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CLINICAL TRIAL REPORT

Topical Airway Lidocaine Spray Reduces the 95% Effective Dose of Sufentanil for Blunting Hemodynamic Response to Tracheal Intubation in Elderly Patients: A Biased-Coin Up-and-Down Sequential Allocation Trial

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Purpose: Topical lidocaine is commonly used to blunt hemodynamic responses to laryngoscopy and intubation. In elderly patients, however, its specific effect on reducing the required dose of sufentanil during induction remains unquantified. We aimed to determine whether pre-intubation lidocaine spray lowers the 95% effective dose (ED_{95}) of sufentanil needed to attenuate this response.

Patients and Methods: Eighty patients aged 65–80 years undergoing elective surgery under general anesthesia with tracheal intubation were enrolled in this randomized, double-blind, dose-finding study. Prior to intubation, patients were randomly assigned to receive an oropharyngeal and laryngeal spray of either 2% lidocaine (Group A) or normal saline (Group B). The induction dose of sufentanil for each subsequent patient was adjusted based on the previous patient's hemodynamic response, following a biased-coin up-and-down sequential allocation method with a step size of 0.05 $\mu g \cdot kg^{-1}$. A positive response was defined as MAP or HR remaining within 30% of baseline values within 3 min after intubation. The ED_{95} and its 95% confidence interval (CI) were estimated using isotonic regression and bootstrapping methods. Extubation time, severity of coughing at emergence, postoperative sore throat (POST), and adverse events, were recorded.

Results: The estimated ED_{95} of sufentanil was 0.419 $\mu g \cdot kg^{-1}$ (95% CI 0.348–0.437) in Group A and 0.530 $\mu g \cdot kg^{-1}$ (95% CI 0.400–0.542) in Group B. Bootstrap analysis yielded a between-group difference (ΔED_{95}) of 0.111 $\mu g \cdot kg^{-1}$ (95% CI 0.001–0.188), indicating a statistically significant difference. Cough during emergence was more severe in Group B ($P < 0.05$). No statistically significant differences were observed between groups in extubation time, POST, or other adverse events.

Conclusion: In elderly patients, topical airway lidocaine spray reduces the ED_{95} of sufentanil to 0.419 $\mu g \cdot kg^{-1}$ for blunting hemodynamic responses to tracheal intubation. This adjunctive intervention decreases sufentanil requirements and improves emergence quality by reducing the severity of coughing in this elderly population.

Keywords: lidocaine, sufentanil, biased coin design, intubation, elderly patients

Introduction

The proportion of surgery performed in elderly patients is rising steadily, with individuals aged over 65 years accounting for approximately 37% of all operations.[1] Physiological changes including autonomic dysfunction, cardiovascular comorbidities, and increased pharmacodynamic sensitivity make elderly patients particularly vulnerable to the hemodynamic stress of tracheal intubation,[2,3] with risks extending to myocardial ischemia, arrhythmia, and hemodynamic instability.[4–6] Precise hemodynamic management during induction is therefore essential.

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Sufentanil, a potent opioid analgesic, is commonly used to blunt the hemodynamic response to tracheal intubation.[7] However, its dosing in older adults remains poorly defined. Excessive doses increase the risk of hypotension and delayed emergence, whereas insufficient doses may lead to a significant intubation response and potential cardiovascular complications.[5,8] Despite well-established principles of geriatric anesthetic pharmacology, clinicians still lack practical guidance on optimal dosing. The 95% effective dose (ED_{95}) is particularly valuable in clinical practice as it identifies the dose expected to be effective in the vast majority of patients. Compared to the 50% effective dose (ED_{50}), the ED_{95} is more clinically significant because it produces a predictable and reliable result.[9] However, the ED_{95} of sufentanil for blunting the response to tracheal intubation has not been established in this specific cohort.

Dexmedetomidine, esmolol, and deepening the depth of anesthesia are commonly employed to attenuate the hemodynamic response to tracheal intubation. However, these systemic interventions are often accompanied by an increased risk of circulatory depression.[10,11] The efficacy of intravenous lidocaine in blunting the intubation response remains controversial,[12,13] while nebulized lidocaine is limited by its prolonged onset time and reliance on specialized equipment.[14] By contrast, direct oropharyngeal lidocaine spray offers a targeted topical approach that precisely blocks the afferent transmission of noxious stimuli at the pharyngeal level, thereby suppressing sympathetic excitation at its source. Topical lidocaine spray modestly attenuates airway reflexes,[15–17] yet its potential synergistic effect with sufentanil remains unquantified. Determining whether lidocaine pretreatment reduces the required sufentanil dose would address an important gap in geriatric airway management.

This study was designed to quantify this interaction by establishing whether topical lidocaine reduces the ED_{95} of sufentanil needed to blunt the hemodynamic response to tracheal intubation in elderly patients, with the response assessed within the first 3 minutes following intubation.

Materials and Methods

Trial Registration

This study was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (2024KY No. 301) and registered with the Chinese Clinical Trial Registry (CHICTR2400086992). It was conducted in accordance with the Declaration of Helsinki from September 2024 to October 2025. Written informed consent was obtained from all 80 participants prior to enrollment.

Patients Eligibility

The inclusion criteria included patients aged 65–80 years, scheduled for elective surgery requiring tracheal intubation, with American Society of Anesthesiologists physical status (ASA) II–III. The exclusion criteria included gastroesophageal reflux disease, difficult airway, body mass index (BMI > 30 $kg.m^{-2}$), uncontrolled hypertension (≥180/110 mmHg), ischemic heart disease, autonomic /psychiatric disorders, and local anesthetic allergy. Protocol violations (spray time >15 seconds, intubation time > 60 seconds) or clinical events (arrhythmias, bradycardia < 45 bpm, delayed emergence) warranted exclusion from analysis.

Randomization and Blinding

Eligible elderly patients were randomly assigned in a 1:1 ratio to either the lidocaine group (Group A) or the control group (Group B) using a computer-generated sequence. Sealed opaque envelopes were maintained allocation concealment until immediately before induction. Study solutions were prepared by a research nurse not involved in clinical care. All anesthesia providers, assessors, and patients remained blinded throughout data collection.

Anesthetic Management

No sedative premedication was administered prior to arrival in the operating room. Upon arrival, s standard monitoring was established. All patients received intravenous lactated Ringer's solution at a rate of 4–6 $mL{\cdot}kg^{-1}{\cdot}h^{-1}$. Under local anesthesia, a radial artery catheter was inserted for invasive blood pressure monitoring. A stabilization period of at least 5 minutes was observed after catheter placement. We calculated all drug doses using ideal body weight (IBW).[18] Anesthesia was induced intravenously with etomidate 0.2 $mg.kg^{-1}$,[3,5] rocuronium 0.6–0.9 $mg.kg^{-1}$, and sufentanil. At 1 minute following anesthesia induction, a 5 mL aliquot of the test solution was administered as a spray using video laryngoscopy (Zhejiang UE Medical Corp., China) combined with a specialized curved cannula (Henan Tuoren Medical Devices Co., Ltd., China). The solution was delivered in a targeted manner: 1 mL to the supraglottic region, 1 mL to the glottic area, and 3 mL into the subglottic space. This sterile, curvature-adjustable cannula features a proximal end that connects to an injector and a distal end with multiple perforations. The solution was rapidly injected through the tube to produce a jet-like spray, ensuring thorough coverage of the supraglottic, glottic, and subglottic areas. Tracheal intubation occurred precisely two minutes post-spray.[16,19] Tracheal intubation was performed by a single attending anesthesiologist with five or more years of clinical experience, and only first-attempt successes were included for analysis. The intubation procedure was required to be completed within 60 seconds, with intubation time measured from insertion of the laryngoscope blade into the oral cavity to inflation of the tracheal tube cuff. The spray procedure was required to be completed within 15 seconds, with spray time measured from insertion of the laryngoscope to completion of the spray delivery. Any procedure exceeding these predefined time limits was considered a protocol deviation and resulted in exclusion from the final analysis. The endotracheal tube size was selected as 7.0 mm internal diameter (ID) for female patients and 7.5 mm ID for male patients, with adjustments as appropriate. Anesthesia was maintained with 1% sevoflurane until three minutes post-intubation, after which ciprofol (1–2.4 $mg.kg^{-1}.h^{-1}$) and remifentanil (0.1–0.2 $\mu g.kg^{-1}.min^{-1}$) were administered to maintain a BIS value between 40 and 60. All anesthetic agents were discontinued upon completion of surgery. The patient was subsequently transferred to the post-anesthesia care unit (PACU) for extubation and recovery before returning to the ward.

Hypertension was defined as a ≥ 30% increase in mean arterial pressure (MAP) from baseline, and tachycardia as a ≥ 30% increase in heart rate (HR) under the same conditions.[8] These were treated with nicardipine (0.2 mg) or esmolol (20 mg), respectively. Hypotension was defined as a decrease of≥30% in MAP from baseline value.[8,17] Norepinephrine (4 μg) was administered. Bradycardia was defined as a HR below 45 bpm,[8] and atropine (0.5mg) was administered.

Biased Coin Design Method

The biased-coin up-and-down sequential allocation method (BCD-UDM) was used to determine the ED_{95} of sufentanil. For dose finding, two independent BCD-UDM processes were conducted in parallel, one within each randomized arm. The starting dose of sufentanil was 0.3 $\mu g \cdot kg^{-1}$ for the first patient in each arm, with a step size of 0.05 $\mu g \cdot kg^{-1}$. For all subsequent patients, the dose was determined exclusively based on the response of the prior patient within the same arm. If a negative response was observed, the next dose increased by one step. When a positive response occurred, the next dose remained unchanged with 95% probability or decreased by one step with 5% probability.[20,21] Randomization for probability assignment was performed using a Random Integer Generator software.[22] A positive response was defined as the MAP or HR remaining within 30% of baseline values with 3 minutes after intubation, while a negative response was defined as an increase of ≥ 30% from baseline in either parameter.[8,17]

Outcome Measures

The primary outcome was the ED_{95} of sufentanil for blunting the haemodynamic response to intubation, along with its 95% confidence interval (CI). We recorded MAP and HR at eight time points: before induction (T0), before laryngoscopy (T1), the time of laryngoscopy (T2), before intubation (T3), immediately after intubation (T4), and at 1, 2 and 3 minutes post-intubation (T5, T6, T7). Secondary outcomes included extubation time, cough severity during emergence ((graded 1–4: 1 = no cough, absence of a cough response to the removal of the tracheal tube; 2 = single mild cough; 3 = moderate cough lasting < 5 seconds; 4 = severe cough or retching lasting ≥5 seconds),[23] postoperative sore throat (POST) and hoarseness (assessed 1 hour after extubation, graded 1–4: 1=no sore throat; 2= mild sore throat; 3= moderate sore throat; 4= severe sore throat),[24] and adverse events (hypertension, hypotension, tachycardia, bradycardia).

Statistical Analysis

Because the sequential design does not assume a parametric dose–response curve, we did not perform a conventional sample-size calculation. Based on established recommendations for dose-finding studies,[25–27] a sample of 20–40 patients per group is generally sufficient to achieve stable estimates of the target dose. Accordingly, 40 patients were enrolled in each group for the present study. The ED_{95} of sufentanil attenuating the intubation response in elderly patients was determined using isotonic regression estimator $\hat{u}_3$.[9] This approach enforces a monotonic dose–response relationship by applying the

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pool-adjacent-violators algorithm (PAVA) to the observed response probabilities. The $\hat{u}_3$ value was then identified as the linear interpolation between the two adjacent, PAVA-adjusted probabilities ($P_k^* and P_{(k+1)}^*$) that bounded the target probability of Γ=0.95. P_k^* and P_{k+1}^* represent the PAVA-adjusted response probabilities at doses X_k and X_{k+1}, respectively, which were calculated by pooling adjacent violators to enforce a monotonic dose-response relationship, following the method of Pace and Stylianou.[9] Furthermore, 95% CI was calculated via a bias-corrected percentile bootstrap method with 2000 resamples of size 40 and a target Γ of 0.95, as previously described.[9,27] Non-overlapping of 83% CIs between groups indicated statistical significance.[9] A bootstrap 95% CI for between-group difference (ΔED_{95}) was constructed. Statistical significance at the α = 0.05 level was inferred if the 95% CI for the difference excluded zero.[28]

Continuous data are reported as mean ± SD or median (interquartile range) and compared using t-tests or Mann–Whitney *U*-tests, as appropriate. Categorical data are presented as n (%) and were analyzed with chi-square or Fisher's exact tests. A two-sided $P < 0.05$ was considered significant. All analyses were performed using R version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 22 (IBM Corp., Armonk, NY, USA).

Results

The study initially involved 109 patients, of whom 29 were excluded: 18 for failing to meet inclusion criteria and 11 for declining participation. Consequently, 80 patients completed the trial protocol and were included in the final analysis, as illustrated in the flow diagram (Figure 1). No patients were excluded after randomization. Baseline demographics and clinical variables did not differ between the Group A and Group B (Table 1; all $P > 0.05$).

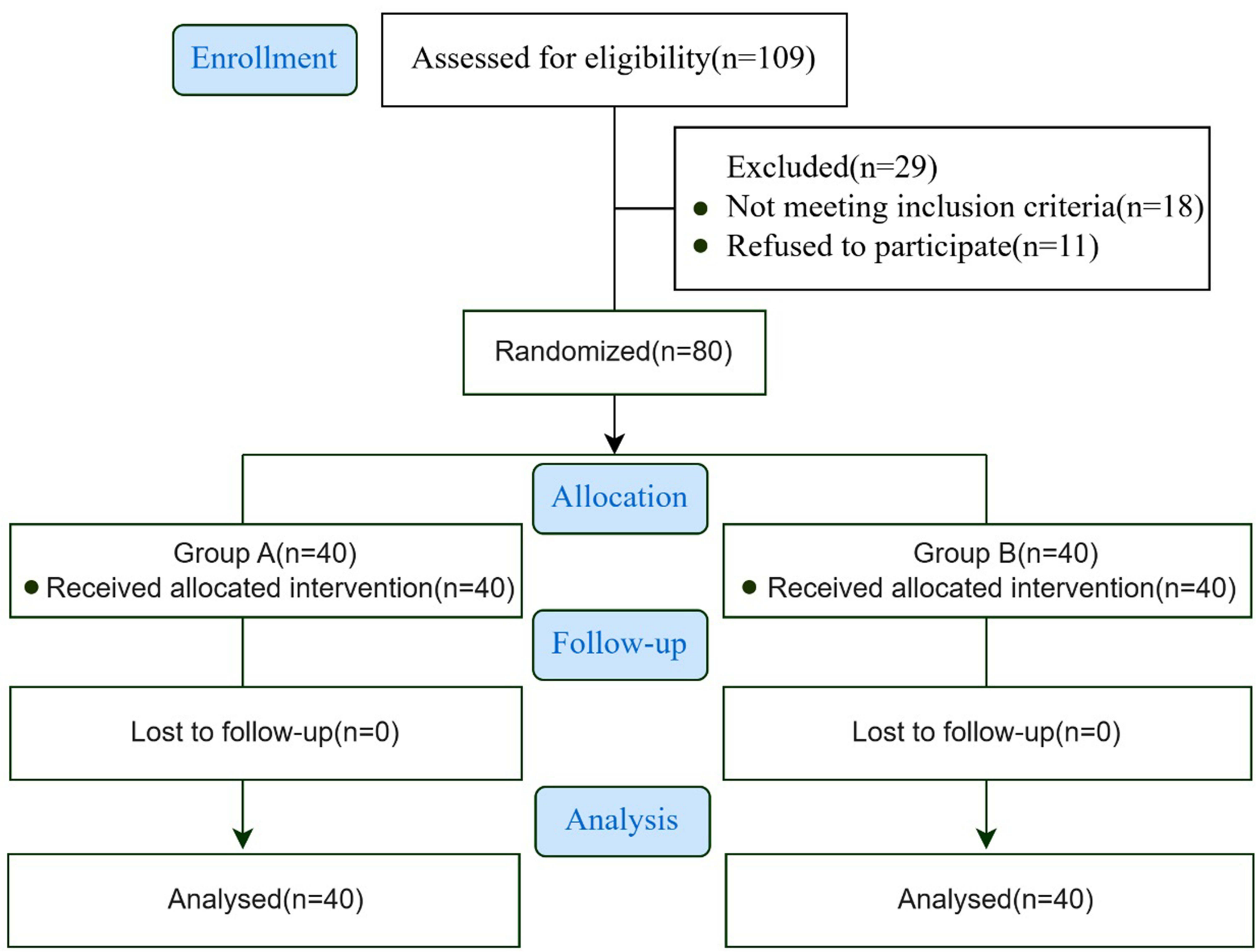

Figure 1 Flow diagram of the study.

Table 1 Demographic Characteristics and Clinical Data of Study Participants

Characteristic	Group A(n=40)	Group B(n=40)	*P* value
Age (years)	71.2±3.9	71.4±3.8	0.864
Gender (M: F)	19/21	12/28	0.108
Weight (kg)	63.7±10.1	65.8±9.8	0.346
Height (cm)	166.0 (157.0–170.0)	166.0 (155.0–164.8)	0.104
IBM (kg)	56.3 (53.6–63.6)	56.3 (52.9–59.7)	0.150
ASA (II/III), n	12/28	9/31	0.612
Comorbidities, n (%)			
Hypertension	29 (72.5%)	31 (77.5%)	0.606
Diabetes mellitus	4 (10%)	5 (12.5%)	1.000
Surgery style, n (%)			
Orthopedic surgery	34 (85%)	33 (82.5%)	1.000
General surgery	4 (10%)	5 (12.5%)	1.000
Urologic surgery	2 (5%)	2 (5%)	1.000

Notes: Data are presented as mean ± SD for normally distributed continuous variables (age, weight), median (interquartile range) for non-normally distributed continuous variables (height, IBM), and number (%) for categorical variables. P values were calculated using independent *t*-test for normally distributed continuous variables, Mann–Whitney *U*-test for non-normally distributed continuous variables, and Chi-square test or Fisher's exact test for categorical variables. P < 0.05 was considered statistically significant.

Abbreviations: IBM, Ideal body mass, calculated as 22 × height^2 (height in meters); ASA, American Society of Anesthesiologists physical status; M, male; F, female.

The sequential dose-response patterns are shown in Figure 2. The estimated ED_{95} of sufentanil was 0.419 $\mu g \cdot kg^{-1}$ (95% CI 0.348–0.437) in Group A and 0.530 $\mu g \cdot kg^{-1}$ (95% CI 0.400–0.542) in Group B. Table 2 summarizes dose-level data, including PAVA-adjusted response rates from centered isotonic regression.[6] The non-overlap of the 83% CIs (0.350–0.433 $\mu g \cdot kg^{-1}$ vs. 0.495–0.539 $\mu g \cdot kg^{-1}$) indicates statistical significance. In addition, the bootstrap analysis revealed a ΔED_{95} of 0.111 $\mu g \cdot kg^{-1}$ between the groups, with a 95% CI (0.001–0.188) that excluded zero, indicating a statistically significant difference.

Hemodynamic changes are displayed in Figure 3. MAP decreased significantly from baseline after induction (T1–T4) in both groups ($P < 0.01$). During T5–T7, MAP was higher in Group B than in Group A ($P < 0.05$). HR increased at post-intubation (T5) in both groups ($P < 0.01$); Group B also exhibited a transient reduction at T1 ($P < 0.05$).

Surgical and recovery measures are presented in Table 3. The severity of cough during emergence differed significantly between the two groups ($p < 0.01$). Patients in the Group A had a lower proportion of Grade 3–4 cough (15% vs. 52.5%) compared to the Group B. No statistically significant differences were observed between groups in operative time, extubation time, POST, or other adverse events.

Discussion

This study demonstrates that topical lidocaine spray applied prior to intubation reduces the ED_{95} of sufentanil required to blunt hemodynamic responses in elderly patients. The ED_{95} was 0.419 $\mu g \cdot kg^{-1}$ in the lidocaine group, compared with 0.530 $\mu g \cdot kg^{-1}$ in the saline group. This pharmacodynamic synergy was reflected in greater hemodynamic stability following intubation and a significant reduce the severity of coughing during emergence.

The efficacy of topical lidocaine is time-dependent. Although onset occurs within 1 minute, adequate mucosal penetration and maximal anesthetic effect typically require 2–5 minutes.[15] Evidence indicates that a 2-minute interval between spray application and intubation attenuates the cardiovascular response more effectively than a 1-minute interval,[16] while also avoiding the increased risk of hypotension associated with longer post-induction waiting periods.[19] Accordingly, we standardized intubation at 2 minutes after lidocaine administration to minimize hemodynamic instability.

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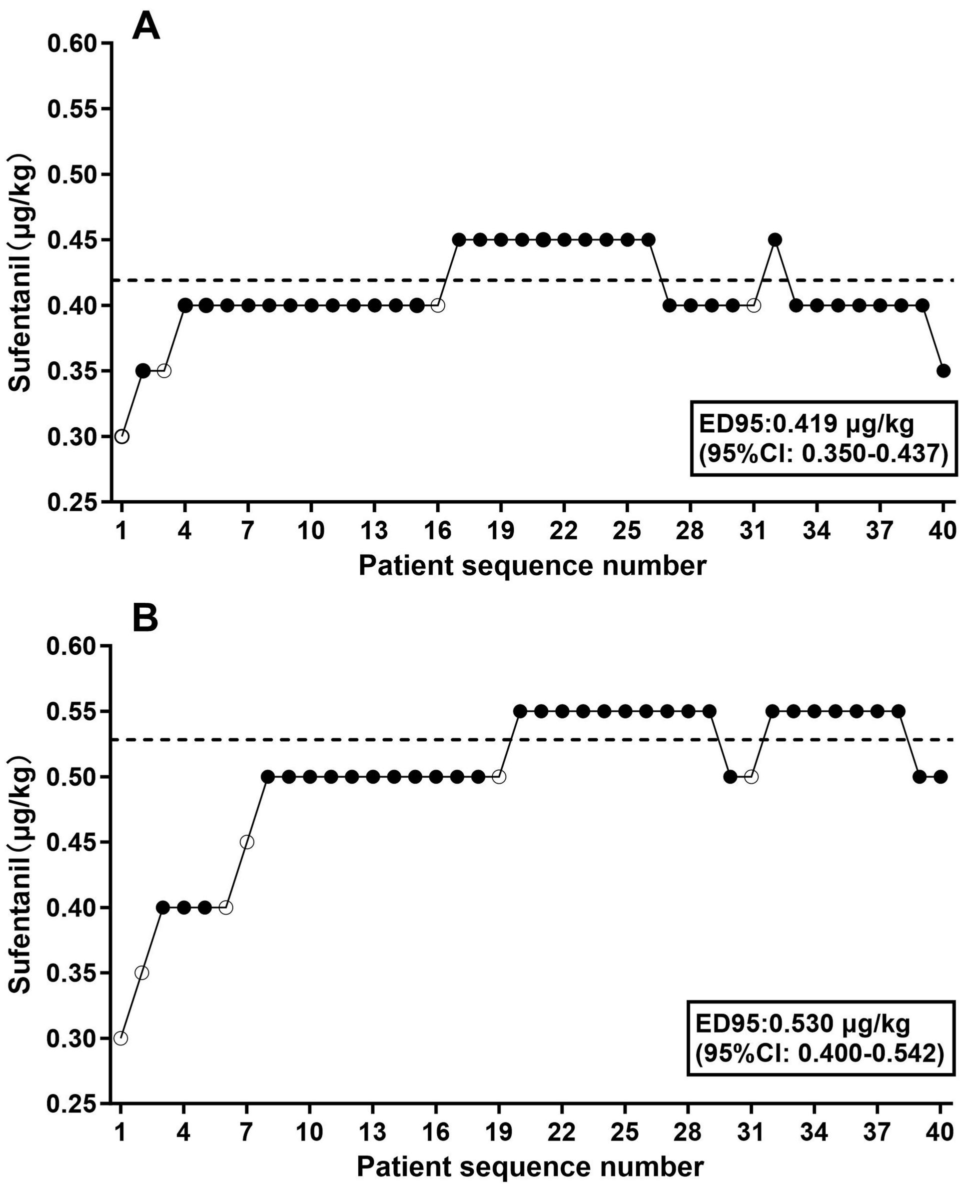

Figure 2 Patient response trajectory for the two groups. (**A**) Experimental trajectories for group A (n = 40) with 4 dose levels. (**B**) Experimental trajectories for group B (n = 40) with 6 dose levels. The x-axis represents the patient sequence number, and the y-axis shows the administered dose of sufentanil. "●" indicates positive response, and "○" indicates negative response. The ED$_{95}$ value is depicted as a thick dashed line.

Laryngoscopy and tracheal tube placement constitute the primary nociceptive stimulus of intubation, provoking a sympathoadrenal response that peaks within 30–45 seconds and subsides over 3–5 minutes.[29,30] Consistent with this time course, MAP and HR peaked approximately 1minute after intubation and largely recovered within the 3-minute observation period in our study. By blocking afferent signals from airway mucosa, topical lidocaine inhibits this nociceptive input, thereby reducing both hemodynamic fluctuations and the opioid dose required.[15,16] This mechanism is clinically corroborated by our findings of more stable post-intubation MAP and reduced emergence coughing.

It is noteworthy that the sufentanil ED$_{95}$ in Group B (0.530 µg.kg^{-1}) was higher than the 0.43 µg.kg^{-1} cited for younger adults.[31] Three factors likely contributed. First, our patients were all over 65—an age group with more comorbidities, and often a heightened hemodynamic reaction to airway manipulation. Second, we estimated the ED$_{95}$ directly using the BCD-UDM combined with isotonic regression, rather than extrapolating from the ED$_{50}$ as some studies have done. The BCD-UDM is designed specifically for reliable estimation of target quantiles in sequential trials and avoids the uncertainties inherent in extrapolation.[2,9,32] Third, the use of IBW for dose calculation in our study may

Table 2 Observed Response Rates and PAVA-Adjusted Rates for Sufentanil

Group	Dose-Level (μg kg^{-1})	Number of Cases	Positive Response	Response Rates	PAVA-Adjusted Responsive Rates
Group A					
	0.30	1	0	0.000	0.000
	0.35	3	2	0.667	0.667
	0.40	25	23	0.920	0.920
	0.45	11	11	1.000	1.000
Group B					
	0.30	1	0	0.000	0.000
	0.35	1	0	0.000	0.000
	0.40	4	3	0.750	0.375
	0.45	1	0	0.000	0.375
	0.50	16	14	0.875	0.875
	0.55	17	17	1.000	1.000

Notes: Data are presented as number of cases, number of positive responses, observed response rates, and PAVA-adjusted response rates. PAVA was applied to ensure monotonicity of the dose-response relationship for ED_{95} calculation.
Abbreviation: PAVA, pooled-adjacent-violators algorithm (isotonic regression).

provide greater consistency and equivalence between sexes,[18] and offers improved generalizability compared to dosing based on actual body weight.

Hemodynamic instability during induction is common in elderly patients, frequently presenting as hypotension just before tracheal intubation.[8] Previous study suggests that pre-intubation hypotension can occur in up to 50% of cases.[33] In our trial, incidence was considerably lower, at roughly 7.5% in Group A and 20% in Group B, and the lowest MAP typically occurred just before laryngoscopy. This pattern can be attributed to our induction design. We employed etomidate and sufentanil, a combination recognized for circulatory stability. Furthermore, the transient hypertensive effect of laryngoscopy likely blunted the post-induction decline in blood pressure. While the difference between the lidocaine and control groups did not reach statistical significance, the trend toward higher incidence in the control group aligns with the expected physiology. The importance of laryngoscopy duration is well documented.[34] Protocols that limit the attempt to under 15 seconds, as we did, minimize associated hemodynamic swings, whereas prolonged attempts exceeding 30 seconds provoke substantial pressor and heart-rate responses.[35] This approach may be beneficial for maintaining hemodynamic stability during induction.

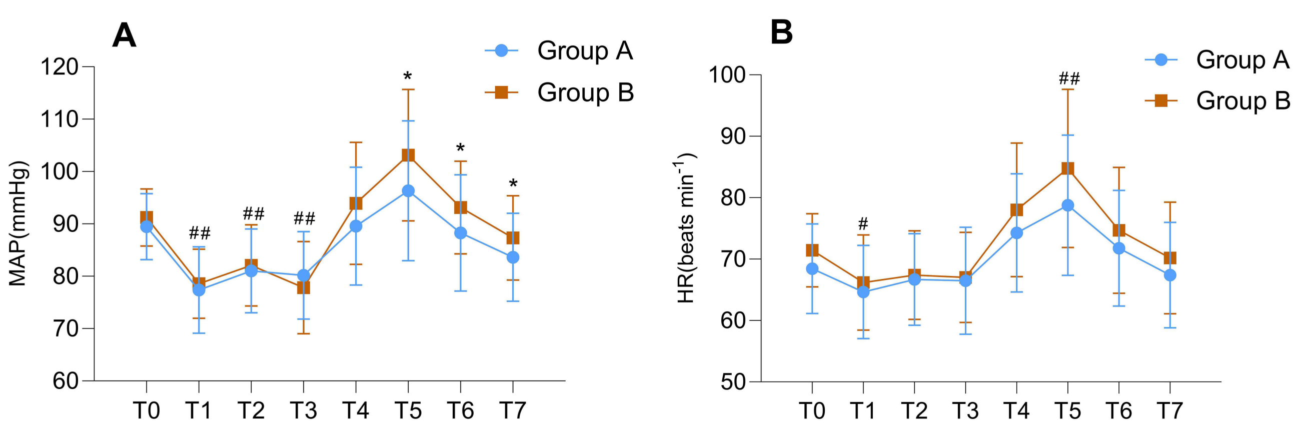

Figure 3 Comparison of hemodynamic parameters between the two groups. (**A**) MAP at different points; (**B**) HR at different points. T0, before induction; T1, before laryngoscopy; T2, the time of laryngoscopy; T3, before intubation; T4, immediately after intubation; T5, 1 min post-intubation; T6, 2 min post-intubation; T7, 3 min post-intubation. HR, heart rate; MAP, mean arterial pressure. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ versus baseline within the same group (paired *t*-test); $^{*}P < 0.05$ versus the other group at the same timepoint (independent *t*-test).

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Table 3 Surgery-Related Characteristics and Adverse Outcomes

	Group A (n = 40)	Group B (n = 40)	*P* value
Duration of surgery (min)	69.5 (60–110)	75 (63–89)	0.798
Duration of anesthesia (min)	94 (84.3–136.5)	100 (90.3–114)	0.455
Extubation time (min)	16 (12–24)	15.5 (12–26.5)	0.732
Adverse events, n (%)			
Hypertension	4 (10%)	6 (15%)	0.737
Hypotension	3 (7.5%)	8 (20%)	0.193
Tachycardia	0 (0%)	1 (2.5%)	1.000
Severity of cough, n (%)			0.000
Grade 1	2(5%)	1 (2.5%)	
Grade 2	32 (80%)	18 (45%)	
Grade 3	4 (10%)	17 (42.5%)	
Grade 4	2 (5%)	4 (10%)	
POST, n (%)			0.814
Grade 1	30 (75%)	28 (70%)	
Grade 2	7 (17.5%)	6 (15%)	
Grade 3	3 (7.5%)	5 (12.5%)	
Grade 4	0 (0%)	1 (2.5%)	

Notes: Data are presented as median (interquartile range) for continuous variables and number (%) for categorical variables. P values were calculated using Mann–Whitney *U*-test for continuous variables (duration of surgery, duration of anesthesia, extubation time), Chi-square test or Fisher's exact test for adverse events (hypertension, hypotension, tachycardia), and Chi-square test for ordered categorical variables (cough severity, POST). A P value <0.05 was considered statistically significant.
Abbreviation: POST, postoperative sore throat.

Topical lidocaine spray significantly improved extubation quality by reducing the severity of coughing. The incidence of moderate or severe coughing dropped to 15% in the treatment group, compared to 52.5% in the control group, a finding consistent with previously reported efficacy.[36] Interestingly, POST after surgery were reported at similar rates in both groups, around one in four patients. This overall incidence was lower than the 57.1% reported in a previous study.[24] A shorter assessment time and residual anesthetic effects likely explain much of that gap. Moreover, lidocaine spray did not prolong extubation time in this elderly cohort. That's consistent with adult data,[23] but diverges from pediatric findings,[37] suggesting age may modulate the emergence response to topical lidocaine. The sample size was determined based on the primary outcome; therefore, the findings related to secondary outcomes should be considered preliminary. Further investigations with larger cohorts are warranted to validate these observations.

Several limitations should be noted. First, hemodynamic response was assessed parameters (MAP and HR) at specific post-intubation timepoint. Although this approach allows standardized data collection, it may not capture peak values occurring outside these intervals, potentially limiting the comparability and generalizability of our findings to studies employing different assessment protocols. Second, the study population consisted predominantly of orthopedic surgery patients with a high prevalence of hypertension, which may influence hemodynamic variability and potentially limit the generalizability. Third, POST assessment was limited to the first hour post-extubation; a 24-hour assessment would yield more definitive clinical data. Finally, although no patients were excluded after randomization and rescue therapy was administered only after primary outcome assessment, the use of rescue medications during the later perioperative period remains a theoretical source of bias for the secondary outcomes.

Conclusion

In conclusion, this study demonstrates that topical lidocaine spray significantly lowers the ED_{95} of sufentanil for blunting the hemodynamic response to tracheal intubation in elderly patients. In addition, tracheal lidocaine spray significantly reduces the severity of cough during emergence. This simple intervention offers a practical approach to enhance airway management in this vulnerable population.

Data Sharing Statement

Deidentified individual participant data will be provided. The data supporting this study are available from Xu Chen or Chengwei Yang upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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