difference may reflect incomplete understanding of PK/PD interactions in 1993, potentially underestimating alfentanil's compensatory potential. By increasing the alfentanil dose to 50 µg/kg, our study more fully exploited its pharmacological reserve to "substitute" for propofol.

In contrast, although the timing of administration in group C had been optimized (with sufentanil and propofol reaching peak effect during intubation), the inadequate blunting rate remained as high as 46.5%, indicating that 0.5 µg/kg sufentanil is insufficient. Kay et al. (1987) discovered that 0.5 µg/kg could only moderately attenuate cardiovascular responses on average, with some patients (5/17) still experiencing significant increases in blood pressure and heart rate—an issue of insufficient stress inhibition that cannot be ignored—while 1.0 µg/kg could effectively suppress hypertensive responses in all patients [18]. Xu et al. (2021), with adjunctive aerosolized lidocaine, derived an EC95 of 0.447 µg/kg (95% CI: 0.364–0.703 µg/kg) [19], whose upper limit exceeds 0.5 µg/kg, further corroborating that this dose is inadequate for a subset of patients. Although the average effect of 0.5 µg/kg sufentanil may be acceptable, its substantial interindividual variability—with nearly half (46.5%) of Group C patients showing inadequate blunting—argues against its universal use. Nevertheless, further dose escalation of sufentanil, while potentially enhancing stress suppression, would incur significantly increased risks of respiratory depression, hypotension, and delayed emergence, warranting careful risk-benefit appraisal.

Clinical implications of age and sex

Beyond the comparison between opioid types, patient-specific factors also emerged as important modulators of induction safety. The 12% per year increase in hypotension risk ($OR = 1.12/\text{year}$) is notable even within our relatively young cohort (excluding $ASA \geq III$ and age > 60 years), indicating that the impact of age on induction hemodynamics is continuous and progressive rather than confined to a "geriatric" threshold. We suggest that middle-aged patients (45–60 years) may benefit from a 20–30% reduction in propofol dose or prophylactic low-dose phenylephrine.

Female sex acted as a factor protecting from inadequate blunting of intubation response ($OR = 0.18$), which correlates well with existing evidence showing that women are more sensitive to opioids and need lower doses to experience the same effects [15]. However, the almost 6-fold increased risk for a marked HR decline ($OR = 5.74$) may reflect higher baseline parasympathetic tone in women, increased sensitivity to μ -opioid-mediated cardiac inhibition, and concurrent vagal suppression of sympathetic excitation. Clinically, for young female patients receiving high-dose alfentanil, it may be necessary to consider prophylactic use of 0.3–0.5 mg of atropine, or to reduce the dose of alfentanil to 30–40 $\mu\text{g/kg}$.

Strengths and limitations

Strengths

(1) Invasive blood pressure monitoring combined with standardized neuromuscular blockade ensured high data quality; (2) Firth penalized logistic regression robustly handled sparse data; (3) The real-world pragmatic design enhances generalizability.

Limitations

There are some limitations that must be acknowledged. First, the grouping was determined by the on-duty anesthesia teams according to the department's schedule, rather than by random allocation. Since each team only operated according to its own protocol, operator-related factors—such as laryngoscopy technique or subtle differences in ventilation practice—were completely collinear with the treatment groups. This complete collinearity eliminates the possibility of statistically adjusting for team effects. Nevertheless, several observations mitigate this concern. The most compelling internal evidence comes from the comparison between Group A and Group D, which used the same induction sequence and the same dose of alfentanil (50 $\mu\text{g/kg}$), differing only in the propofol dose (1 mg/kg vs. 2 mg/kg). The incidence of hypotension in Group D (55.8%) was significantly higher than in Group A (16.3%), with an adjusted OR of 8.00; this difference cannot be reasonably explained by subtle inter-operator variations, and the pharmacological dose-response relationship is the most parsimonious explanation. In addition, all teams followed a unified monitoring protocol, neuromuscular blockade timing, intubation time window, fluid management (administering 8 mL/kg of lactated Ringer's solution after entering the operating room), and a 5-minute observation period; the primary outcome measures were objective physiological parameters obtained through invasive arterial monitoring; and baseline characteristics

were balanced across groups (Table 1), collectively indicating that the schedule did not create systematic differences in patient risk profiles.

Second, and most importantly, the difference in induction sequences between the sufentanil group (Group C, with a 4-minute waiting interval) and the alfentanil groups (Groups A, B, D, using rapid intubation) is not a methodological flaw, but a deliberate optimization based on pharmacokinetics. As mentioned in the methods section, these sequences were designed to match the peak times of each opioid. Therefore, this study is not a pure pharmacological comparison of equianalgesic doses between alfentanil and sufentanil, but rather a comparison of two different clinical induction strategies — the rapid-onset strategy (based on alfentanil, suitable for rapid-sequence intubation) and the slow-onset strategy (based on sufentanil, requiring a longer waiting period). This distinction is crucial when interpreting comparative results: the fact that Group A outperformed Group C should be understood as the advantage offered by a fast-onset, time-matched protocol in a rapid-sequence intubation scenario, rather than just differences in opioid potency.

Third, this study only included patients with ASA I ~ II aged 18 ~ 60, limiting the generalization of results to elderly, ASA III ~ IV, or morbidly obese populations. Fourth, plasma drug concentrations were not measured, making PK/PD modeling impossible. Fifth, the quality of recovery and long-term prognosis were not assessed.

Finally, the subgroup analysis of patients with baseline bradycardia was a post hoc analysis with a small sample size ($n = 30$), insufficient to support such comparisons. Since the number of patients with sinus bradycardia could not be predicted prior to data collection, these results are strictly of a hypothesis-generating nature and need to be confirmed in future prospective studies with sufficient sample sizes specifically targeting this population.

Conclusions

In this prospective, non-randomized intervention study, the low-dose propofol (1 mg/kg) combined with high-dose alfentanil (50 µg/kg) regimen was associated with better hemodynamic stability during rapid-sequence induction, with the lowest incidence of hypotension and excellent blunting of the intubation stress response, while maintaining intubating conditions comparable to those of conventional protocols. Age and female sex were identified as independent determinants of induction safety, necessitating individualized dose adjustments. Additionally, the matched pharmacokinetic timing of low-dose propofol and high-dose alfentanil—both peaking within the tight 1.5-minute intubation window—may contribute to the superior hemodynamic profile of Group A, supporting the clinical value of adjusting induction timing based on opioid equilibration kinetics. In this ASA I-II patient cohort, these findings challenge the traditional practice of using a fixed high dose of propofol and support a modern general anesthesia strategy of reducing propofol while compensating with opioids.

Declarations

Ethics approval and consent to participate.

The study protocol was reviewed and approved by the Medical Ethics Committee of Zhangjiagang Aoyang Hospital (Approval No. 2025-018, dated July 24, 2025). The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participating patients.

Consent for publication.

Not applicable.

Conflicts of Interest.

The authors declare no conflicts of interest related to this study.

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Author Contribution

ZX designed the study, performed the statistical analysis, drafted the initial manuscript, and acted as the corresponding author responsible for submission and all correspondence. WY and WZ collected the data. ZX, YA, JF, and XG performed the clinical procedures. SC supervised the study and provided critical guidance. All authors critically revised the manuscript for important intellectual content and approved the final version.

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Data Availability

Data availability. The datasets generated and/or analyzed during the current study are available as Supplementary Data 1 and Supplementary Data 2.

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Figures

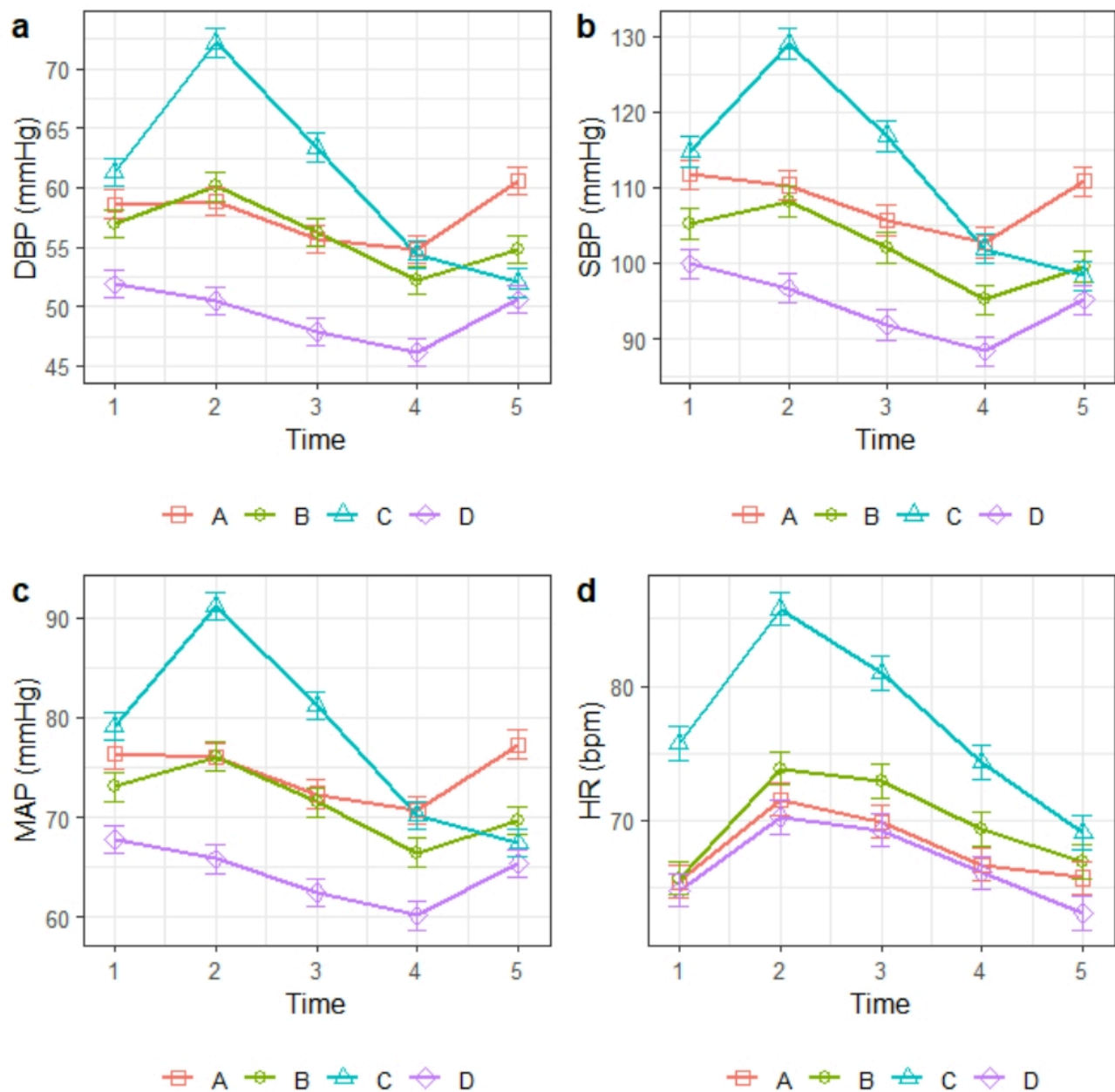


Figure 1

LMM estimated marginal means ($\pm$ SEM) for DBP, SBP, MAP, HR over time.

(a) Diastolic Blood Pressure, (b) Systolic Blood Pressure, (c) Mean Arterial Pressure, (d) Heart Rate.

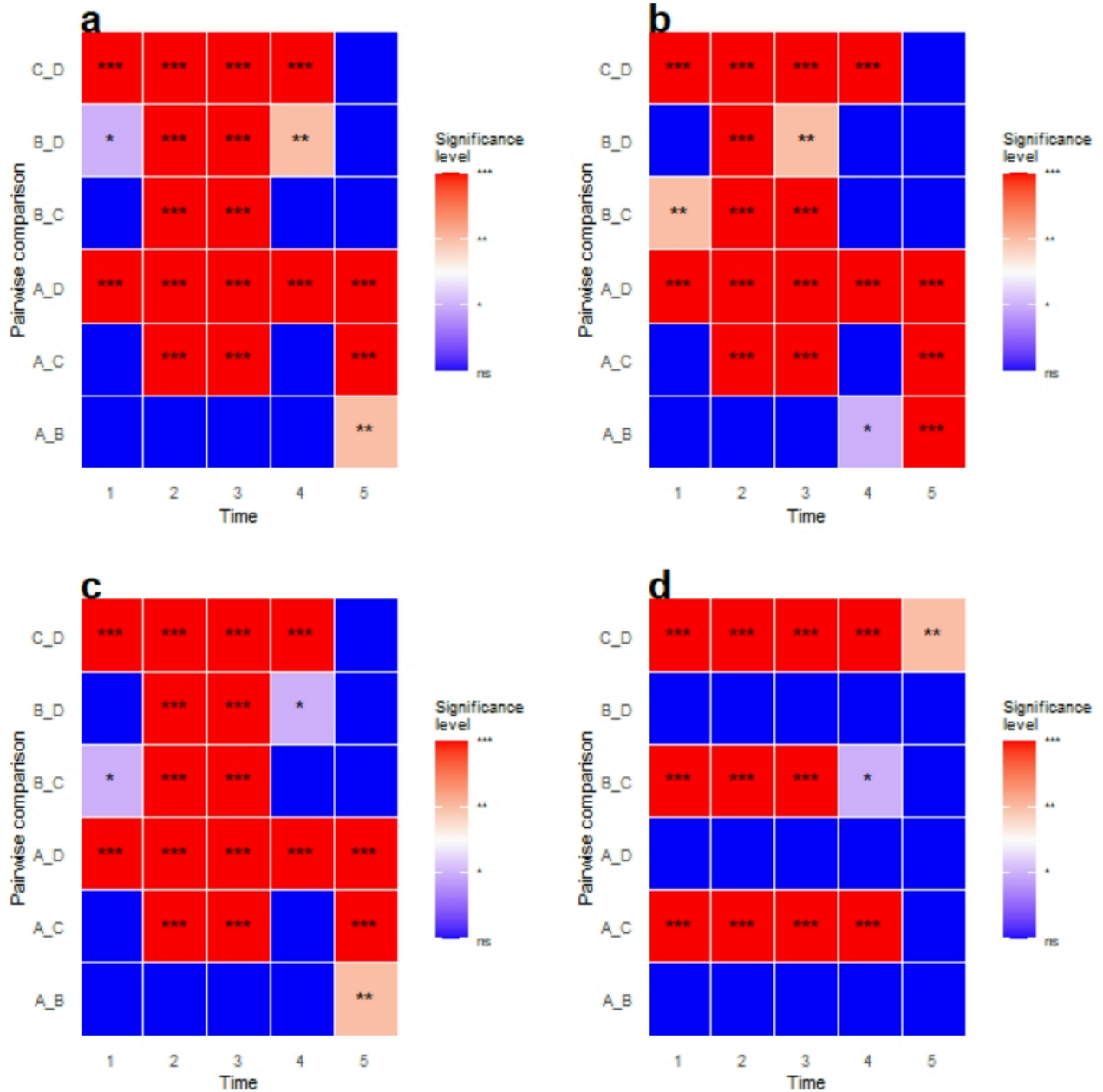


Figure 2

Heatmap of Bonferroni-adjusted P values for pairwise comparisons.

(a) Diastolic Blood Pressure (DBP), (b) Systolic Blood Pressure (SBP), (c) Mean Arterial Pressure (MAP), (d) Heart Rate (HR). Note: ns $p \geq 0.05$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

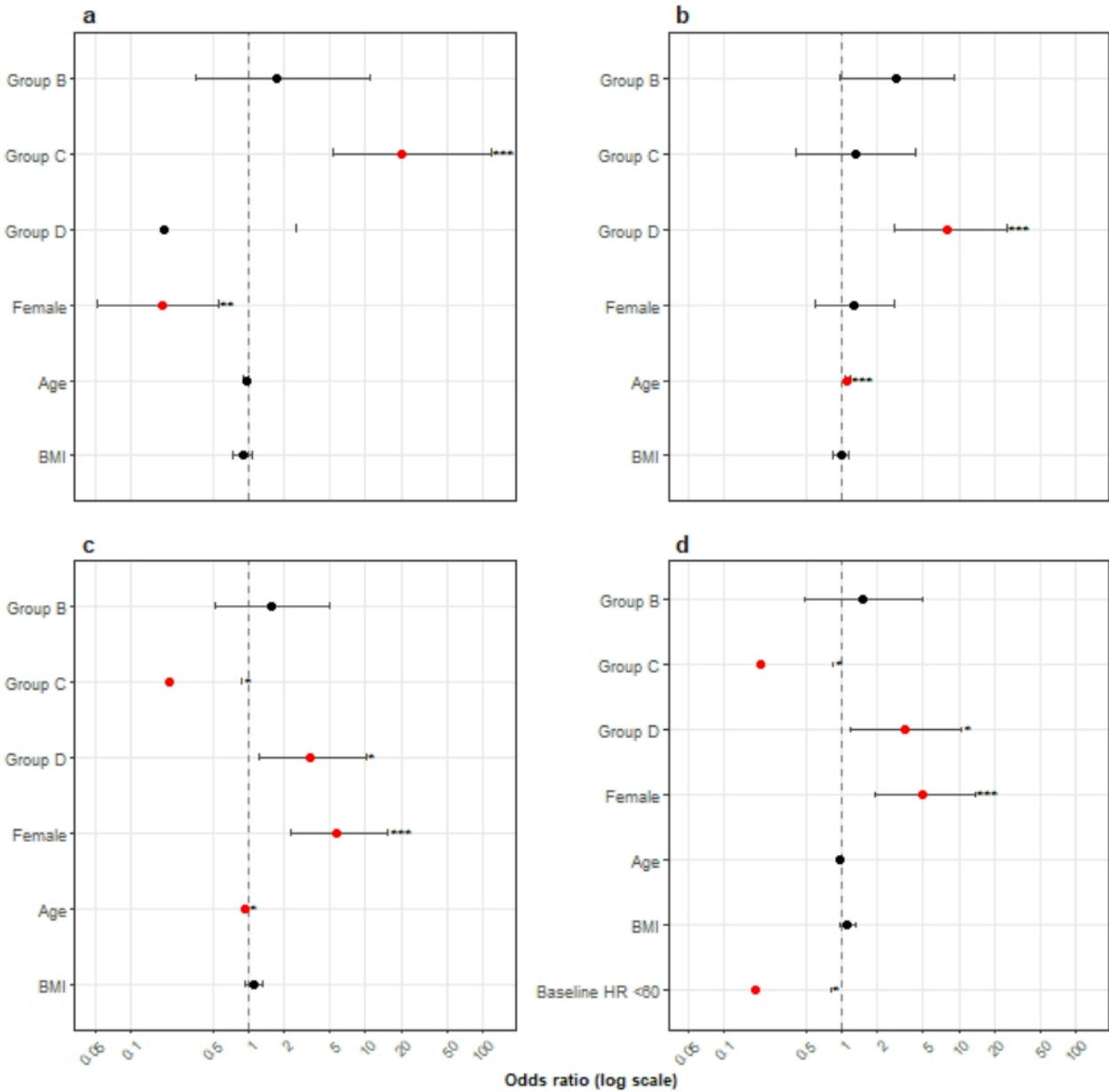


Figure 3

Firth Logistic Regression: Adjusted Odds Ratios and 95% CI for Four Clinical Outcomes.

(a) Inadequate blunting of intubation response, (b) Hypotension, (c) Max HR drop $\geq 20\%$, (d) Max HR drop $\geq 20\%$ (baseline HR < 60 subgroup). Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. In (a), Group C OR = 20.44 (95% CI: 5.32 118.17), *** $p < 0.001$; the lower bound of Group D CI is 0.0014 (below axis limit).

Supplementary Files

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