

ORIGINAL ARTICLE

Dexmedetomidine versus Lidocaine for Intubation in Traumatic Brain Injury: A Double-Blind Randomized Trial with Post Hoc Equivalence Analysis

Shallahudin^{1*}, Aswoco Andyk Asmoro¹, Ristiawan Muji Laksono¹, Buyung Hartiyo Laksono¹¹ Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia

ARTICLE INFO

Article history

Received: August 29, 2025
Revised: September 20, 2025
Accepted: October 14, 2025
Available online: October 27, 2025
Published: October 29, 2025

Keywords

Dexmedetomidine
Lidocaine
Intubation, Intratracheal
Hemodynamics
Brain Injuries, Traumatic

DOI

<https://doi.org/10.37275/jacr.v6i2.985>

Corresponding author

Shallahudin
udinexus@gmail.com

ABSTRACT

Background. Laryngoscopy-induced pressure surges and induction-related hypotension threaten the injured brain. Dexmedetomidine and lidocaine blunt the intubation response, but their relative effect in traumatic brain injury (TBI) is uncertain.

Objective. To estimate the difference in the mean arterial pressure (MAP) response to intubation between the two agents and to define, post hoc, the differences excluded.

Methods. In a double-blind randomized trial, 71 adults with TBI received dexmedetomidine 1 µg/kg over 10 min (n = 37) or lidocaine 1.5 mg/kg over 2 min plus an 8-min saline sham (n = 34) before standardized induction; lidocaine ended about 11 min before laryngoscopy. The primary outcome was the change in MAP from baseline to 1 min after intubation. The trial was not registered. Analyses included Welch estimation, post hoc two one-sided tests (TOST), ANCOVA and exact tests.

Results. MAP fell by 11.5 mmHg with lidocaine and 12.8 mmHg with dexmedetomidine; no pressor response occurred. The difference (dexmedetomidine – lidocaine) was –1.30 mmHg (95% CI –4.14 to 1.54; p = 0.365); adjusted, –1.66 mmHg (–4.31 to 1.00). Post hoc, differences beyond ±4 mmHg were excluded (TOST p = 0.031). Heart rate did not differ (Holm p = 1.000). Ephedrine was needed in 3/37 versus 2/34 and atropine in 2/37 versus 1/34 (both p = 1.000).

Conclusion. In adults with predominantly mild-to-moderate TBI, MAP responses to intubation with the two agents differed by about 4 mmHg or less post hoc, with infrequent rescue therapy. Without a placebo arm, neither agent's own effect can be quantified.

Access licence: Open access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Licence (CC BY-NC-SA 4.0), which permits non-commercial use, sharing, adaptation and reproduction in any medium, provided the original author and source are credited and derivative works are licensed under identical terms.

Copyright: © 2025 The Author(s). Published by HM Publisher in collaboration with CMHC Research Center. e-ISSN 2745-9497.

1. Introduction

Traumatic brain injury (TBI) remains a leading cause of injury-related disability worldwide. The Global Burden of Disease 2021 analysis counted 20.84 million incident and 37.93 million prevalent cases, and falls were the leading cause of TBI, followed by road injury.¹ The age-standardized incidence of TBI has fallen since 1990, but the absolute number of cases has risen.² Place of treatment matters. In the prospective Global Neurotrauma Outcomes Study, the case-mix-adjusted odds of death after emergency neurosurgery for TBI were more than twice as high in medium as in very-high Human Development Index settings.³ An Indian cohort was younger and more often severely injured than European ones,⁴ and a single-center Indonesian registry found that more than nine in ten road-traffic brain injuries involved motorcycles, with an in-hospital mortality of 9.3%.⁵ These figures describe the patients treated daily in Indonesian referral hospitals. For them, airway management during craniotomy and for associated injuries is routine. It is also high-stakes.

The injured brain tolerates swings in perfusion pressure poorly. A meta-analysis of 51 studies and more than

384,000 patients with moderate-to-severe TBI linked hypotension to an adjusted odds ratio for death of 2.22, and hypotension occurred in about one patient in five.⁶ Blood pressure and outcome are related continuously rather than through a single threshold. Among more than 12,000 patients with major TBI, adjusted mortality fell steadily as systolic pressure rose towards 130 mmHg and climbed again above 180 mmHg.⁷ An Asian multicenter cohort found the lowest mortality at a triage systolic pressure of 100–119 mmHg, with higher risk at both lower and higher values.⁸ Short-term variability of systolic pressure has been associated with in-hospital mortality,⁹ and time spent below the autoregulation-derived optimal cerebral perfusion pressure, or below the lower limit of autoregulation, was associated with an unfavorable six-month outcome.^{10,11} When autoregulation fails, cerebral blood flow follows pressure passively. A surge raises cerebral blood volume and intracranial pressure, whereas a fall risks ischemia. During laryngoscopy the physiological goal is therefore a narrow pressure corridor, and preventing hypertension alone is not enough.

Tracheal intubation threatens that corridor from both sides. Laryngoscopy stimulates airway afferents and provokes a sympathoadrenal discharge. The induction agents that suppress this discharge also reduce vascular tone and

sympathetic drive. In the international INTUBE cohort, 45.2% of critically ill patients had a major peri-intubation adverse event, overwhelmingly cardiovascular instability,¹² and propofol was the only modifiable factor independently associated with cardiovascular collapse.¹³ Among patients with TBI intubated before hospital arrival, any secondary insult was associated with higher 28-day mortality.¹⁴ After prehospital rapid-sequence induction, post-intubation hypotension occurred in 19.1% of patients with severe TBI and carried an adjusted odds ratio of 13.55 for 30-day death in isolated TBI.¹⁵ In-hospital series report rates as high as 62%.¹⁶ After prehospital emergency anesthesia, hypotension within 10 minutes of induction occurred in 21.8% of 998 trauma patients.¹⁷ Collapse is also frequent after intubation during critical care transport (29.1% in one cohort of 333 patients),¹⁸ yet delaying airway control to hospital arrival in severe TBI was associated with fewer favorable six-month outcomes in a randomized trial (39% versus 51%).¹⁹ The anesthesiologist's question is how to blunt the laryngoscopic response without deepening the post-induction fall.

Dexmedetomidine and lidocaine are two widely used adjuncts for this purpose. They act at different points of the reflex arc. Dexmedetomidine is a selective α_2 -adrenoceptor agonist that reduces central sympathetic outflow. Across 99 randomized trials it lowered mean arterial pressure (MAP) by 12.8 mmHg and heart rate by 16.9 beats/min at laryngoscopy compared with no dexmedetomidine, at the cost of clinically relevant bradycardia and hypotension.²⁰ Doses of 0.5 to 1 $\mu\text{g}/\text{kg}$ appear similarly effective, with more hypotension and bradycardia at the upper dose.²¹ Lidocaine acts differently. It blocks voltage-gated sodium channels in airway afferents, central reflex pathways and myocardium. Its pooled effect on the intubation response is smaller (MAP -3.85 mmHg, heart rate -4.72 beats/min) and heterogeneous,²² and it depends on the dose and on the interval between injection and laryngoscopy.^{23,24} In pairwise meta-analyses, dexmedetomidine lowered MAP and heart rate more than lidocaine did relative to no drug,^{20,22} and it lowered heart rate more than esmolol.²⁵ Lidocaine is generally cheaper and more widely stocked, so the size of the difference between the two drugs has direct consequences for practice in resource-constrained hospitals.

Direct comparisons are few and come from other populations. In elective surgical patients in Thailand, lidocaine 1.5 mg/kg with a small additional propofol dose was non-inferior to dexmedetomidine 1 $\mu\text{g}/\text{kg}$ for blood pressure and caused far less bradycardia and hypotension.²⁶ Trials in cardiac surgery and in craniotomy for tumor favored dexmedetomidine.^{27,28} In ventilated patients with severe TBI, the two drugs have been compared only for the response to tracheal suctioning,²⁹ and the only intubation data for lidocaine in severe TBI are observational.³⁰ Cohort studies of dexmedetomidine in moderate-to-severe TBI address intensive-care sedation rather than airway management.^{31,32}

Two further gaps shaped this report. First, Indonesian randomized evidence on either agent is limited to lidocaine infusion during tumor craniotomy,³³⁻³⁴ randomized evidence on intranasal dexmedetomidine for intubation comes from children,³⁵ and Southeast Asian trials of dexmedetomidine for intubation have used esmolol, not lidocaine, as the comparator.³⁶ Second, anesthesia trials are typically small.³⁷ A non-significant difference from a modest trial cannot by itself show that two treatments are interchangeable. Only the confidence interval of the difference shows which differences remain compatible with the data.³⁸ The objective

of this report was to estimate the difference between intravenous dexmedetomidine and intravenous lidocaine in the change in MAP from baseline to one minute after intubation in adults with TBI, and to determine which magnitudes of difference the data exclude. Secondary objectives were to compare heart-rate responses, the full hemodynamic time course and the need for rescue vasoactive therapy.

2. Methods

2.1. Study design and reporting

This was a prospective, single-center, parallel-group, double-blind randomized controlled trial with 1:1 allocation. It is reported in accordance with the CONSORT 2010 statement. The prespecified hypothesis was one of superiority: the change in MAP from baseline to one minute after intubation would differ between the two arms. The equivalence, baseline-adjusted and Bayesian analyses described below were not prespecified and are reported as post hoc analyses.

2.2. Setting

The trial took place in the central operating theaters of Dr. Saiful Anwar Regional General Hospital, Malang, East Java, Indonesia. The hospital is the teaching hospital of the Faculty of Medicine, Universitas Brawijaya, and the regional trauma referral center for southern East Java. Patients were recruited between June and December 2024. Follow-up ended ten minutes after intubation.

2.3. Participants and eligibility

Eligible patients were adults aged 18–65 years with TBI of any severity, confirmed by clinical assessment and computed tomography. They were classified as American Society of Anesthesiologists (ASA) physical status I–III and scheduled for surgery that required general anesthesia with orotracheal intubation. Exclusion criteria were as follows: refusal by the patient or legal representative; known hypersensitivity to dexmedetomidine, lidocaine or other amide local anesthetics; severe cardiovascular disease (uncontrolled hypertension, significant coronary artery disease, high-grade atrioventricular block or a pacemaker); chronic β -blocker or antiarrhythmic therapy; stage 4–5 hepatic or renal impairment; pregnancy; and a known or anticipated difficult airway in which adherence to the protocol could compromise safety. The investigators approached consecutive eligible patients.

2.4. Randomization, allocation concealment and blinding

A hospital statistician with no clinical involvement generated a computer-based random sequence for 1:1 allocation to the dexmedetomidine group (Group D) or the lidocaine group (Group L). Allocation was concealed in sequentially numbered, sealed, opaque envelopes, opened after enrollment and immediately before drug preparation. An anesthesiologist who took no part in patient care or data collection prepared each study solution in 50 mL of normal saline, in an identical syringe labeled only with the participant's study code.

Infusion duration was equal, because both arms received a 10-minute infusion. Group D received dexmedetomidine 1 $\mu\text{g}/\text{kg}$ over 10 minutes. Group L received lidocaine 1.5 mg/kg over 2 minutes, followed at once by normal saline over the remaining 8 minutes from an identical syringe and pump. Patients, attending anesthesiologists and the outcome assessor were unaware of allocation. The pump rate

differed between the two phases of the lidocaine regimen, and shielding of the pump display was not described. The attending anesthesiologist could therefore, in principle, have inferred allocation. Outcomes were monitor readings, not observer judgments, which limits the scope for detection bias.

2.5. Interventions and anesthetic protocol

On arrival in the operating room, standard ASA monitoring was applied and an 18-gauge intravenous cannula was inserted. After a 5-minute stabilization period, baseline hemodynamic values were recorded. Patients were then pre-oxygenated with 100% oxygen for 3 minutes before the blinded infusion began. The doses were chosen from the range shown to attenuate the airway response. Dexmedetomidine 1 µg/kg is a dose commonly studied in the randomized literature,^{20,21,39} and lidocaine 1.5 mg/kg is a dose commonly used in lidocaine trials and in the only head-to-head trial of the two agents for intubation.^{22,23,26}

Immediately after the infusion, an attending anesthesiologist with more than five years of experience induced anesthesia with fentanyl 2 µg/kg, followed by propofol titrated to loss of the eyelash reflex. The total propofol dose was recorded. Rocuronium 0.6 mg/kg followed confirmation of mask ventilation. Direct laryngoscopy with a Macintosh blade (size 3 or 4) was performed exactly three minutes after the propofol bolus. The duration of laryngoscopy (blade insertion to removal) and the Cormack–Lehane grade were recorded. Capnography and auscultation confirmed tube position, and anesthesia was maintained with sevoflurane in air–oxygen. Individual intervals were not time-stamped, so the timeline in Figure 1 was reconstructed from the protocol. It shows that the lidocaine bolus ended approximately 11 minutes, and the dexmedetomidine infusion approximately 3 minutes, before laryngoscopy.

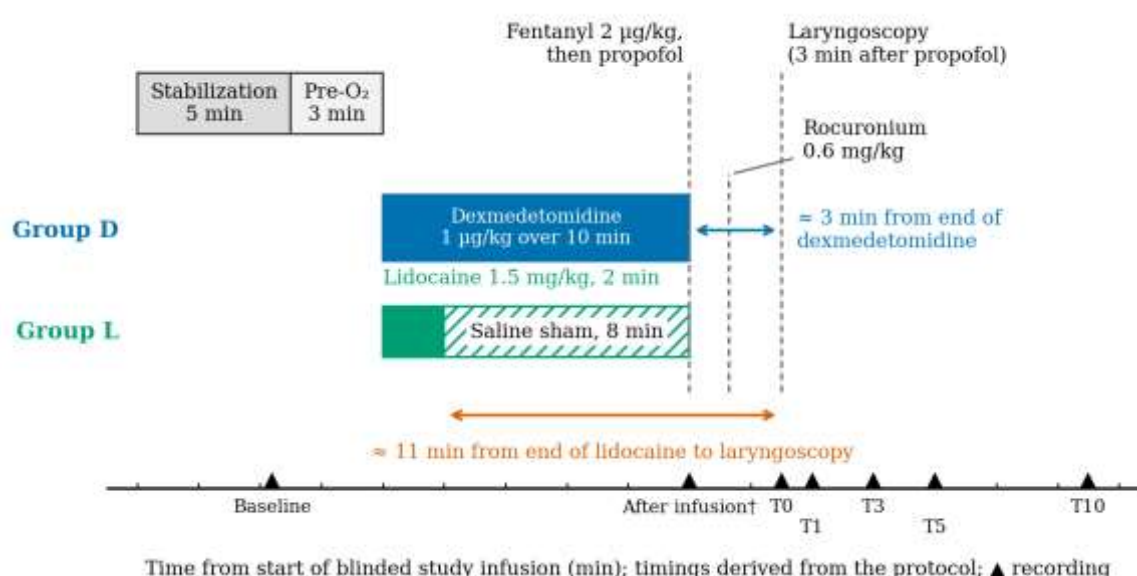


Figure 1. Protocol timeline. The blinded 10-minute infusion delivered dexmedetomidine 1 µg/kg (Group D) or lidocaine 1.5 mg/kg over 2 minutes followed by an 8-minute saline sham (Group L). Induction (fentanyl 2 µg/kg, then propofol) followed the infusion, rocuronium followed mask ventilation, and laryngoscopy took place exactly 3 minutes after propofol. Triangles mark hemodynamic recordings; † values after the infusion and after induction were recorded but not reported.

2.6. Outcomes and operational definitions

Heart rate (HR), systolic and diastolic blood pressure and MAP were measured non-invasively with standard ASA monitoring. They were recorded at baseline, immediately after the study infusion, immediately after induction, immediately after intubation (T0), and at 1, 3, 5 and 10 minutes after intubation (T1, T3, T5, T10). The cuff cycling interval, and whether each reading was manually triggered, were not recorded. The primary outcome was the change in MAP from baseline to T1. Secondary outcomes were the change in HR from baseline to T1; MAP and HR at every post-intubation time point; propofol dose, laryngoscopy duration and Cormack–Lehane grade; and adverse events requiring rescue therapy.

Hypotension was defined as MAP below 65 mmHg for more than one minute and was treated with intravenous ephedrine 5 mg. Bradycardia was defined as HR below 50 beats/min for more than one minute and was treated with intravenous atropine 0.5 mg. TBI severity was classified by

the Glasgow Coma Scale as severe (3–8), moderate (9–12) or mild (13–15).

2.7. Sample size

The protocol specified 30 patients per group to detect a 10 mmHg between-group difference in the change in MAP, with 80% power at a two-sided α of 0.05. The standard deviation assumed in that calculation was not recorded. Thirty per group corresponds to an assumed standard deviation of about 13.8 mmHg. Seventy-one patients were randomized to allow for protocol deviations. The observed standard deviation of the change was much smaller (pooled 6.0 mmHg). The precision actually achieved is therefore reported in the Results as the minimum detectable difference.

2.8. Statistical analysis

2.8.1. Basis of the analyses

All randomized patients were analyzed in the group to which they were allocated. No outcome data were missing.

The source analysis used SPSS Statistics version 26.0: the Shapiro–Wilk test for normality, the Mann–Whitney U test for continuous variables, the χ^2 or Fisher exact test for categorical variables, and the Wilcoxon signed-rank test for within-group change. Continuous data are summarized as mean $\pm$ standard deviation (SD), the form in which they were reported. Medians and interquartile ranges were not available. Every additional analysis reported here was computed from the group-level summary statistics (group sizes, means, SDs and counts, given to one decimal place), not from patient-level records.

2.8.2. Primary, equivalence and baseline-adjusted analyses

The analysis hierarchy was as follows. The primary analysis is the Welch estimate of the between-group difference in the change in MAP at T1, with its 95% CI. The baseline-adjusted, equivalence and Bayesian analyses are secondary analyses of the same outcome, and the time-point, heart-rate and rescue-therapy analyses are secondary outcomes. The comparison with published incidences is descriptive and carries no inferential weight. Some quantities follow exactly from the reported values: the primary difference and its CI, the TOST results, the ANCOVA given the recovered correlations, and the exact tests on counts. Others depend on an assumption: the heart-rate change depends on an unrecorded correlation. A patient-level ANCOVA or mixed-effects model would be preferable and should replace these summary-level analyses when the dataset is released. Welch intervals were used because both arms exceeded 30 patients and the reported change scores had SDs close to the baseline SDs. The sampling distribution of the mean difference is then well approximated by the *t* distribution even if individual values are skewed.

Between-group differences (dexmedetomidine minus lidocaine) were estimated with Welch's unequal-variance method and reported with 95% confidence intervals (CIs). Hedges' *g*, with a large-sample normal-approximation CI, was the standardized effect size, and standardized mean differences describe baseline balance. Within-group change at T1 was estimated with paired-sample *t* intervals from the reported SD of the change. Equivalence was examined post hoc with two one-sided tests (TOST, $\alpha = 0.05$ for each side, equivalent to a 90% CI) across symmetric margins from 1 to 10 mmHg. No margin was prespecified, so the smallest margin for which equivalence holds is reported, which is equivalent to reporting the 90% CI. For interpretation, 5 mmHg was regarded as the smallest difference likely to matter clinically. That value is about 5% of baseline MAP and one quarter of the width of the 55–75 mmHg cerebral perfusion pressure range associated with favorable outcome in neuromonitored TBI.⁴⁰ The margin was a judgment made after the data were seen, and cerebral perfusion pressure and MAP are related but different quantities.

A baseline-adjusted analysis of MAP at T1 (analysis of covariance, ANCOVA) was computed exactly from group sizes, means, SDs and the within-group baseline–T1 correlation. That correlation is identified by the reported SDs of baseline, T1 and change ($r = (\text{SD}_{\text{base}}^2 + \text{SD}_{\text{T1}}^2 - \text{SD}_{\text{change}}^2) / (2 \cdot \text{SD}_{\text{base}} \cdot \text{SD}_{\text{T1}})$). The sensitivity of every estimate to rounding of the reported values was assessed by 20,000 random perturbations within ± 0.05 of each reported mean and SD.

2.8.3. Secondary analyses

The SD of the HR change was not reported. For that outcome, the between-group difference and its CI were computed across assumed baseline–T1 correlations from 0 to 0.95, with the MAP-derived correlations as the most plausible range. Between-group differences at each post-intubation time point were adjusted for multiplicity with the Holm procedure. Within-group decline from baseline at every time point was tested under the most conservative assumption ($r = 0$). A normal–normal Bayesian analysis of the primary difference used four priors. These were a vague prior $N(0, 100^2)$; a skeptical prior $N(0, 2.5^2)$, which places 95% of prior probability within ± 5 mmHg and reflects the expectation that two adjuncts given with the same induction differ little; and two directional priors centered at ± 5 mmHg with SD 2.5 mmHg. The directional priors represent the advantage for dexmedetomidine suggested by pooled trial data, or an equal advantage for lidocaine. Posterior probabilities that the absolute difference lies below 3 and 5 mmHg are reported.

2.8.4. Rescue-therapy analyses

Proportions are reported with Wilson 95% CIs, risk differences with Newcombe hybrid-score CIs, and odds ratios with exact conditional CIs. Comparisons used the Fisher exact test. The overlap between hypotension and bradycardia within patients was not recorded, so the composite of any rescue therapy was bounded over all admissible overlaps. As descriptive context, the observed incidences are shown beside those reported in published trials using the same drugs and doses and in a severe-TBI intubation cohort with Wilson 95% CIs calculated from the published counts.

2.8.5. Software

Re-analyses were performed in Python 3.14.6 with NumPy 2.4.4 and SciPy 1.18.1, and figures were drawn with Matplotlib 3.10.8. All tests were two-sided. The significance level was $\alpha = 0.05$. *P* values are reported to three decimal places.

2.9. Ethics

The CMHC Research Center Ethics Committee, Indonesia, approved the protocol in 2024, before enrollment began (Approval No. 2024/8943). Written informed consent was obtained from each participant or, when the participant lacked capacity, from a legally authorized representative. The trial followed the Declaration of Helsinki. It was not registered in a public trial registry before enrollment.

3. Results

3.1. Participant flow and baseline characteristics

Of 80 patients assessed for eligibility, 9 were excluded (5 did not meet the inclusion criteria, 2 declined and 2 for other reasons), and 71 were randomized: 34 to lidocaine and 37 to dexmedetomidine (Figure 2). Every patient received the allocated intervention, none was lost to follow-up, and all 71 were analyzed in the allocated group. The arms were similar at baseline (Table 1). Mean age was 33.7 ± 14.8 years in the lidocaine arm and 32.4 ± 15.8 years in the dexmedetomidine arm, and about four in five patients in each arm were men (79.4% and 78.4%). Severe TBI accounted for 9 of 34 (26.5%) and 9 of 37 (24.3%) patients, moderate TBI for 15 (44.1%) and 17 (45.9%), and mild TBI for 10 (29.4%) and 11 (29.7%), respectively. Baseline MAP was 98.0 ± 6.8 and 97.0 ± 6.2 mmHg, and baseline HR 92.2 ± 10.2 and 91.4 ± 10.3 beats/min. Every standardized mean difference was 0.15 or smaller in absolute value.

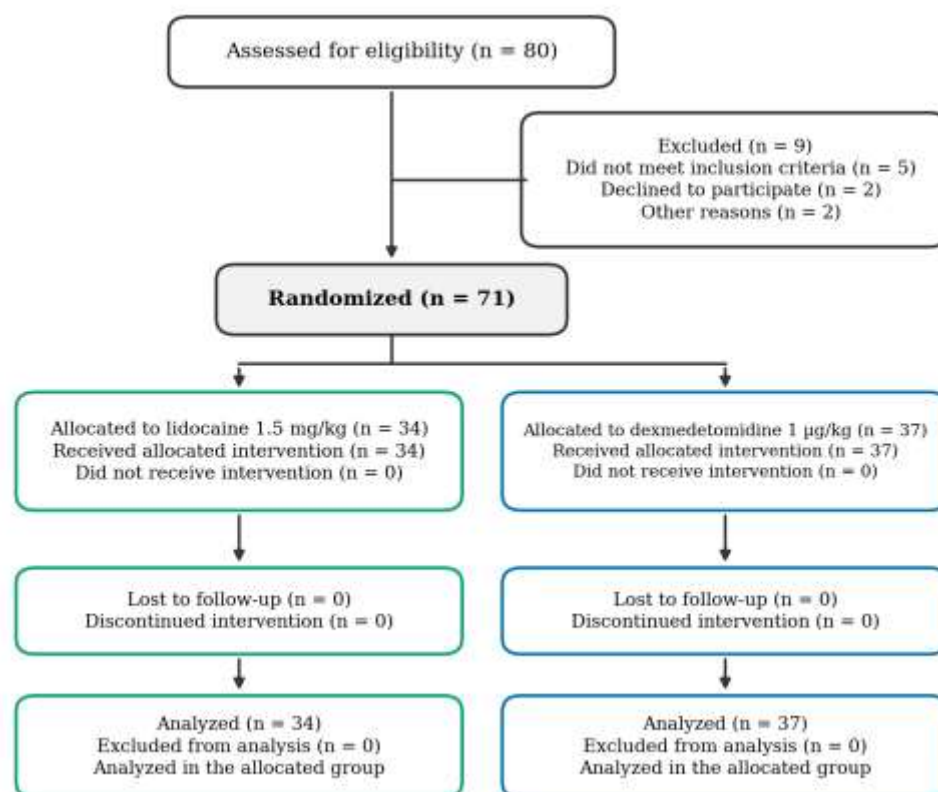


Figure 2. CONSORT flow diagram of enrollment, allocation, follow-up and analysis.

Table 1. Baseline demographic, clinical and hemodynamic characteristics.

Characteristic	Lidocaine (n = 34)	Dexmedetomidine (n = 37)	Difference D – L (95% CI)	SMD	p
Age, years, mean ± SD	33.7 ± 14.8	32.4 ± 15.8	–1.3 (–8.55 to 5.95)	–0.08	0.721 ^a
Male sex, n (%)	27 (79.4)	29 (78.4)	–1.0 (–19.7 to 18.1) ^b	–0.03	0.915 ^c
GCS severe (3–8), n (%)	9 (26.5)	9 (24.3)			0.889 ^d
GCS moderate (9–12), n (%)	15 (44.1)	17 (45.9)			
GCS mild (13–15), n (%)	10 (29.4)	11 (29.7)			
Heart rate, beats/min, mean ± SD	92.2 ± 10.2	91.4 ± 10.3	–0.8 (–5.66 to 4.06)	–0.08	0.764 ^a
MAP, mmHg, mean ± SD	98.0 ± 6.8	97.0 ± 6.2	–1.0 (–4.09 to 2.09)	–0.15	0.449 ^a

Notes: Difference and standardized mean difference (SMD) are dexmedetomidine (D) minus lidocaine (L); for categorical rows the difference is in percentage points. ^a Mann–Whitney U test (source analysis). ^b Newcombe 95% CI. ^c χ^2 test (source analysis; Fisher exact $p = 1.000$). ^d Linear-by-linear trend test across the three categories (source $p = 0.887$). Baseline p values are shown for completeness; balance is judged from the SMD. GCS, Glasgow Coma Scale; MAP, mean arterial pressure.

3.2. Anesthetic and procedural characteristics

Induction and laryngoscopy were comparable (Table 2). The propofol dose was 2.1 ± 0.4 mg/kg with lidocaine and 2.0 ± 0.5 mg/kg with dexmedetomidine (difference -0.10 mg/kg, 95% CI -0.31 to 0.11 ; standardized difference

-0.22). Laryngoscopy lasted 18.3 ± 4.1 and 17.9 ± 3.8 seconds (difference -0.40 s, 95% CI -2.28 to 1.48). A Cormack–Lehane grade I view was obtained in 25 of 34 (73.5%) and 28 of 37 (75.7%) patients (Fisher $p = 1.000$); no patient had a grade III or IV view.

Table 2. Anesthetic and procedural characteristics.

Variable	Lidocaine (n = 34)	Dexmedetomidine (n = 37)	Difference D – L (95% CI)	SMD	p
Propofol induction dose, mg/kg, mean ± SD	2.1 ± 0.4	2.0 ± 0.5	–0.10 (–0.31 to 0.11)	–0.22	0.511 ^a
Laryngoscopy duration, s, mean ± SD	18.3 ± 4.1	17.9 ± 3.8	–0.40 (–2.28 to 1.48)	–0.10	0.689 ^a
Cormack–Lehane grade I, n (%)	25 (73.5)	28 (75.7)	2.2 (–17.6 to 22.1) ^b	0.05	1.000 ^c
Cormack–Lehane grade II, n (%)	9 (26.5)	9 (24.3)			
Fentanyl, µg/kg (protocol)	2	2	—	—	—
Rocuronium, mg/kg (protocol)	0.6	0.6	—	—	—
Propofol bolus to laryngoscopy, min (protocol)	3	3	—	—	—

Notes: ^a Mann–Whitney U test (source analysis). ^b Percentage points, Newcombe 95% CI. ^c Fisher exact test (the source reported $p = 0.913$, which could not be reproduced from the counts). No grade III or IV view occurred. SMD, standardized mean difference.

3.3. Hemodynamic time course

No pressor response to laryngoscopy was detected at the recorded time points (T0–T10) in either arm (Table 3; Figure 3). Immediately after intubation (T0), MAP was 89.2 ± 7.0 mmHg with lidocaine and 87.1 ± 6.5 mmHg with dexmedetomidine, 8.8 and 9.9 mmHg below baseline. MAP reached its nadir at T1 (86.5 ± 7.2 and 84.2 ± 6.7 mmHg, 11.7% and 13.2% below baseline) and recovered gradually

to 90.1 ± 8.0 and 88.5 ± 7.4 mmHg at T10. HR followed the same course, with a nadir at T1 of 84.4 ± 9.1 and 82.9 ± 8.8 beats/min (8.5% and 9.3% below baseline). Under the most conservative assumption for the within-patient correlation ($r = 0$), the decline in MAP from baseline remained significant at every post-intubation time point in both arms (largest $p < 0.001$). The decline in HR remained significant from T0 to T5 (largest $p = 0.017$) but not at T10 ($p = 0.086$ with lidocaine and $p = 0.059$ with dexmedetomidine).

Table 3. Hemodynamic variables at each time point and between-group differences.

Time point	Lidocaine (n = 34)	Dexmedetomidine (n = 37)	Change from baseline, L / D (% of baseline)	Difference D – L (95% CI)	p	Holm p
Mean arterial pressure, mmHg						
Baseline	98.0 ± 6.8	97.0 ± 6.2	—	–1.0 (–4.09 to 2.09)	0.521	—
T0	89.2 ± 7.0	87.1 ± 6.5	–8.8 (–9.0%) / –9.9 (–10.2%)	–2.1 (–5.31 to 1.11)	0.196	0.846
T1	86.5 ± 7.2	84.2 ± 6.7	–11.5 (–11.7%) / –12.8 (–13.2%)	–2.3 (–5.60 to 1.00)	0.169	0.846
T3	87.1 ± 7.5	85.0 ± 6.9	–10.9 (–11.1%) / –12.0 (–12.4%)	–2.1 (–5.52 to 1.32)	0.225	0.846
T5	88.4 ± 7.8	86.3 ± 7.1	–9.6 (–9.8%) / –10.7 (–11.0%)	–2.1 (–5.64 to 1.44)	0.241	0.846
T10	90.1 ± 8.0	88.5 ± 7.4	–7.9 (–8.1%) / –8.5 (–8.8%)	–1.6 (–5.26 to 2.06)	0.386	0.846
Heart rate, beats/min						
Baseline	92.2 ± 10.2	91.4 ± 10.3	—	–0.8 (–5.66 to 4.06)	0.743	—
T0	85.1 ± 9.1	83.9 ± 8.9	–7.1 (–7.7%) / –7.5 (–8.2%)	–1.2 (–5.47 to 3.07)	0.577	1.000
T1	84.4 ± 9.1	82.9 ± 8.8	–7.8 (–8.5%) / –8.5 (–9.3%)	–1.5 (–5.75 to 2.75)	0.483	1.000
T3	85.0 ± 9.3	83.5 ± 9.0	–7.2 (–7.8%) / –7.9 (–8.6%)	–1.5 (–5.84 to 2.84)	0.493	1.000
T5	86.2 ± 9.5	84.8 ± 9.2	–6.0 (–6.5%) / –6.6 (–7.2%)	–1.4 (–5.84 to 3.04)	0.531	1.000
T10	87.9 ± 9.8	86.9 ± 9.5	–4.3 (–4.7%) / –4.5 (–4.9%)	–1.0 (–5.58 to 3.58)	0.664	1.000

Notes: Values are mean $\pm$ SD. Differences are dexmedetomidine minus lidocaine, Welch 95% CI and p; Holm adjustment across the five post-intubation time points within each variable. Within-group decline tested under the most conservative within-patient correlation ($r = 0$): MAP $p < 0.001$ at every time point in both arms; heart rate $p \leq 0.017$ from T0 to T5, and $p = 0.086$ (lidocaine) and 0.059 (dexmedetomidine) at T10. T0, immediately after intubation; T1–T10, minutes after intubation. Values after the study infusion and after induction were recorded but not reported.

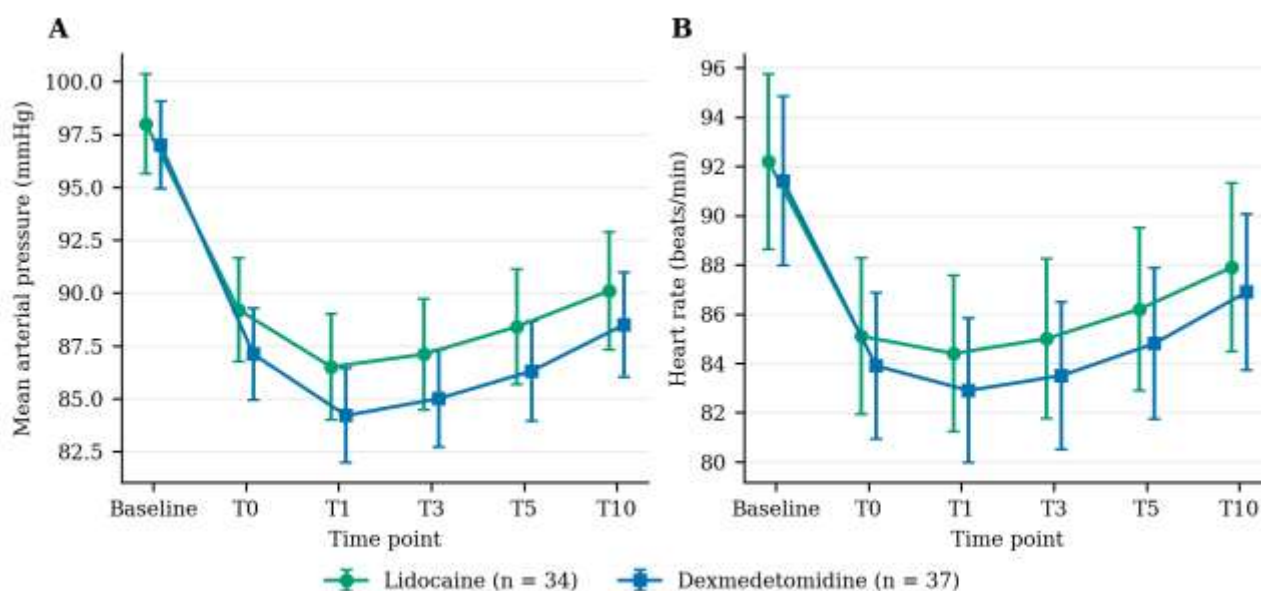


Figure 3. Mean arterial pressure (panel A) and heart rate (panel B) from baseline to 10 minutes after intubation. Points are means and bars 95% confidence intervals (t-based, from the reported SDs). T0, immediately after intubation; T1–T10, minutes after intubation. Green circles, lidocaine (n = 34); blue squares, dexmedetomidine (n = 37).

3.4. Primary outcome

The primary analysis is shown in Table 4 and Figure 4. MAP changed from baseline to T1 by -11.5 mmHg (95% CI -13.56 to -9.44) with lidocaine and by -12.8 mmHg (95% CI -14.83 to -10.77) with dexmedetomidine. The between-

group difference was -1.30 mmHg (95% CI -4.14 to 1.54 ; Welch $p = 0.365$; Mann-Whitney $p = 0.412$ in the source analysis), corresponding to Hedges' $g = -0.21$ (95% CI -0.68 to 0.25). Across rounding of the reported summary values, the CI limits ranged from -4.25 to 1.66 mmHg. Adjusted for baseline MAP, using the within-group baseline-

T1 correlations of 0.646 (lidocaine) and 0.555 (dexmedetomidine) identified by the reported SDs, the difference

was -1.66 mmHg (95% CI -4.31 to 1.00 ; $p = 0.218$). The rounding range was -1.82 to -1.50 mmHg.

Table 4. Primary outcome: change in mean arterial pressure from baseline to one minute after intubation.

Analysis	Estimate (95% CI)	p or probability
Within-group change in MAP, baseline → T1		
Lidocaine (n = 34), mmHg	-11.5 (-13.56 to -9.44)	<0.001
Dexmedetomidine (n = 37), mmHg	-12.8 (-14.83 to -10.77)	<0.001
Between-group difference, D – L		
Unadjusted (Welch), mmHg	-1.30 (-4.14 to 1.54)	0.365^a
Hedges' g	-0.21 (-0.68 to 0.25)	—
Rounding sensitivity of 95% CI limits, mmHg	-4.25 to 1.66	0.327 – 0.404
Baseline-adjusted (ANCOVA), mmHg ^b	-1.66 (-4.31 to 1.00)	0.218
Rounding sensitivity of ANCOVA estimate, mmHg	-1.82 to -1.50	0.177 – 0.262
Equivalence (TOST; 90% CI -3.68 to 1.08)		
Margin ± 3 mmHg	Not shown	0.118
Margin ± 4 mmHg	Equivalent	0.031
Margin ± 5 mmHg	Equivalent	0.006
Smallest margin at which equivalence holds, mmHg	± 3.68	—
Bayesian posterior, D – L (95% credible interval)		$P(\delta < 3) / P(\delta < 5) / P(\delta < 0)$
Vague $N(0, 100^2)$ prior	-1.30 (-4.09 to 1.49)	$0.882 / 0.995 / 0.819$
Skeptical $N(0, 2.5^2)$ prior	-0.98 (-3.41 to 1.44)	$0.948 / 0.999 / 0.786$
Dexmedetomidine-favoring $N(-5, 2.5^2)$ prior	-2.21 (-4.63 to 0.22)	$0.739 / 0.988 / 0.963$
Lidocaine-favoring $N(+5, 2.5^2)$ prior	0.24 (-2.18 to 2.67)	$0.983 / 1.000 / 0.422$
Precision		
Pooled SD of the change in MAP, mmHg	6.0	—
Minimum detectable difference, 80% / 90% power, mmHg	$4.0 / 4.6$	—

Notes: ^a Mann–Whitney U $p = 0.412$ in the source analysis. ^b Adjusted for baseline MAP using within-group baseline–T1 correlations of 0.646 (lidocaine) and 0.555 (dexmedetomidine) recovered from the reported SDs; pooled slope 0.644. Equivalence, ANCOVA and Bayesian analyses were post hoc. TOST, two one-sided tests; D – L, dexmedetomidine minus lidocaine; δ , true between-group difference.

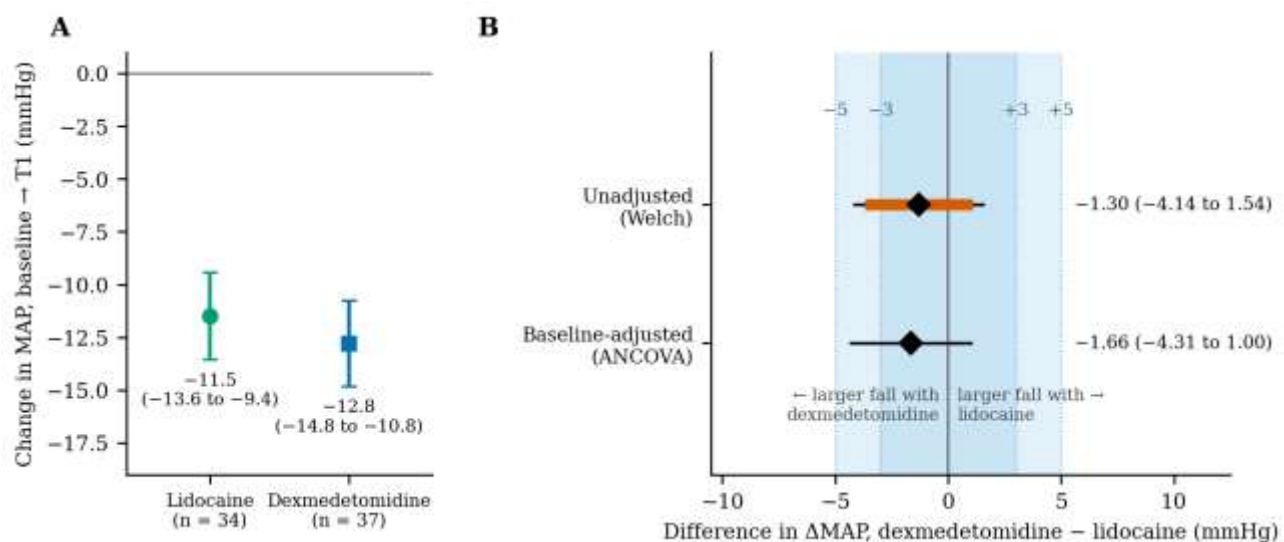


Figure 4. Primary outcome. Panel A: change in mean arterial pressure (MAP) from baseline to 1 minute after intubation in each arm (mean and 95% CI). Panel B: between-group difference (dexmedetomidine – lidocaine) unadjusted and adjusted for baseline MAP; thin lines are 95% CIs, the thick orange bar the 90% CI used for two one-sided tests, and shaded bands the ± 3 and ± 5 mmHg margins.

In the post hoc equivalence analysis (Figure 5), the 90% CI of the difference was -3.68 to 1.08 mmHg. In this post hoc analysis, the 90% CI therefore lay within any symmetric margin of 3.7 mmHg or more, although no margin had been prespecified. TOST p was 0.118 at ± 3 mmHg, 0.031 at ± 4 mmHg and 0.006 at ± 5 mmHg. Bayesian estimation gave the same picture. With a vague prior, the posterior mean difference was -1.30 mmHg (95% credible interval -4.09

to 1.49), the posterior probability that the absolute difference was below 5 mmHg was 0.995 and below 3 mmHg 0.882. The probability that dexmedetomidine produced the larger fall was 0.819. Even a prior centered on a 5 mmHg larger fall with dexmedetomidine left a posterior probability of 0.988 that the absolute difference was below 5 mmHg. At the observed pooled SD of the change (6.0

mmHg), the trial had 80% power to detect a difference of 4.0 mmHg and 90% power to detect 4.6 mmHg.

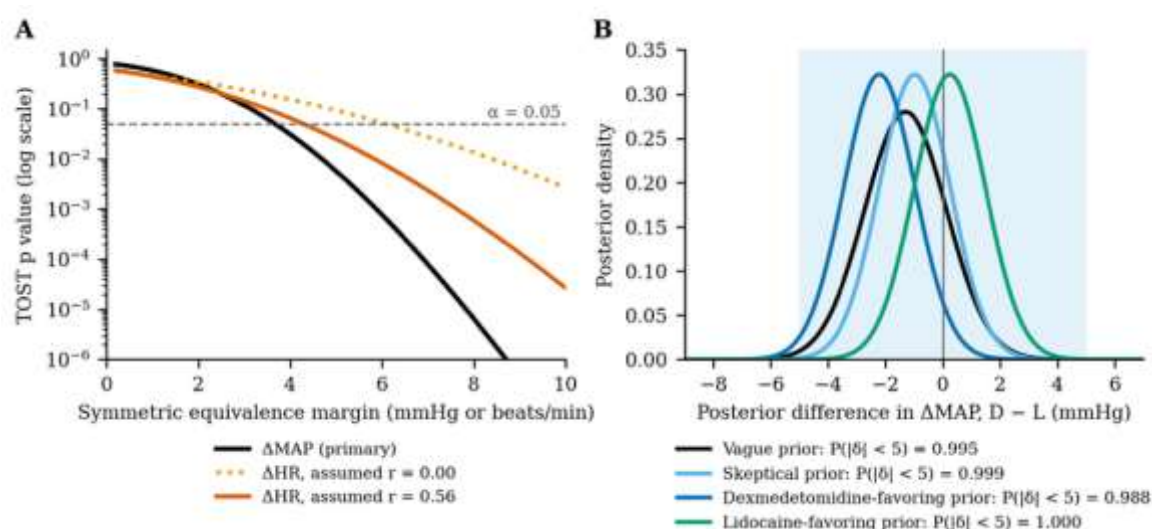


Figure 5. Equivalence and Bayesian analyses (post hoc). Panel A: p value of two one-sided tests (log scale) across symmetric margins for the change in MAP and for the change in heart rate under two assumed within-patient correlations; equivalence holds where the curve falls below $\alpha = 0.05$. Panel B: posterior distributions of the between-group difference in the change in MAP under vague, skeptical and directional priors; the shaded band is ± 5 mmHg.

3.5. Between-group differences at each time point

MAP was 1.6–2.3 mmHg lower with dexmedetomidine at every post-intubation time point, and HR 1.0–1.5 beats/min lower, but every 95% CI included zero (Figure 6). The largest MAP difference was at T1 (–2.3 mmHg, 95%

CI –5.60 to 1.00; $p = 0.169$), and the largest HR difference at T1 and T3 (–1.5 beats/min). After Holm adjustment across the five time points, p was 0.846 for every MAP comparison and 1.000 for every HR comparison. The baseline MAP difference (–1.0 mmHg, 95% CI –4.09 to 2.09) was of the same sign and similar size.

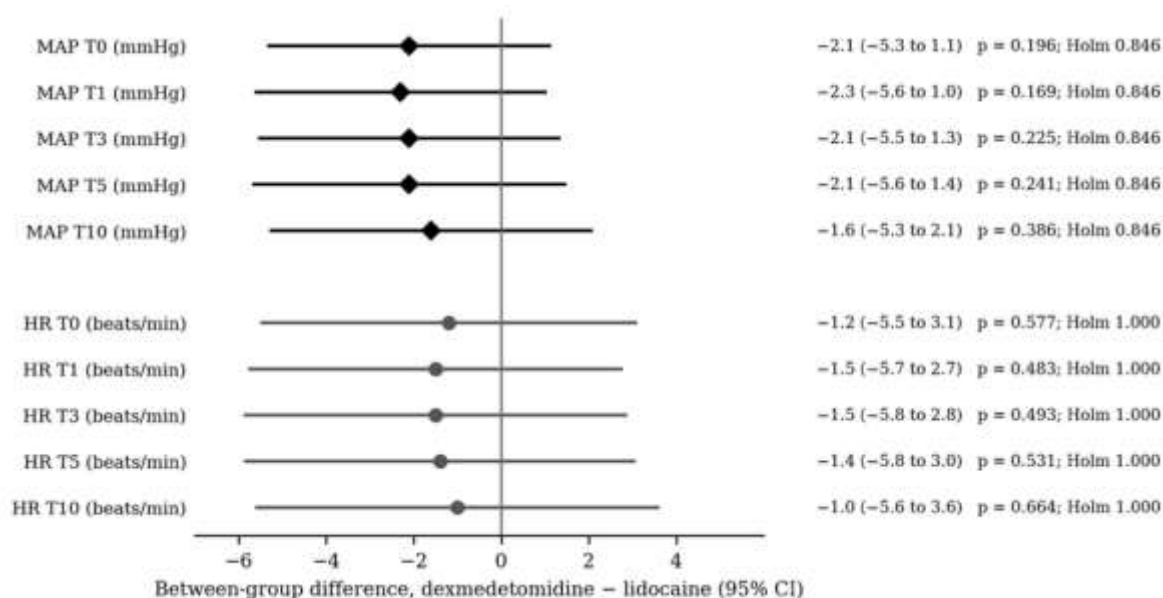


Figure 6. Between-group differences (dexmedetomidine – lidocaine) in mean arterial pressure (diamonds, mmHg) and heart rate (circles, beats/min) at each time point after intubation, with 95% CIs, unadjusted p values and Holm-adjusted p values.

3.6. Heart-rate change

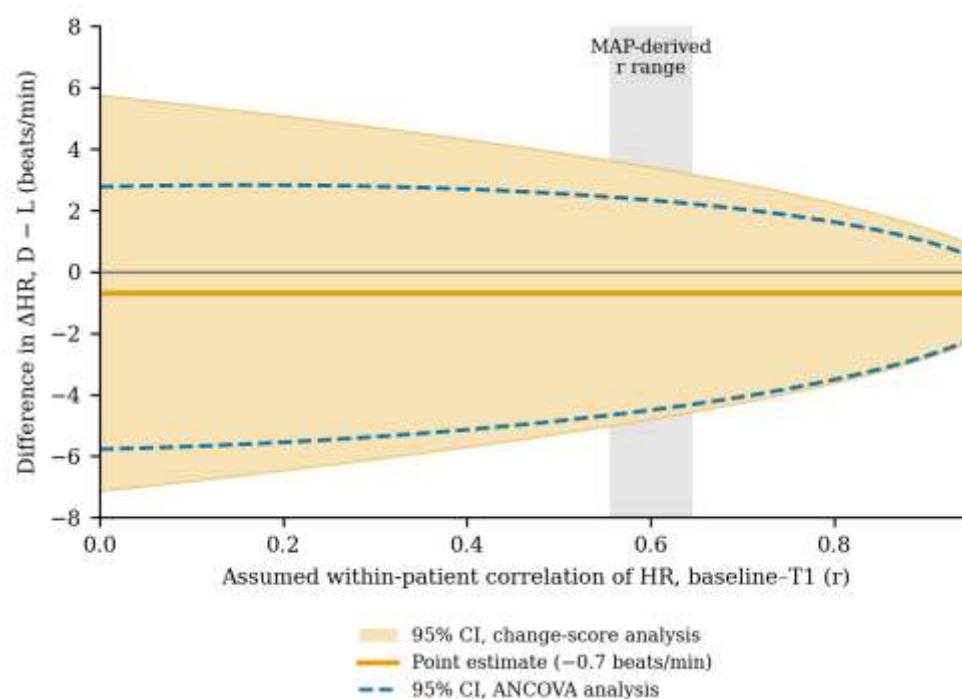
HR fell from baseline to T1 by 7.8 beats/min with lidocaine and 8.5 beats/min with dexmedetomidine, a difference of –0.7 beats/min (Table 5; Figure 7). Because the SD of the HR change was not recorded, its precision depends on the within-patient correlation of HR. Across every assumed

correlation from 0 to 0.9 the 95% CI included zero; at the MAP-derived correlations (0.555–0.646) it was –5.03 to 3.63 and –4.57 to 3.17 beats/min. The baseline-adjusted difference was –1.11 (95% CI –4.67 to 2.44) and –1.05 (–4.31 to 2.21) beats/min. Equivalence within ± 4.3 beats/min was shown at $r = 0.555$, but would require a margin of ± 6.1 beats/min if the correlation were zero.

Table 5. Heart-rate change from baseline to T1 across assumed within-patient correlations.

Assumed <i>r</i>	SD of change, L / D	Δ HR difference D – L (95% CI)	<i>p</i>	ANCOVA D – L (95% CI)	Smallest equivalence margin
0.000	13.7 / 13.5	–0.7 (–7.15 to 5.75)	0.829	–1.50 (–5.77 to 2.77)	±6.1
0.300	11.5 / 11.4	–0.7 (–6.11 to 4.71)	0.797	–1.29 (–5.37 to 2.79)	±5.2
0.500	9.7 / 9.6	–0.7 (–5.28 to 3.88)	0.761	–1.15 (–4.85 to 2.55)	±4.5
0.555 (MAP-derived)	9.2 / 9.1	–0.7 (–5.03 to 3.63)	0.748	–1.11 (–4.67 to 2.44)	±4.3
0.646 (MAP-derived)	8.2 / 8.1	–0.7 (–4.57 to 3.17)	0.719	–1.05 (–4.31 to 2.21)	±3.9
0.700	7.5 / 7.5	–0.7 (–4.27 to 2.87)	0.697	–1.01 (–4.07 to 2.04)	±3.7
0.800	6.2 / 6.2	–0.7 (–3.64 to 2.24)	0.636	–0.94 (–3.51 to 1.62)	±3.2
0.900	4.4 / 4.5	–0.7 (–2.82 to 1.42)	0.513	–0.87 (–2.74 to 0.99)	±2.5

Notes: Observed change: lidocaine –7.8 and dexmedetomidine –8.5 beats/min. The SD of the change was not recorded; it is derived for each assumed baseline–T1 correlation *r*. Units are beats/min.

**Figure 7.** Sensitivity of the between-group difference in heart-rate change (baseline to T1) to the unrecorded within-patient correlation. The shaded band is the 95% CI of the change-score difference and the dashed lines the 95% CI of the baseline-adjusted (ANCOVA) difference; the grey band marks the correlations recovered for mean arterial pressure.

3.7. Rescue therapy and comparison with published incidences

Hypotension requiring ephedrine occurred in 3 of 37 patients (8.1%, 95% CI 2.8–21.3) with dexmedetomidine and 2 of 34 (5.9%, 1.6–19.1) with lidocaine (risk difference 2.2 percentage points, 95% CI –12.0 to 16.1; odds ratio 1.41, exact 95% CI 0.15–17.85; *p* = 1.000) (Table 6; Figure 8). Bradycardia requiring atropine occurred in 2 of 37 (5.4%, 1.5–17.7) and 1 of 34 (2.9%, 0.5–14.9) patients (risk difference 2.5 points, –10.1 to 15.0; *p* = 1.000). Because the overlap of the two events within patients was not recorded, 3–5 patients in the dexmedetomidine arm and 2–3 in the lidocaine arm received any rescue therapy; across all six admissible combinations the risk difference ranged from –0.7 to 7.6 percentage points and no combination reached significance (*p* 0.432–1.000).

As descriptive context, and bearing in mind that definitions differ between studies, hypotension with dexmedetomidine occurred in 8.1% of patients here and in 52.8% (95% CI 39.7–65.6) in the only head-to-head trial using the same doses,²⁶ and bradycardia with dexmedetomidine occurred in 5.4% here and 18.9% (10.6–31.4) there. Hypotension with lidocaine (5.9%) was less frequent than the 15.1% (7.9–27.1) and 13.8% (7.5–24.3) reported with lidocaine 1.5 mg/kg, although the intervals overlap.^{23,26} Across both arms, 5 of 71 patients (7.0%) required ephedrine, compared with 19.1% (16.0–22.6) post-intubation hypotension reported after prehospital induction in severe TBI (Table 7),¹⁵ a comparison limited by differences in setting, severity and definition.

Table 6. Adverse events requiring rescue therapy.

Event	Lidocaine n (%; 95% CI)	Dexmedetomidine n (%; 95% CI)	Risk difference D – L, % (95% CI)	Odds ratio (exact 95% CI)	Fisher p
Hypotension requiring ephedrine	2 (5.9; 1.6–19.1)	3 (8.1; 2.8–21.3)	2.2 (–12.0 to 16.1)	1.41 (0.15–17.85)	1.000
Bradycardia requiring atropine	1 (2.9; 0.5–14.9)	2 (5.4; 1.5–17.7)	2.5 (–10.1 to 15.0)	1.87 (0.09–114.57)	1.000
Any rescue therapy (bounds) ^a	2–3 (5.9–8.8)	3–5 (8.1–13.5)	–0.7 to 7.6	—	0.432–1.000

Notes: Percentages with Wilson 95% CIs; risk differences with Newcombe 95% CIs. ^a The overlap of hypotension and bradycardia within patients was not recorded; the range covers all six admissible overlaps (risk-difference CI limits –15.8 to 22.7 percentage points).

Table 7. Observed incidences compared with published incidences (descriptive).

Event and arm	Observed n/N (%; 95% CI)	Published n/N (%; 95% CI)	Source
Bradycardia, dexmedetomidine 1 µg/kg	2/37 (5.4; 1.5–17.7)	10/53 (18.9; 10.6–31.4)	Seangrung et al., 2021 ²⁶
Hypotension, dexmedetomidine 1 µg/kg	3/37 (8.1; 2.8–21.3)	28/53 (52.8; 39.7–65.6)	Seangrung et al., 2021 ²⁶
Hypotension, lidocaine 1.5 mg/kg	2/34 (5.9; 1.6–19.1)	8/53 (15.1; 7.9–27.1)	Seangrung et al., 2021 ²⁶
Hypotension, lidocaine 1.5 mg/kg	2/34 (5.9; 1.6–19.1)	9/65 (13.8; 7.5–24.3)	Xiao et al., 2025 ²³
Hypotension, both arms (TBI context)	5/71 (7.0; 3.0–15.4)	106/555 (19.1; 16.0–22.6)	Price et al., 2025 ¹⁵

Notes: Wilson 95% CIs; the published counts are those reported in the cited studies. Definitions of hypotension and bradycardia differ between studies, and the severe-TBI comparison refers to prehospital rapid-sequence induction (systolic pressure < 90 mmHg) and is contextual only. No formal test is applied to the comparisons.

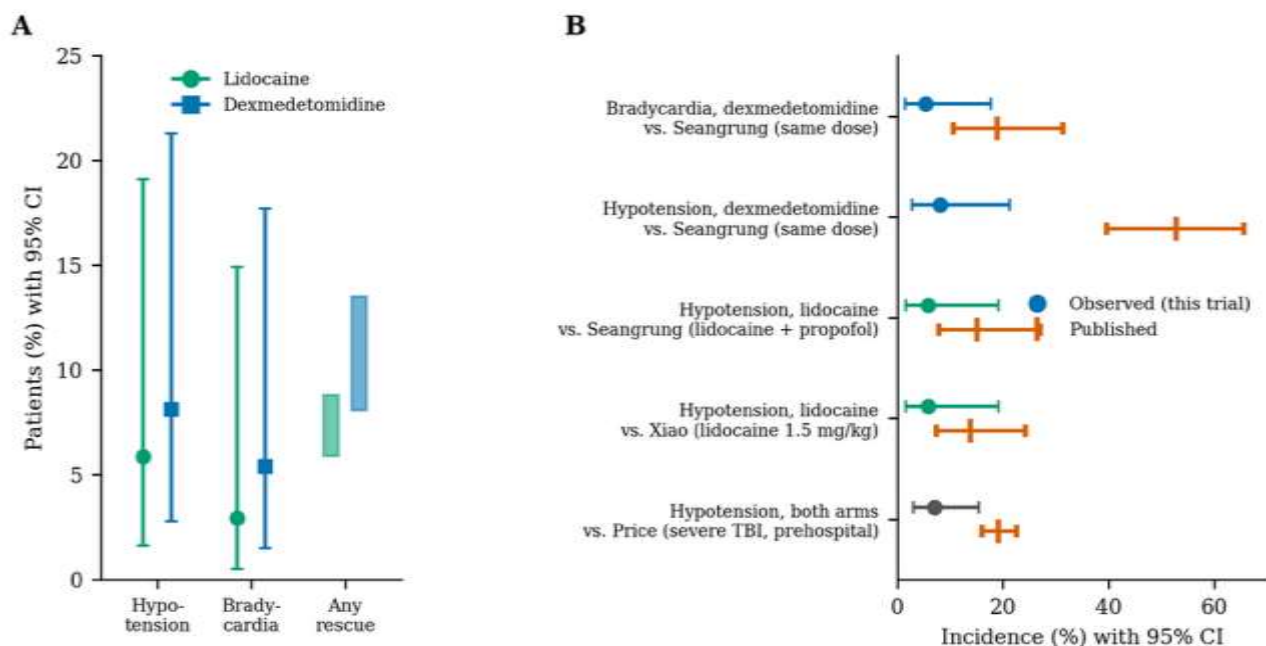


Figure 8. Rescue therapy. Panel A: incidence of hypotension requiring ephedrine and bradycardia requiring atropine with Wilson 95% CIs, and the bounded incidence of any rescue therapy (bars span all admissible overlaps). Panel B: observed incidences (circles, 95% CI) beside published incidences (vertical marks, 95% CI from the published counts) from trials using the same drugs and doses and from a severe-TBI intubation cohort.

4. Discussion

4.1. Principal findings

In adults with TBI undergoing intubation at Dr. Saiful Anwar Regional General Hospital, dexmedetomidine 1 µg/kg and lidocaine 1.5 mg/kg were given before a standardized fentanyl-propofol induction. The resulting changes in MAP differed by about 4 mmHg or less: the 90% CI of the difference was –3.68 to 1.08 mmHg, and the 95% CI was –4.14 to 1.54 mmHg. The difference in the primary outcome was –1.30 mmHg, and its 95% CI excluded any difference larger than 4.1 mmHg in favor of dexmedetomidine and 1.5 mmHg in favor of lidocaine. No pressor response to laryngoscopy was detected in either arm. Heart-rate re-

sponses were indistinguishable between the arms, and rescue therapy, whether for hypotension or for bradycardia, was uncommon in both groups.

The trial does not show that either drug attenuated the intubation response, because both arms received the same induction and there was no placebo arm. It shows that substituting one adjunct for the other changes the MAP response by a small amount. That interval lies within the 5 mmHg we regard as the smallest clinically relevant difference. It does not lie within 3 mmHg.

4.2. Comparison with the published literature

The closest comparator is the Thai trial. It used the same doses in 106 elective surgical patients and found lidocaine 1.5 mg/kg with 0.5 mg/kg of additional propofol non-inferior to dexmedetomidine 1 µg/kg for blood pressure at

most time points, with lower heart rates throughout in the dexmedetomidine arm.²⁶ The present trial reproduces the blood-pressure finding in a different population and without supplementary propofol in the lidocaine arm, and its 95% CI is narrow enough to exclude differences of the size usually regarded as clinically important. The heart-rate separation was not reproduced. The fentanyl dose given to both arms, or the smaller sample, may explain why.

Other trials point the other way. In cardiac surgery, dexmedetomidine 1 µg/kg attenuated heart rate and blood pressure more than lidocaine 1.5 mg/kg or fentanyl 2 µg/kg, and MAP rose one minute after lidocaine, although the authors judged fentanyl more effective for blood pressure.²⁷ In tumor craniotomy, a dexmedetomidine infusion suppressed the responses to intubation, pinning and incision better than a lidocaine infusion.²⁸ A three-arm trial found labetalol most effective, with esmolol and lidocaine less effective.⁴¹ These trials gave lidocaine without an equivalent induction-depth control and, in most cases, without opioid at the doses used here. Pooled estimates help to put them in context: relative to no drug, dexmedetomidine lowered MAP and heart rate more than lidocaine did.^{20,22}

Pooled analyses frame what difference might reasonably have been expected. Dexmedetomidine lowered MAP at laryngoscopy by 12.8 mmHg relative to no dexmedetomidine,²⁰ whereas lidocaine reduced the intubation-related rise in MAP by 3.85 mmHg relative to no lidocaine.²² Subtracting these pooled effects naively would predict a dexmedetomidine–lidocaine difference of about 9 mmHg, although the two meta-analyses measured different quantities in different populations. The observed difference was –1.30 mmHg. The CI excluded differences beyond –4.14 mmHg. Two explanations fit this result. First, a fentanyl 2 µg/kg–propofol induction, with laryngoscopy timed three minutes after propofol, may have abolished most of the reflex in both arms and so compressed any difference attributable to the adjuncts. The absence of a detected pressor response at T0 is consistent with this hypothesis, but only a trial with a placebo arm can test it. Second, the pooled estimates come largely from elective patients with lighter induction and show high heterogeneity. They may overstate what either drug adds in a deeply induced patient. Comparisons of dexmedetomidine with fentanyl show a similar ceiling: low-dose dexmedetomidine and fentanyl 2 µg/kg were equipotent in two trials,^{42,43} and dexmedetomidine was superior in a third only when fentanyl was the sole comparator.⁴⁴ Against esmolol, dexmedetomidine produced lower heart rates in a meta-analysis and an Indian trial,^{25,45} whereas the two drugs were equally effective in a Malaysian trial.³⁶ This trial did not detect such an advantage against lidocaine.

These pooled effects also define the main limit of the equivalence claim. The difference excluded here, about 4 mmHg in favor of dexmedetomidine, is of the same size as the pooled effect of lidocaine relative to no lidocaine (3.85 mmHg).²² Equivalence to an active comparator is informative only if that comparator is known to work under the conditions of the trial, a property usually called assay sensitivity. No placebo arm was included, and lidocaine was given well before laryngoscopy, so the data cannot distinguish two equally effective adjuncts from a dexmedetomidine effect of up to about 4 mmHg added to a lidocaine dose that contributed little. What the trial does establish is the practical quantity: the difference a clinician should expect in MAP response when one of these drugs is substituted for the other under this induction.

The missing heart-rate separation needs explanation. In the Thai trial, dexmedetomidine produced lower heart rates than lidocaine at every time point,²⁶ and across 99 trials it lowered heart rate by 16.9 beats/min at laryngoscopy.²⁰ Here the difference was 1.0–1.5 beats/min, with 95% CIs of about ±4.3 to ±4.6 beats/min. Three features of the protocol may account for this. Fentanyl 2 µg/kg was given to both arms and itself reduces central sympathetic drive and heart rate, the dexmedetomidine infusion ended when induction began, about three minutes before laryngoscopy, and the trial was sized for MAP, not for heart rate. A difference of 3–4 beats/min therefore cannot be excluded. The fentanyl–propofol–dexmedetomidine combination was reported to give the best heart-rate control in a network meta-analysis. Co-administered fentanyl therefore does not by itself abolish the heart-rate effect of dexmedetomidine, and the timing of the infusion and the size of the trial are the more likely explanations.

Dose, route and timing modify both agents. Dexmedetomidine 0.5 and 1 µg/kg blunted the hemodynamic response to intubation similarly, with fewer adverse effects (hypotension and bradycardia) at 0.5 µg/kg.²¹ In cardiac surgery, 0.5 µg/kg left more post-intubation hypertension.³⁹ Intravenous dexmedetomidine attenuated the response more than the nebulized route in one trial and equally in another, and bradycardia was confined to the intravenous route.^{46,47} In neurosurgical patients, intranasal and intravenous dexmedetomidine both kept hemodynamics within 20% of baseline, at the price of more sedation and bradycardia with the intravenous route.⁴⁸ Combining intravenous dexmedetomidine with nebulized lidocaine controlled post-intubation MAP better than either alone.⁴⁹ For lidocaine, hypotension under propofol–remifentanyl induction was 51.4% at 0.5 mg/kg but 13.8% at 1.5 mg/kg.²³ Lidocaine-based propofol induction abolished the hypotension seen with fentanyl-based induction in older adults,⁵⁰ and transtracheal lidocaine produced a smaller three-minute MAP surge than intravenous lidocaine.⁵¹ Pupillary dilation may reveal nociceptive responses to intubation that blood pressure alone does not capture,⁵² and lidocaine may have antinociceptive effects of this kind that were not measured here.

Timing deserves emphasis. It may have handicapped lidocaine in this trial. Lidocaine is often injected about three minutes before laryngoscopy. At that interval, lidocaine 1.5 mg/kg reduced the sufentanil concentration needed for intubation by more than a quarter.²⁴ Here the bolus ended about 11 minutes before laryngoscopy (Figure 1), by which time redistribution would have lowered plasma concentrations substantially. The dexmedetomidine infusion, by contrast, ended about three minutes before laryngoscopy, because induction began as the infusion ended. For dexmedetomidine the opposite argument applies: intravenous premedication lowered the sufentanil concentration needed to block the intubation response,⁵³ and an earlier injection may add to this effect. A design that delivered lidocaine at the conventional interval might have made lidocaine look better, not worse. The observed similarity may therefore, if anything, understate the contribution of lidocaine, although it cannot be separated from the induction-ceiling explanation.

4.3. Interpretation and possible mechanisms

The two drugs act at different points of the reflex (Figure 9). Dexmedetomidine reduces locus coeruleus firing and presynaptic norepinephrine release, which lowers central sympathetic outflow. Lidocaine blocks sodium channels in

airway afferents, raises the threshold of central reflex processing and stabilizes the myocardium. What this trial measured, however, was the net hemodynamic course after both drugs had been combined with fentanyl and propofol, which themselves reduce sympathetic tone and vascular resistance. MAP was already below baseline at T0 in both arms and fell further to T1. This suggests that induction dominated the hemodynamic course and that the

laryngoscopic stimulus was largely absorbed. The trial therefore tests whether two mechanistically different adjuncts lead to different net trajectories under deep induction. They do not, by more than a few mmHg. The trial cannot distinguish an equal contribution from both drugs from a negligible contribution from both. The induction-ceiling explanation remains a hypothesis.

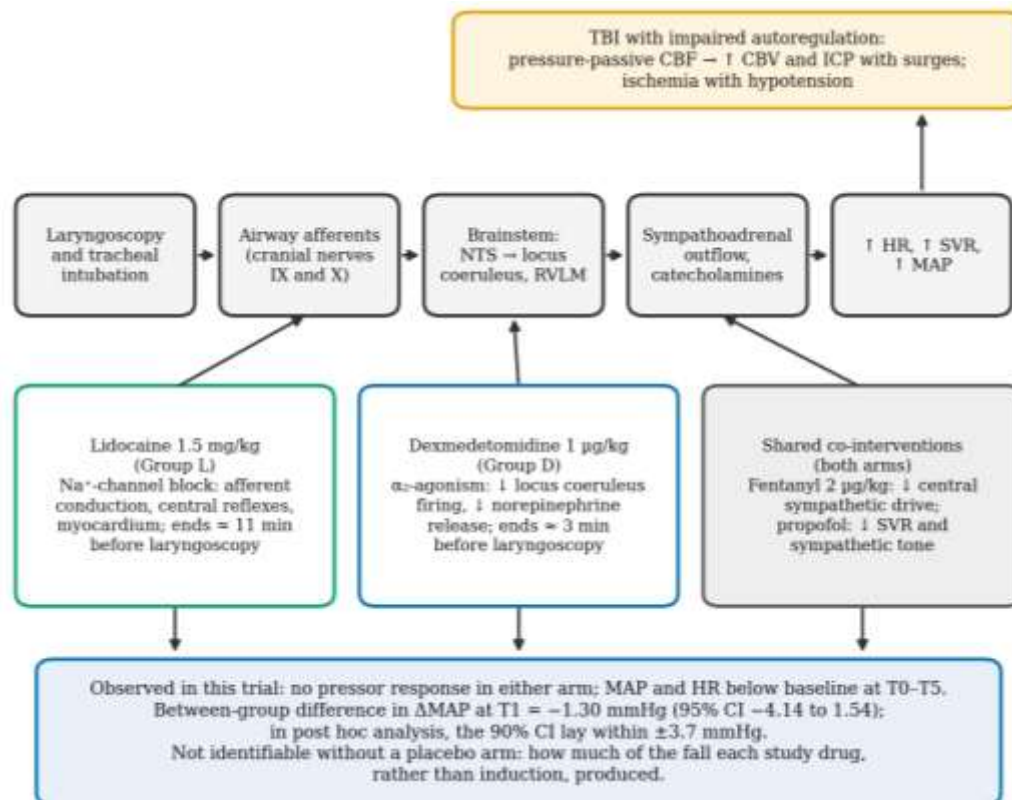


Figure 9. Sites of action of the study drugs and the shared induction agents along the laryngoscopic reflex, and what the trial can and cannot attribute. Both arms received fentanyl and propofol; without a placebo arm, the contribution of each study drug to the observed fall in pressure cannot be separated from that of induction. CBF, cerebral blood flow; CBV, cerebral blood volume; ICP, intracranial pressure; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla; SVR, systemic vascular resistance.

Effects beyond blood pressure may still separate the agents in TBI, although none was measured here. Intravenous lidocaine 1.5 mg/kg attenuated the distension of the optic nerve sheath, a correlate of intracranial pressure, during intubation compared with placebo.⁵⁴ In ventilated severe TBI, lidocaine did not lower MAP or cerebral perfusion pressure, whereas dexmedetomidine lowered both.²⁹ During surgery for traumatic subdural hematoma, dexmedetomidine-based anesthesia reduced propofol consumption with comparable intracranial pressure,⁵⁵ and intravenous lidocaine reduced propofol requirements in a meta-analysis of sedation for colonoscopy.⁵⁶ Intensive-care studies link prolonged dexmedetomidine sedation with better jugular venous oxygenation and lower inflammatory mediators,⁵⁷ neutral biomarker profiles,³² no overall functional benefit,³¹ lower mortality^{58,59} and more bradycardia.⁶⁰ These concern hours to days of infusion, however, and do not bear on a single pre-intubation dose.

The low incidence of rescue therapy is the most clinically reassuring observation. Its contrast with published rates must nevertheless be read cautiously. Hypotension with dexmedetomidine was 8.1% here and 52.8% in the Thai trial with the same dose.²⁶ That gap more likely reflects definitions and populations than the drug. This trial counted only hypotension that required treatment, defined as MAP

below 65 mmHg for more than one minute, a stricter threshold than many trials use, and the patients were young (mean age about 33 years), most had mild or moderate TBI, and none had severe cardiovascular disease. These features limit the post-induction fall. Conversely, the incidence of relative hypotension, a fall of 20% or more from baseline that did not reach the treatment threshold, is unknown. With a mean nadir 12–13% below baseline, it may not have been rare. In TBI more broadly, induction depth itself drives post-intubation hypotension. Reducing induction depth may limit post-intubation hypotension, which was associated with higher 30-day mortality in severe TBI,¹⁵ propofol was the modifiable factor associated with collapse in INTUBE,¹³ and hypotension within 10 minutes of induction occurred in 21.8% of trauma patients after prehospital induction.¹⁷ These data suggest that the choice of adjunct matters less than the depth of the whole induction.

4.4. Implications for practice

Consider hemodynamically stable adults with predominantly mild-to-moderate TBI who are intubated for scheduled surgery. For them, the trial indicates that substituting lidocaine 1.5 mg/kg for dexmedetomidine 1 µg/kg, or the reverse, changes the MAP response by less than about 4

mmHg under a fentanyl–propofol induction. Within that limit the choice can rest on availability, cost, the need for postoperative sedation and the risk of bradycardia. Lidocaine is short-acting and suits patients who need an early neurological examination, whereas dexmedetomidine provides sedation and sympatholysis that may help when continued sedation is planned. The MAP nadir at T1 was about 12–13% below baseline in both arms, and pressure was still below baseline at ten minutes. The practical message is therefore to anticipate a post-intubation fall and treat it promptly. Pursuing additional suppression of a surge that was not detected under this induction is the lesser priority.

In the Indonesian context, these findings matter for district and provincial hospitals, where most patients with TBI are first managed. Motorcycle crashes produce a young, predominantly male TBI population,⁵ and outcomes after emergency neurosurgery are worse in lower-resource settings.³ Where dexmedetomidine is unavailable, or its cost competes with other priorities, the data indicate that lidocaine 1.5 mg/kg with a standardized opioid–propofol induction yields a MAP response within about 4 mmHg of that seen with dexmedetomidine in scheduled surgery. The caveat is that neither drug's own contribution was measured. An Indonesian trial has shown benefits of lidocaine infusion on brain relaxation during craniotomy,³⁴ and intranasal dexmedetomidine has lowered the anesthetic requirement for intubation in children,³⁵ and the present data extend this evidence to adult airway management in TBI. Institutional protocols should specify the timing of lidocaine relative to laryngoscopy, and a threshold and drug for treating post-intubation hypotension. They should also require documentation of every rescue event, so that the cross-classification missing from this trial is captured in future practice.

The findings should not be generalized to emergency rapid-sequence induction in hemodynamically unstable patients with severe TBI, in whom post-intubation hypotension is common¹⁶ and associated with higher mortality.¹⁵ In that setting, pre-intubation vasopressors and hypertonic saline were associated with lower odds of post-intubation hypotension,¹⁶ and the risks of delaying definitive airway control, or of collapse during transport, are substantial.^{18,19} Neither study drug was tested under those conditions, and the 10-minute infusion used here is incompatible with rapid-sequence induction.

4.5. Strengths

The trial was randomized with concealed allocation, an independent drug preparer and identical 10-minute infusions. Every randomized patient was analyzed, with no missing outcome data. Induction, neuromuscular blockade and the interval from propofol to laryngoscopy were standardized. Laryngoscopy duration and laryngoscopic view were recorded and balanced, so the stimulus was comparable between arms. Outcomes were monitor readings, not observer judgments. The analysis reports the quantity a clinician needs, the CI of the difference and the margins it excludes, rather than a single p value. The conclusion is stable across rounding of the reported values, baseline adjustment and prior assumptions. Wherever a result depended on an unrecorded quantity, its dependence was shown explicitly rather than assumed away.

4.6. Limitations

First, the absence of a placebo arm means that neither drug's attenuating effect can be estimated. The difference excluded (about 4 mmHg) is close to the pooled effect of

lidocaine itself,²² so equivalence between the two drugs does not establish that either was effective. Second, the equivalence, baseline-adjusted and Bayesian analyses were post hoc, no equivalence margin was prespecified, and the trial was not registered. These analyses should be read as estimation rather than confirmation. Third, the analyses used group-level summary statistics. The heart-rate interval depends on an assumed correlation, the baseline adjustment relies on correlations recovered from values rounded to one decimal place, medians were unavailable, and the associations of rescue therapy with severity and laryngoscopic grade could not be assessed, because the cross-classification was not recorded.

Fourth, the measurements recorded after the infusion and after induction were not reported. The effect of each drug before induction therefore cannot be separated from the effect of induction. Releasing these data is the single most useful addition to this evidence. Fifth, blood pressure was measured non-invasively at discrete times with an unrecorded cycling interval, which may miss a brief surge or trough. The statement that no pressor response occurred applies to the recorded time points. Intracranial pressure, cerebral perfusion pressure and optic nerve sheath diameter were not measured. Sixth, rescue therapy was defined by an absolute threshold, so relative hypotension was not captured. Seventh, lidocaine was given about 11 minutes before laryngoscopy, later than its usual window, which may have reduced its contribution. Eighth, the pump display could have revealed allocation to the attending anesthesiologist, although the outcomes were monitor readings. Ninth, acquisition costs were not measured, so the economic argument is qualitative. Finally, the patients were young, hemodynamically stable and scheduled for surgery, and three-quarters had mild or moderate TBI. Anesthesia trials are typically small,³⁷ and trials of this size are often fragile,⁶¹ so the results should not be extrapolated to emergency intubation in severe TBI.

4.7. Recommendations for future research

The next trial should answer the questions this one could not. How much does each drug contribute beyond induction, and does the induction-ceiling hypothesis hold? A prospectively registered, three-arm, double-blind design would address both. It would compare dexmedetomidine 0.5–1 µg/kg, lidocaine 1.5 mg/kg given three minutes before laryngoscopy, and saline placebo, with a prespecified equivalence margin of 5 mmHg between the active arms and continuous invasive arterial pressure monitoring. Such a trial would separate each drug's effect from that of induction. Assume an SD of the change of 6 mmHg and a true difference of zero. Then 25 patients per active arm give 80% power (31 for 90% power) to show equivalence within ±5 mmHg, and 69 per arm are needed for a ±3 mmHg margin. Assume an SD of 7 mmHg. Then the comparison with placebo needs 31 patients per arm to detect a 5 mmHg attenuation with 80% power.

The primary outcome should be the area of MAP outside a predefined corridor (for example, more than 20% above or below baseline) over the first ten minutes, because this captures both surges and troughs. Patients with moderate-to-severe TBI should be stratified by Glasgow Coma Scale and by intracranial pressure monitoring, with optic nerve sheath diameter as a non-invasive intracranial surrogate. Relative hypotension (a fall of 20% or more from baseline) should be a prespecified secondary outcome. Cuff or arterial sampling should be synchronized to laryngoscopy, and

acquisition costs should be collected for a cost-consequence analysis. Rescue events should be recorded per patient with time stamps. The dataset should be deposited for re-analysis, a step that would allow patient-level estimates to replace the summary-based estimates in this report.

5. Conclusion

Adults with predominantly mild-to-moderate traumatic brain injury received dexmedetomidine 1 µg/kg or lidocaine 1.5 mg/kg before a standardized fentanyl–propofol induction for scheduled surgery. One minute after intubation, the change in mean arterial pressure differed between the two drugs by –1.30 mmHg (95% CI –4.14 to 1.54). The 95% CI excludes an advantage of more than 4.1 mmHg for dexmedetomidine or 1.5 mmHg for lidocaine, and in post hoc analysis the 90% CI lay within ±3.7 mmHg. Neither drug stood out. Heart-rate responses were similar. Rescue therapy was infrequent. No pressor response was detected in either arm, and the main hemodynamic risk was a post-intubation fall. Without a placebo arm, and because the equivalence analyses were post hoc, the similarity of the two drugs does not show that either attenuated the response. For Indonesian hospitals, the choice between them can rest on availability, cost, sedation needs and heart rate rather than on MAP control. A registered three-arm trial with a placebo arm, correctly timed lidocaine and invasive monitoring is needed to establish how much either drug contributes beyond induction itself.

6. Declarations

Ethical approval and consent to participate. This study was approved by the CMHC Ethics Committee, Indonesia, under reference number 2024/8943. Written informed consent was obtained from all participants or, for participants lacking capacity, from their legally authorized representatives. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication. Not applicable; no individually identifiable data are presented.

Availability of data and materials. The aggregate data analyzed are contained within the article. Patient-level data are available from the corresponding author on reasonable request.

Artificial intelligence (AI) use statement. The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

Author contribution statement. S., A.A.A., R.M.L. and B.H.L. contributed to conceptualization, methodology, investigation, data curation, formal analysis, and writing – original draft. All authors contributed to writing – review & editing, approved the final manuscript and agree to be accountable for all aspects of the work.

Funding statement. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest (competing interests) statement. The authors declare that they have no competing interests.

Acknowledgements. None declared.

7. References

- Zhong H, Feng Y, Shen J, et al. Global burden of traumatic brain injury in 204 countries and territories from 1990 to 2021. *Am J Prev Med*. 2025;68(4):754–63. doi:10.1016/j.amepre.2025.01.001
- Gu L, Zhang L, Li C, et al. Global, regional, and national burden of traumatic brain injury, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *J Neurotrauma*. 2025;42(19–20):1805–15. doi:10.1089/neu.2025.0039
- Clark D, Joannides A, Adeleye AO, et al. Casemix, management, and mortality of patients receiving emergency neurosurgery for traumatic brain injury in the Global Neurotrauma Outcomes Study: a prospective observational cohort study. *Lancet Neurol*. 2022;21(5):438–49. doi:10.1016/S1474-4422(22)00037-0
- Gupta D, Singh RD, Vreeburg RJ, et al. Disparities in casemix, acute interventions, discharge destinations and mortality of patients with traumatic brain injury between Europe and India. *J Glob Health*. 2024;14:04227. doi:10.7189/jogh.14.04227
- Nugroho AW, Masrika NUE. The epidemiology of motorcycle-related acute traumatic brain injury: the NOMADEN study. *Surg Neurol Int*. 2025;16:27. doi:10.25259/SNI.929.2024
- Lee JW, Wang W, Rezk A, et al. Hypotension and adverse outcomes in moderate to severe traumatic brain injury: a systematic review and meta-analysis. *JAMA Netw Open*. 2024;7(11):e2444465. doi:10.1001/jamanetworkopen.2024.44465
- Spaite DW, Hu C, Bobrow BJ, et al. Optimal out-of-hospital blood pressure in major traumatic brain injury: a challenge to the current understanding of hypotension. *Ann Emerg Med*. 2022;80(1):46–59. doi:10.1016/j.annemergmed.2022.01.045
- Chen JM, Su YC, Cheng CY, et al. Association between admission systolic blood pressure and outcomes in patients with isolated traumatic brain injury: a cross-national multicenter cohort study. *J Neurotrauma*. 2024;41(23–24):2590–601. doi:10.1089/neu.2023.0392
- Zhang SY, Li CL, Yin J, et al. Blood pressure variability and prognostic significance in traumatic brain injury: analysis of the eICU-CRD database. *BMC Emerg Med*. 2024;24(1):141. doi:10.1186/s12873-024-01054-2
- Bögli SY, Olakorede I, Beqiri E, et al. Cerebral perfusion pressure targets after traumatic brain injury: a reappraisal. *Crit Care*. 2025;29(1):207. doi:10.1186/s13054-025-05458-9
- Svedung Wettervik T, Beqiri E, Hånell A, et al. Visualization of cerebral pressure autoregulatory insults in traumatic brain injury. *Crit Care Med*. 2024;52(8):1228–38. doi:10.1097/CCM.0000000000006287
- Russotto V, Myatra SN, Laffey JG, et al. Intubation practices and adverse peri-intubation events in critically ill patients from 29 countries. *JAMA*. 2021;325(12):1164–72. doi:10.1001/jama.2021.1727
- Russotto V, Tassistro E, Myatra SN, et al. Peri-intubation cardiovascular collapse in patients who are critically ill: insights from the INTUBE study. *Am J Respir Crit Care Med*. 2022;206(4):449–58. doi:10.1164/rccm.202111-25750C
- Butterfield M, Bodnar D, Williamson F, et al. Prevalence of secondary insults and outcomes of patients with traumatic brain injury intubated in the prehospital setting: a retrospective cohort study. *Emerg Med J*. 2023;40(3):167–74. doi:10.1136/emered-2022-212513
- Price J, Lachowycz K, Major R, et al. Prehospital postintubation hypotension and survival in severe traumatic brain injury. *JAMA Netw Open*. 2025;8(11):e2544057. doi:10.1001/jamanetworkopen.2025.44057
- Anand T, Hejazi O, Conant M, et al. Impact of resuscitation adjuncts on postintubation hypotension in patients with isolated traumatic brain injury. *J Trauma Acute Care Surg*. 2024;97(1):112–8. doi:10.1097/TA.0000000000004306
- Price J, Moncur L, Lachowycz K, et al. Predictors of post-intubation hypotension in trauma patients following prehospital emergency anaesthesia: a multi-centre observational study. *Scand J Trauma Resusc Emerg Med*. 2023;31(1):26. doi:10.1186/s13049-023-01091-z
- Fjeld KJ, Esteves AM, Ding RJ, et al. Hemodynamic collapse after intubation in critical care transport. *Prehosp Emerg Care*. 2025;29(6):719–24. doi:10.1080/10903127.2024.2396949
- Bernard SA, Nguyen V, Cameron P, et al. Prehospital rapid sequence intubation improves functional outcome for patients with severe traumatic brain injury. *Ann Surg*. 2010;252(6):959–65. doi:10.1097/SLA.0b013e3181efc15f
- De Cassai A, Boscolo A, Geraldini F, et al. Effect of dexmedetomidine on hemodynamic responses to tracheal intubation: a meta-analysis with meta-regression and trial sequential analysis. *J Clin Anesth*. 2021;72:110287. doi:10.1016/j.jclinane.2021.110287
- Sharma N, Mehta N. Therapeutic efficacy of two different doses of dexmedetomidine on the hemodynamic response to intubation, the intubating conditions, and the effect on the induction dose of propofol: a randomized, double-blind, placebo-controlled study. *Anesth Essays Res*. 2018;12(2):566–71. doi:10.4103/aer.AER_45_18
- Qin J, He C, Chen Z, et al. Effects of intravenous lignocaine on haemodynamic responses to laryngoscopy and tracheal intubation in adults under general anaesthesia: a systematic review and meta-analysis. *Indian J Anaesth*. 2025;69(8):748–58. doi:10.4103/ija.ija_201_25
- Xiao F, Xu LQ, Yan HY, et al. Comparison of hemodynamic status with three different doses of lidocaine as an adjunct to propofol–remifentanyl during endotracheal intubation in elderly female patients: a prospective randomized study. *Drug Des Devel Ther*. 2025;19:6461–8. doi:10.2147/DDDT.S534226

24. Jia D, Yuan X, He C, et al. Intravenous lidocaine decreased the median effective concentration of sufentanil for tracheal intubation in obese patients. *Drug Des Devel Ther.* 2023;17:2431-9. doi:10.2147/DDDT.S415872
25. Saleh A, Kan S, Singhal S, et al. Effects of dexmedetomidine vs esmolol on postintubation hemodynamics: a meta-analysis. *Anesth Prog* 2025;72(1):9-23. doi:10.2344/23-0059
26. Seangrungs R, Pasutharnchat K, Injampa S, et al. Comparison of the hemodynamic response of dexmedetomidine versus additional intravenous lidocaine with propofol during tracheal intubation: a randomized controlled study. *BMC Anesthesiol.* 2021;21(1):265. doi:10.1186/s12871-021-01484-6
27. Mahjoubifard M, Heidari M, Dahmardeh M, et al. Comparison of dexmedetomidine, lidocaine, and fentanyl in attenuation hemodynamic response of laryngoscopy and intubation in patients undergoing cardiac surgery. *Anesthesiol Res Pract* 2020;2020:4814037. doi:10.1155/2020/4814037
28. Shekhar S, Goyal N, Mirza AA, et al. Evaluation of effects of intravenous infusion of dexmedetomidine or lignocaine on stress response and postoperative pain in patients undergoing craniotomy for intracranial tumors: a randomized controlled exploratory study. *Saudi J Anaesth.* 2024;18(3):402-9. doi:10.4103/sja.sja_141_24
29. Singh S, Chouhan RS, Bindra A, et al. Comparison of effect of dexmedetomidine and lidocaine on intracranial and systemic hemodynamic response to chest physiotherapy and tracheal suctioning in patients with severe traumatic brain injury. *J Anesth.* 2018;32(4):518-23. doi:10.1007/s00540-018-2505-9
30. Lin CC, Yu JH, Lin CC, et al. Postintubation hemodynamic effects of intravenous lidocaine in severe traumatic brain injury. *Am J Emerg Med.* 2012;30(9):1782-7. doi:10.1016/j.ajem.2012.02.013
31. Liu SY, Kelly-Hedrick M, Temkin N, et al. Association of early dexmedetomidine utilization with clinical and functional outcomes following moderate-severe traumatic brain injury: a Transforming Clinical Research and Knowledge in Traumatic Brain Injury study. *Crit Care Med.* 2024;52(4):607-17. doi:10.1097/CCM.00000000000006106
32. Wongsripuemtet P, Ohnuma T, Temkin N, et al. Association of early dexmedetomidine exposure with brain injury biomarker levels following moderate-severe traumatic brain injury: a TRACK-TBI study. *J Clin Neurosci.* 2024;126:338-47. doi:10.1016/j.jocn.2024.07.003
33. Chandras S, Pryambodho P, Omega A. Evaluation of continuous intravenous lidocaine on brain relaxation, intraoperative opioid consumption, and surgeon's satisfaction in adult patients undergoing craniotomy tumor surgery: a randomized controlled trial. *Medicine (Baltimore).* 2022;101(36):e30216. doi:10.1097/MD.00000000000030227
34. Yao Y, Qian B, Chen Y, et al. Intranasal dexmedetomidine premedication reduces the minimum alveolar concentration of sevoflurane for tracheal intubation in children: a randomized trial. *J Clin Anesth.* 2014;26(4):309-14. doi:10.1016/j.jclinane.2013.12.012
35. Koh V, Ali S, Hassan MH, et al. Comparison of esmolol and dexmedetomidine infusion in attenuating haemodynamic and blood glucose response to laryngoscopy and intubation: a single blinded study. *Malays J Med Sci.* 2021;28(3):46-55. doi:10.21315/mjms2021.28.3.4
36. Tajima R, Aoki Y, Mizobuchi Y, et al. A decade of change in sample size and study setting in leading anesthesiology journals: a cross-sectional meta-research study. *Cureus.* 2025;17(9):e91767. doi:10.7759/cureus.91767
37. Altman DG, Bland JM. Statistics notes: absence of evidence is not evidence of absence. *BMJ.* 1995;311(7003):485. doi:10.1136/bmj.311.7003.485
38. Silpa AR, Koshy KA, Subramanian A, et al. Comparison of the efficacy of two doses of dexmedetomidine in attenuating the hemodynamic response to intubation in patients undergoing elective cardiac surgery: a randomized double-blinded study. *J Anaesthesiol Clin Pharmacol.* 2020;36(1):83-7. doi:10.4103/joacp.JOACP.235_18
39. Svedung Wettervik T, Hånell A, Howells T, et al. Autoregulatory management in traumatic brain injury: the role of absolute pressure reactivity index values and optimal cerebral perfusion pressure curve shape. *J Neurotrauma.* 2023;40(21-22):2341-52. doi:10.1089/neu.2023.0017
40. Sanjeev O, Ratnani E, Singh A, et al. A comparative study of intravenous esmolol, labetalol and lignocaine in low doses for attenuation of sympathomimetic responses to laryngoscopy and endotracheal intubation. *Anesth Essays Res.* 2017;11(3):745-50. doi:10.4103/aer.AER_9_17
41. Shukla S, Kadni RR, Chakravarthy JJ, et al. A comparative study of intravenous low doses of dexmedetomidine, fentanyl, and magnesium sulfate for attenuation of hemodynamic response to endotracheal intubation. *Indian J Pharmacol.* 2022;54(5):314-20. doi:10.4103/ijp.ijp_923_20
42. Mahiswar AP, Dubey PK, Ranjan A. Comparison between dexmedetomidine and fentanyl bolus in attenuating the stress response to laryngoscopy and tracheal intubation: a randomized double-blind trial. *Braz J Anesthesiol.* 2022;72(1):103-9. doi:10.1016/j.bjane.2021.02.060
43. Pandey M, Bana M, Agrawal N, et al. An evaluation of haemodynamic responses to tracheal intubation following intravenous dexmedetomidine and fentanyl in patients undergoing laparoscopic cholecystectomy. *Niger Med J.* 2024;65(5):737-48. doi:10.60787/nmj-v65i3.563
44. Roy RA, Kesavan R, Rajan S, et al. Prospective randomized study comparing the usefulness of dexmedetomidine versus esmolol in blunting hemodynamic responses to intubation in surgical patients. *Anesth Essays Res.* 2021;15(4):357-61. doi:10.4103/aer.aer_155_21
45. Singh V, Pahade A, Mowar A. Comparison of intravenous versus nebulized dexmedetomidine for laryngoscopy and intubation-induced sympathoadrenal stress response attenuation. *Anesth Pain Med.* 2022;12(5):e132607. doi:10.5812/aapm-132607
46. Singh S, Gupta P, Dhar M, et al. Effect of preoperative intravenous and inhalational dexmedetomidine on the hemodynamic response of laryngoscopy: a prospective double-blinded randomized study. *J Res Pharm Pract.* 2023;12(4):123-9. doi:10.4103/jrpp.jrpp_12_24
47. Singh G, Lnu H, Verma R, et al. Effects of intranasal and intravenous dexmedetomidine on hemodynamic responses to tracheal intubation and skull pin holder fixation: a double-blinded, randomized controlled trial. *Cureus.* 2025;17(1):e76980. doi:10.7759/cureus.76980
48. Sriramka B, Warsi ZH, Sahoo J. Effects of adding dexmedetomidine to nebulized lidocaine on control of hemodynamic responses to laryngoscopy and intubation: a randomized clinical trial. *J Anaesthesiol Clin Pharmacol.* 2023;39(1):11-7. doi:10.4103/joacp.JOACP_93_21
49. Amin SM, Hasanin A, ElSayed OS, et al. Comparison of the hemodynamic effects of opioid-based versus lidocaine-based induction of anesthesia with propofol in older adults: a randomized controlled trial. *Anaesth Crit Care Pain Med.* 2023;42(4):101225. doi:10.1016/j.jaccpm.2023.101225
50. Pramanik M, Chattopadhyay U, Chaudhuri S, et al. Comparison between transtracheal and intravenous 2% lignocaine in attenuating hemodynamic stress response following direct laryngoscopy and endotracheal intubation: a randomized controlled trial. *BMC Anesthesiol.* 2025;25(1):262. doi:10.1186/s12871-025-03102-1
51. Liu H, Xing L, Xie H, et al. Ultrasound measurement of pupillary dilation reflex during induction of general anesthesia using sufentanil: a randomized controlled trial. *Med Sci Monit* 2025;31:e948209. doi:10.12659/MSM.948209
52. Zeng Q, Li J, Liu Y, et al. Effect of intravenous dexmedetomidine premedication on sufentanil median effective concentration during tracheal intubation in obese patients: a randomized controlled study. *Drug Des Devel Ther.* 2025;19:1323-32. doi:10.2147/DDDT.S491599
53. Maissan IM, Hollestelle RV, Rijs K, et al. Intravenous lidocaine attenuates distention of the optical nerve sheath, a correlate of intracranial pressure, during endotracheal intubation. *Minerva Anesthesiol.* 2023;89(3):131-7. doi:10.23736/S0375-9393.22.16574-0
54. Chandar Chinnarasan V, Bidkar PU, Swaminathan S, et al. Comparison of dexmedetomidine versus fentanyl-based total intravenous anesthesia technique on the requirement of propofol, brain relaxation, intracranial pressure, neuronal injury, and hemodynamic parameters in patients with acute traumatic subdural hematoma undergoing emergency craniotomy: a randomized controlled trial. *Surg Neurol Int.* 2024;15:462. doi:10.25259/SNI_892_2024
55. Barbosa EC, Aguirre JM, Bertoldi PFE, et al. Intravenous lidocaine with propofol-based sedation for colonoscopy: a systematic review and meta-analysis with trial sequential analysis. *Anaesthesia* 2025;80(6):694-703. doi:10.1111/anae.16563
56. Lu S, Song H, Lin Y, et al. A randomized controlled trial investigating the impact of early goal-directed sedation dominated by dexmedetomidine on cerebral oxygen metabolism and inflammatory mediators in patients with severe brain injury. *Neurol Sci.* 2025;46(4):1741-50. doi:10.1007/s10072-024-07916-8
57. Xu J, Xiao Q. Assessment of the effects of dexmedetomidine on outcomes of traumatic brain injury using propensity score analysis. *BMC Anesthesiol.* 2022;22(1):280. doi:10.1186/s12871-022-01822-2
58. Wang J, Sun JQ, Lu Y, et al. Delirium as a mediating factor in the survival benefits of dexmedetomidine in acute brain injury management. *Sci Rep.* 2025;15(1):30937. doi:10.1038/s41598-025-14180-z
59. Deng Z, Gu Y, Luo L, et al. The effect of dexmedetomidine on the postoperative recovery of patients with severe traumatic brain injury undergoing craniotomy treatment: a retrospective study. *Eur J Med Res.* 2024;29(1):256. doi:10.1186/s40001-024-01861-0
60. Demarquette A, Perrault T, Alapetite T, et al. Spin and fragility in randomised controlled trials in the anaesthesia literature: a systematic review. *Br J Anaesth.* 2023;130(5):528-35. doi:10.1016/j.bja.2023.01.001