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Emergency Department Airway Management

Clinical Policy Guideline- EMAT

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EMAT Türkiye Acil Tıp Derneği | EMERGENCY MEDICINE ASSOCIATION OF TURKEY

Emergency Department Airway Management – 2026: EMAT Clinical Policy Guideline

This guideline was developed and approved by the Research Committee (RC) of EMAT (Emergency Medicine Association of Türkiye).

Authors

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ABSTRACT

This clinical policy was developed by EMAT (Emergency Medicine Association of Türkiye) to evaluate current evidence on airway management in the emergency department and to provide clinicians with practical, evidence-based recommendations. Although rapid sequence intubation in the emergency department is a life-saving intervention in critically ill patients, the choice of techniques and medications during its implementation has a decisive impact on patient safety and clinical outcomes. This policy was developed by the Research Committee (RC) using the *"Grading of Recommendations, Assessment, Development, and Evaluations"* (GRADE) methodology, based on systematic literature reviews and expert opinion.

Within the framework of five key clinical questions, the following topics were examined: preoxygenation strategies (noninvasive mechanical ventilation, high-flow nasal oxygen, face mask, and conventional techniques); the effectiveness and safety of apneic oxygenation; the use of a gum elastic bougie during intubation; the role of push-dose vasopressors in patients at high risk of hypotension; and the safety of ketamine use in patients at risk of increased intracranial pressure.

This policy aims to reduce complications related to airway management and improve patient outcomes by providing emergency physicians with an evidence-based framework for pre-intubation preparation, medication selection, and equipment use.

INTRODUCTION

Airway management in the emergency department, particularly rapid sequence intubation (RSI), is one of the most fundamental and highest-priority interventions in the evaluation and treatment of critically ill patients. Unlike the operating room and intensive care unit, the emergency department is a dynamic, high-stress environment that often lacks sufficient time for patient preparation, requiring rapid and accurate decision-making. Under these conditions, establishing an effective and safe airway is of vital importance to prevent serious complications such as hypoxemia, cardiac arrest, and mortality.[1,2] To this end, numerous studies conducted in recent years have evaluated pre-intubation preoxygenation strategies, apneic oxygenation techniques, the use of high-flow nasal oxygen (HFNO), the role of alternative induction agents, and the effectiveness of intubation adjuncts (rigid and flexible stylets, gum elastic bougie, etc.), generating ongoing debate regarding airway management

flexible stylets, gum elastic bougies (GEB), etc.), generating ongoing debate regarding airway management practices in the ED.[3,4]

However, most of these studies were conducted in different patient populations and under controlled anesthesia settings or in the ICU. Therefore, careful interpretation is required when applying these data directly to the ED setting.

This clinical policy guideline was developed during 2025–2026 by the Research Committee (RC) of the Emergency Medicine Association of Türkiye (EMAT) to provide evidence-based answers to clinically important questions in ED airway management and to guide physicians across different clinical scenarios. Rather than adopting a perspective that encompasses all aspects of airway management or revisits questions with established consensus in the literature, this guideline focuses on emerging debates highlighted by recent studies.

A summary of all recommendations included in this guideline is presented in Table 1.

Table 1. Summary of Recommendations (for all five scenarios)

SCENARIO-1	
COMPARISON OF NIMV, HFNO, AND CONVENTIONAL TECHNIQUES FOR PREOXYGENATION	
In adult patients undergoing rapid sequence intubation in the emergency department, does the choice of preoxygenation technique (noninvasive mechanical ventilation, high-flow nasal oxygen, or conventional techniques) affect the incidence of severe hypoxemia?	
Strength of Recommendation and Recommendations	**Level of Evidence**
Moderate	
For adult patients in the emergency department with severe hypoxemia or a high risk of hypoxia, preoxygenation with noninvasive mechanical ventilation is recommended during rapid sequence intubation instead of a standard face mask or bag-valve mask.	High
Weak	
In the emergency department, for patients with severe hypoxemia or a high risk of hypoxia undergoing rapid sequence intubation, high-flow nasal oxygen therapy may be used as an alternative for preoxygenation when noninvasive mechanical ventilation is not feasible.	Very low

SCENARIO-2	
APNEIC OXYGENATION	
In patients undergoing rapid sequence intubation in the emergency department, does the addition of apneic oxygenation to standard preoxygenation reduce the incidence of severe hypoxia (SpO_2 < 80%) or improve the lowest SpO_2 values?	
Strength of Recommendation and Recommendations	**Level of Evidence**
Moderate	
The routine use of apneic oxygenation in addition to preoxygenation during rapid sequence intubation in the emergency department is not recommended.	Moderate
Expert Opinion: In patients at high risk of hypoxemia who receive high-flow nasal oxygen therapy during the preoxygenation phase, continuing high-flow nasal oxygen during the apneic period may be considered.	

SCENARIO-3	
COMPARISON OF GUM ELASTIC BOUGIE AND STANDARD INTUBATION	
In patients undergoing intubation in the emergency department, does the use of a gum elastic bougie, compared with standard intubation (with or without a stylet), increase first-pass intubation success or affect intubation duration?	
Strength of Recommendation and Recommendations	**Level of Evidence**
Moderate	
In adult patients with a predicted difficult airway in the emergency department, the use of a gum elastic bougie is recommended over standard intubation (with or without a stylet).	Low
Weak	
The routine use of a gum elastic bougie may be considered during the intubation of adult patients in the emergency department.	Low

SCENARIO-4
PUSH-DOSE VASOPRESSOR ADMINISTRATION DURING RAPID SEQUENCE INTUBATION
In adult emergency department patients who are hypotensive or at high risk of hypotension, does the administration of a push-dose vasopressor (e.g., phenylephrine, epinephrine) during or immediately before rapid sequence intubation, added to standard care, reduce the incidence of peri-intubation hypotension and improve clinical outcomes?
RECOMMENDATION
As the available evidence is indirect, of low quality, and insufficient to conclusively answer this question, the panel makes **no recommendation** for or against this intervention.
Expert Opinion: Although the panel refrained from making a formal recommendation on this issue, it acknowledges that push-dose vasopressor therapy is utilized in certain clinical practices. Consequently, the panel suggests that each institution determine via local clinical protocols whether push-dose vasopressors should be administered during rapid sequence intubation in critically ill adult patients who are hypotensive or at risk of hypotension.

SCENARIO-5	
KETAMINE USE IN PATIENTS AT RISK OF INCREASED INTRACRANIAL PRESSURE	
In adult emergency department patients at risk of increased intracranial pressure, is the use of ketamine during rapid sequence intubation a safe option?	
Strength of Recommendation and Recommendations	**Level of Evidence**
Moderate Against	
Concerns that ketamine use during rapid sequence intubation causes an increase in intracranial pressure (ICP) in patients with acute brain injury at risk of elevated ICP are anecdotal, and current literature does not support this. Therefore, ketamine should not be avoided solely due to concerns regarding increased intracranial pressure.	Very low

METHODS

This clinical policy guideline was developed using the "Grading of Recommendations, Assessment, Development, and Evaluations" (GRADE) methodology and a systematic evaluation of the evidence available in the literature[5]. The formulation of recommendations was guided by the level of evidence. In cases where the evidence was insufficient or conflicting, relevant clinical questions were resolved via voting by the advisory board members of the RC, adhering to the principle of majority decision. The final clinical policy guideline was disseminated via the EMAT and RC websites, social media, and EMAT-affiliated outlets. EMAT–RC clinical policy guidelines are scheduled for routine updates every three years, with provisions for earlier revision in the event of significant developments.

Identification of clinical questions

The EMAT-RC Advisory Board identified priority clinical policy topics. Clinical questions related to these topics were solicited from the emergency medicine community. Calls for contributions were disseminated via the EMAT and RC websites and social media platforms, and submissions were collected via Google Forms. Over a 60-day period, 11 members of the EMAT-RC Advisory Board prioritized the questions by rating the importance of the outcomes using a 9-point Likert scale **(1–3: not important; 4–6: important but not critical; 7–9: critical)**. Based on the voting results, questions addressing "important but not critical" and "critical" outcomes were selected for evidence-based evaluation.

Systematic literature search and article selection

For each identified clinical question, a systematic literature search was conducted in the SCOPUS, MEDLINE, and Web of Science databases using predefined keywords (detailed search strategies are provided separately in the section corresponding to each clinical question).

Articles identified through the systematic literature search were imported into the Rayyan software for each clinical question[6]. Two independent, blinded reviewers screened titles and abstracts for relevance. Articles deemed eligible were included for full-text assessment, while those considered ineligible were excluded. Discrepancies between the two reviewers were resolved by a third reviewer, who made the final decision.

When performing meta-analyses using data from primary studies, in cases where the reported effect size metrics varied, the following approaches were preferred where feasible: mathematical conversion of effect sizes, requesting the relevant data directly from the study authors, or extracting data from existing systematic reviews that had previously analyzed the primary studies and reported the relevant effect size.

Evidence Grading and Risk of Bias Assessment

For each clinical question, the included studies underwent critical appraisal by at least two researchers, and the certainty of evidence was assessed using the GRADEpro software in accordance with the GRADE approach (categorized as very low, low, moderate, or high). The risk of bias was evaluated using the RoB 2 tool for randomized controlled trials (RCTs), whereas observational studies were inherently considered to be at high risk of bias. Assessments were conducted by two blinded

reviewers; discrepancies were resolved by a third reviewer, who made the final decision.

Determination of the Strength of Recommendations

Recommendations were formulated based on the evidence tables generated using the GRADE approach. The definitions for the strength of recommendations are presented in Table 2.

Table 2. Strength of recommendation

STRENGTH OF RECOMMENDATION	RECOMMENDATION
Strong	Recommendations supported by moderate or high levels of evidence where the benefits of the intervention clearly outweigh the harms. This category also includes recommendations—particularly regarding critical outcomes—where, despite low levels of evidence, the majority of the panel deems the intervention to be clearly beneficial.
Moderate	Recommendations regarding interventions for which there is conflicting moderate- or high-level evidence regarding whether the benefits outweigh the harms, or for which the evidence supporting that benefits outweigh harms is of low or very low level.
Weak	Recommendations for which there is conflicting low- or very low-level evidence regarding whether the benefits of the intervention outweigh the harms. Recommendations characterized by a lack of consensus among panel members regarding the benefit of the intervention.

STRENGTH OF RECOMMENDATION AGAINST	RECOMMENDATION AGAINST
Strong Against	Recommendations supported by moderate or high levels of evidence indicating that the harms of the intervention clearly outweigh the benefits. Recommendations—particularly regarding critical outcomes—where, despite low levels of evidence, the majority of the panel deems the intervention to be clearly harmful.
Moderate Against	Recommendations regarding interventions for which there is conflicting moderate- or high-level evidence regarding whether the harms outweigh the benefits. Recommendations for which the evidence supporting that harms outweigh benefits is of low or very low level.
Weak Against	Recommendations for which there is conflicting low- or very low-level evidence indicating that the harm of the intervention outweighs the benefits. Recommendations characterized by a lack of consensus among panel members regarding the harms of the intervention.

This clinical policy guideline is intended to guide physicians working in EDs. The target population includes adult patients presenting to EDs. Pediatric patients are excluded from the scope of this guideline.

EMAT-RC clinical policy guidelines reflect the official position of the EMAT-RC, providing evidence-based answers and recommendations derived from current literature. However, they do not constitute definitive or absolute mandates. The EMAT-RC acknowledges the importance of physicians' clinical judgment and patients' preferences in final decision-making.

Following panel voting, all five clinical questions addressed in this guideline were categorized as "noncritical but important," with none classified as "critical."

Noncritical but Important questions

This guideline addresses the following clinical questions:

1. In adult patients undergoing rapid sequence intubation in the emergency department, does the choice of preoxygenation technique (noninvasive mechanical ventilation, high-flow nasal oxygen, or conventional techniques) affect the incidence of severe hypoxemia?

2. In patients undergoing rapid sequence intubation in the emergency department, does the addition of apneic oxygenation to standard preoxygenation reduce the incidence of severe hypoxia (SpO_2 < 80%) or improve the lowest SpO_2 values?

3. In patients undergoing intubation in the emergency department, does the use of a gum elastic bougie, compared with standard intubation (with or without a stylet), increase first-pass intubation success or affect intubation duration?

4. In adult emergency department patients who are hypotensive or at high risk of hypotension, does the administration of a push-dose vasopressor (e.g., phenylephrine, epinephrine) during or immediately before rapid sequence intubation, added to standard care, reduce the incidence of peri-intubation hypotension and improve clinical outcomes?

5. In adult emergency department patients at risk of increased intracranial pressure, is the use of ketamine during rapid sequence intubation a safe option?

NONCRITICAL BUT IMPORTANT QUESTIONS

SCENARIO-1: In adult patients undergoing rapid sequence intubation in the emergency department, does the choice of preoxygenation technique (noninvasive mechanical ventilation, high-flow nasal oxygen, or conventional techniques) affect the incidence of severe hypoxemia?

1. COMPARISON OF NIMV, HFNO, AND CONVENTIONAL TECHNIQUES FOR PREOXYGENATION	
Strength of Recommendation and Recommendations	**Level of Evidence**
Moderate	
For adult patients in the emergency department with severe hypoxemia or a high risk of hypoxia, preoxygenation with noninvasive mechanical ventilation is recommended during rapid sequence intubation instead of a standard face mask or bag-valve mask.	High
Weak	
In the emergency department, for patients with severe hypoxemia or a high risk of hypoxia undergoing rapid sequence intubation, high-flow nasal oxygen therapy may be used as an alternative for preoxygenation when noninvasive mechanical ventilation is not feasible.	Very Low

Rationale and background

During the rapid sequence intubation (RSI) procedure in EDs, preventing hypoxia during the period until a definitive airway is secured is critical. To mitigate this risk, the administration of oxygen for several minutes prior to the procedure is recommended; this practice is referred to as preoxygenation. The aim of this intervention is to maximize pulmonary oxygen reserves and subsequently delay the onset of hypoxia during the apneic period. While standard practice typically involves oxygen delivery via nasal cannula or face mask, alternative methods such as noninvasive mechanical ventilation (NIMV) and HFNO have increasingly been used during the preoxygenation phase in recent years. In this guideline, the effectiveness and safety of preoxygenation methods used during RSI in critically ill patients requiring intubation in the ED are evaluated based on evidence, with the goal of providing recommendations to emergency physicians regarding which method is more effective and safe.

Study selection

Studies comparing preoxygenation methods often present substantial heterogeneity due to methodological differences in intervention arms. To address the relevant clinical question, only well-defined clinical studies comparing different oxygen delivery methods specifically during the preoxygenation period were considered. The literature contains studies with varying designs regarding the timing of oxygen administration. In some instances, the oxygen delivery method initiated during preoxygenation was continued through the apneic oxygenation phase. In others, oxygen support was provided exclusively during either the preoxygenation phase or the apneic phase.

To provide a definitive answer to the clinical question, studies comparing different oxygen delivery methods strictly during the preoxygenation phase—without the application of apneic oxygenation—were selected for final evaluation. Data from these

studies were utilized for quantitative synthesis and meta-analysis.

Due to the significant overlap in keywords between studies comparing preoxygenation methods and those investigating apneic oxygenation, along with the lack of conceptual clarity in the existing literature, a combined literature search was performed for both topics. Articles were subsequently stratified into two main categories via abstract screening. Consequently, the systematic literature search identified a total of 119 articles (Supplementary File 1).

Excluded from this pool were observational studies, pediatric studies, studies irrelevant to the clinical question, and—consistent with the criteria outlined above—studies where oxygen therapy extended beyond the preoxygenation phase into the apneic period. Ultimately, five randomized controlled trials (RCTs) were included in the final evaluation. These RCTs specifically compared oxygen therapy methods administered exclusively during the preoxygenation phase (Supplementary File 2) [7-11].

Four randomized controlled trials (RCTs) involving oxygen administration during both the preoxygenation and apneic oxygenation phases did not meet the strict inclusion criteria specified above. However, due to their indirect relevance to the topic, these studies are discussed separately at the end of this section under the heading "Other Relevant Articles."

In the risk of bias assessment conducted using the Cochrane RoB 2 tool, four articles were evaluated as having "some concerns"[7-10], while one article was identified as having a high risk of bias[11] (Figure 1). Summaries of the included studies are presented in Supplementary File 3).

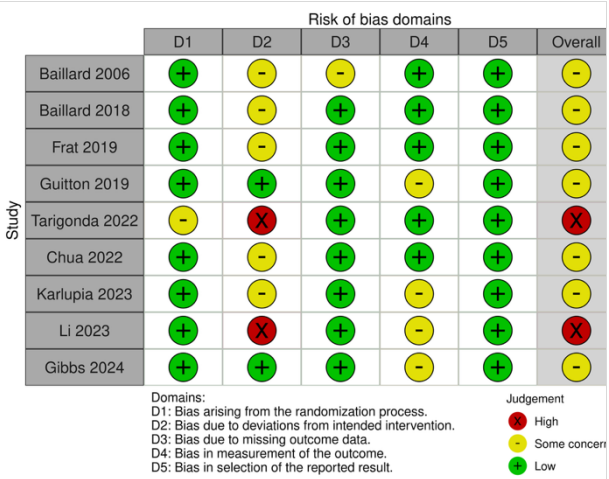


Figure 1. Traffic light plot of randomized clinical trials comparing preoxygenation methods during rapid sequence intubation in the emergency department (RoB 2 risk of bias assessment).

Overview of the studies and outcome measures

Regarding clinical settings, the majority of the studies were conducted in intensive care units (ICUs); four were performed exclusively in the ICU, while one involved both the ICU and the ED.

In terms of patient populations, the two studies by Baillard et al. (2006, 2018) focused on hypoxic patients[7,10], whereas Guitton et al. included patients without severe hypoxemia[8]. Gibbs et al. studied patients described as "severely ill," although the article did not provide a detailed definition of this term[9]. Finally, only the study by Li et al. was conducted in a patient population requiring emergency surgery[11].

Across the included studies, the standard treatment arms utilized oxygen delivery via face mask (specified as a non-rebreather mask in one instance) or bag-valve mask. Notably, Li et al. administered oxygen solely via face mask, excluding the use of a bag-valve mask[11]. Regarding the intervention arms,

three of the five RCTs employed NIMV, while the remaining two utilized HFNO[7-11].

The included studies reported a wide variety of heterogeneous outcomes. Commonly reported metrics included mean/median SpO_2 values at the end of intubation, lowest SpO_2 values, and pre- versus post-preoxygenation comparisons.

However, the clinical utility of these endpoints is limited. An increase in oxygen saturation following supplemental oxygen administration is physiologically expected; thus, pre–post comparisons offer little clinical insight in this context. Similarly, comparing mean/median SpO_2 values between arms at the end of intubation lacks robust clinical relevance. Statistically significant differences may not translate to clinical significance. For instance, a difference between 96% and 94% SpO_2, while potentially statistically significant, has negligible impact on clinical decision-making or patient-centered outcomes.

Consequently, the incidence of severe hypoxia was identified as the primary clinically meaningful outcome for this meta-analysis. Consistent with the definitions in the majority of studies, severe hypoxia was defined as SpO_2 < 80% or < 85%. Lowest SpO_2 values recorded during intubation were included as a secondary outcome, despite their limited clinical significance.

Other outcomes were excluded from the meta-analyses, either due to a lack of clinical significance or because the data were not amenable to pooling. However, clinically relevant outcomes unsuitable for quantitative synthesis are discussed narratively on a study-by-study basis.

Incidence of severe hypoxia (SpO_2 < 80%/85%) during intubation

This guideline identifies the occurrence of severe hypoxia during the procedure as the primary critical outcome, prioritizing it over clinically negligible fluctuations in oxygen saturation.

Study Characteristics Of the four studies reporting this outcome, three compared NIMV against standard oxygen therapy (face mask with or without BVM) [7,9,11], while one compared HFNO against standard therapy[8].

NIMV Control Groups: In two studies[7,11], the control group received oxygen via a non-rebreather mask combined with a BVM. In the third study [9], the control group utilized either a BVM or face mask alone; importantly, the authors emphasized that BVM use did not involve active ventilation.

Given the heterogeneity in treatment arms, a stratified meta-analysis was conducted. The subgroup analysis comparing NIMV to standard care (three studies) revealed a significantly lower incidence of severe hypoxia favoring NIMV (OR 0.40, 95% CI 0.28–0.59). Preoxygenation with NIMV reduces the odds of severe desaturation by approximately 60% compared to a standard face mask. The absolute risk reduction was approximately 7%, indicating that one episode of severe hypoxia is prevented for every 14 patients treated (NNT ≈ 14).

Only Guitton et al. compared HFNO with standard therapy[8]. Although a trend favoring HFNO was observed, it did not reach statistical significance (OR 0.25, 95% CI 0.05–1.25). Due to the reliance on a single study with a small sample size, the isolated effect of HFNO could not be definitively established.

Pooling data from all four studies demonstrated a significantly lower incidence of severe hypoxia in the intervention arms (NIMV or HFNO) compared to standard care (OR 0.39,

95% CI 0.20–0.57). The low-to-moderate heterogeneity ($I^2 \leq 39\%$) indicates consistency across results (Figure 2).

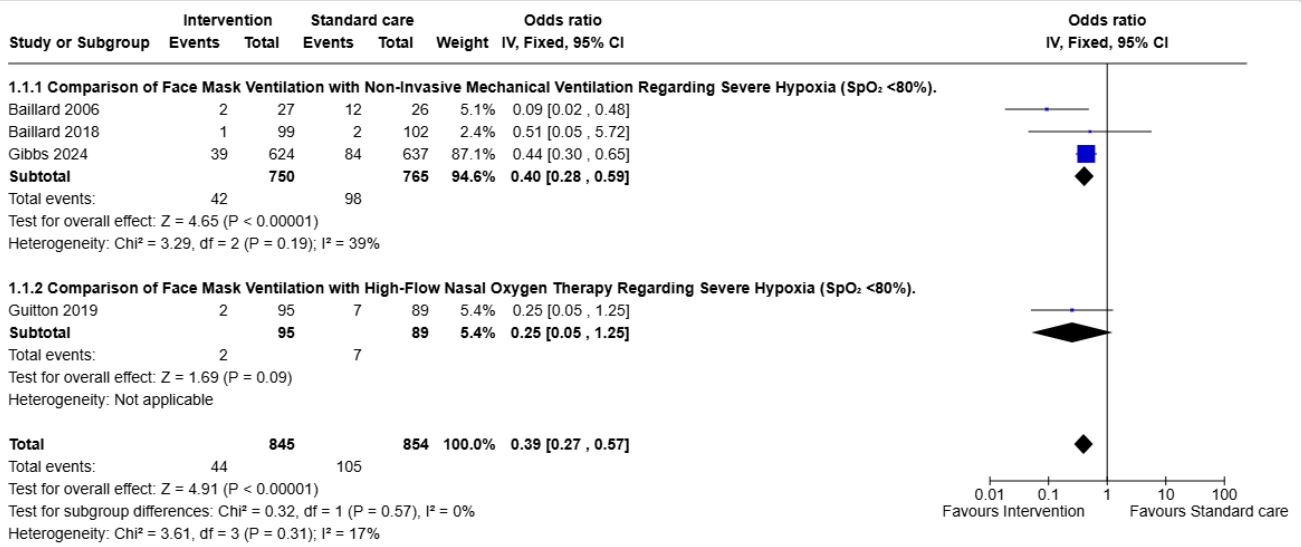


Figure 2. Forest plot of the meta-analysis comparing the incidence of severe hypoxia (SpO_2 < 80% or < 85%) across different preoxygenation methods during rapid sequence intubation in the emergency department.

Lowest SpO_2 level during intubation

Three RCTs reporting the lowest SpO_2 levels during intubation were deemed amenable to pooled analysis. Among these, Baillard et al. (2006) and Gibbs et al. compared NIMV with face mask, while Guitton et al. compared HFNO with face mask [6–10].

In the study by Gibbs et al., data were originally reported as median and interquartile range (IQR). For the purpose of this meta-analysis, these values were converted to mean and standard deviation using the method described by Luo et al. [12].

All three included RCTs were assessed as having a moderate risk of bias (some concerns).

Subgroup Analyses: Although a trend favoring the intervention arm was observed in both subgroups, neither reached statistical significance:

- NIMV vs. Face Mask: Mean Difference (MD) 6.76 (95% CI −2.28 to 15.81).
- HFNO vs. Face Mask: MD 2.0 (95% CI −0.69 to 4.69).

When data from both intervention arms (NIMV and HFNO) were combined, a statistically significant benefit was identified in favor of the intervention (MD 3.92, 95% CI 0.78 to 7.05).

The discrepancy between the significant pooled result and the non-significant subgroup results suggests that the lack of statistical significance in the subgroup analyses is likely attributable to insufficient statistical power due to small sample sizes (Figure 3).

In-hospital mortality, aspiration, regurgitation, and risk of reflux

None of the included studies reported periresuscitative mortality. Instead, reflecting the predominant intensive care setting of the trials, in-hospital mortality was the reported endpoint. However, the clinical relevance of this outcome regarding the choice of NIMV or HFNO

for preoxygenation is considered limited. Establishing a direct causal link between the intubation procedure and mortality occurring days or weeks later is difficult due to the presence of numerous confounding factors during the hospital course. Nevertheless, in the three RCTs reporting this outcome, no statistically significant differences were observed between treatment groups[8-10].

Attempts to compare aspiration-related risks revealed that the available data were not amenable to pooling. Reporting varied across the included trials: two studies assessed aspiration, two evaluated regurgitation, and one focused on reflux risk. While these outcomes are clinically related, they represent distinct pathophysiological conditions, precluding their combination into a single

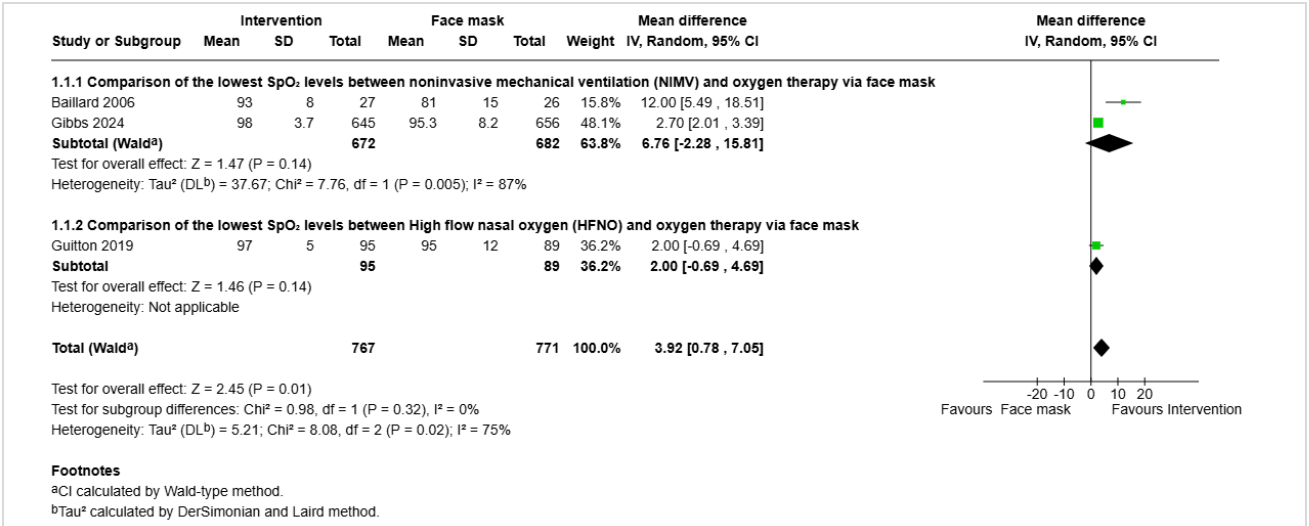


Figure 3. Forest plot showing the meta-analysis of the lowest SpO_2 values reported in three randomized clinical trials comparing intervention arms using NIMV or HFNO for preoxygenation with a standard face mask during rapid sequence intubation in the emergency department, demonstrating a trend toward higher lowest SpO_2 levels in favor of the intervention arm in the combined analysis.

composite outcome. Furthermore, given the significant methodological heterogeneity between intervention arms, a quantitative meta-analysis was deemed inappropriate. Consequently, these adverse effects are evaluated through a narrative review of individual studies rather than statistical pooling.

Baillard et al. (2006) detected no significant difference in regurgitation rates between the NIMV and control (BVM + face mask) groups (1 [4%] vs. 2 [8%], P = 1.0)[10]. Similarly, their 2018 study evaluating the same treatment arms yielded consistent findings, reporting no significant disparity in regurgitation risk (NIMV: 0 [0%] vs. Control: 1 [2.2%])[7].

Gibbs et al. evaluated aspiration rates, noting that the control group received either a face mask alone or a BVM without active ventilation. They detected no statistically significant difference between the arms (NIMV: 6 [0.9%] vs. Control: 9 [1.4%]; Risk Difference −0.4, 95% CI −1.6 to 0.7)[9] Similarly, Guitton et al., comparing HFNO against standard face mask therapy, reported no significant difference; zero aspiration events occurred in the HFNO

group, compared to two events in the control group (P = 0.15)[8].

Regarding gastric reflux, Li et al. (comparing HFNO vs. face mask) reported no incidents in either treatment arm[11].

The absence of statistically significant differences regarding mortality, aspiration, regurgitation, and reflux may stem from insufficient statistical power due to small sample sizes. Alternatively—particularly concerning mortality, which is an inherently multifactorial outcome—it is plausible that while these interventions successfully mitigate severe hypoxia, this physiological improvement alone may not be sufficient to significantly reduce overall mortality rates.

These results allow for dual interpretation. While they indicate no proven benefit regarding these secondary outcomes, they crucially suggest that the intervention arms (NIMV/HFNO) were not harmful. This establishes that these advanced preoxygenation methods possess a safety profile comparable to standard therapy regarding aspiration and reflux risks.

Other safety outcomes

While various other adverse events and complications were reported across the included studies, data heterogeneity precluded quantitative synthesis. Consequently, these outcomes are presented narratively.

Baillard et al. (2006)[10] Comparing NIMV against standard face mask preoxygenation, the authors found no significant differences between groups regarding: Radiographic outcomes (presence of new infiltrates on post-procedure chest radiography), Resource utilization (duration of mechanical ventilation and length of intensive care unit (ICU) stay), and Mortality (ICU mortality rates).

Baillard et al. (2018) In their subsequent study evaluating the same treatment arms, the authors reported the following:

The incidence of overall adverse events was 21.4% in the NIMV group versus 28.7% in the face mask group, a difference that was not statistically significant (P = 0.24).

No significant differences were observed regarding the number of ventilator-free days (within 28 days post-intubation) or the number of days spent outside the ICU[7].

Consistent with the findings above, Gibbs et al. (comparing NIMV vs. face mask) reported similar safety profiles between the two study groups. No significant differences were detected regarding: Complications (the incidence of new opacities on chest radiography and pneumothorax) and Physiological Status (oxygenation parameters (SpO_2 and FiO_2 levels) measured 24 hours post-intubation)[9].

Comparing HFNO with standard face mask preoxygenation, Guitton et al. reported significant differences in complication rates, while resource utilization remained similar:

No significant difference was observed between the HFNO and standard face mask groups in terms of duration of mechanical ventilation (Median: 3 [IQR 2–6] days vs. 3 [IQR 2–7] days; P = 0.80).

The study demonstrated a statistically significant benefit in favor of HFNO in terms of intubation-related complications. At least one intubation-related complication occurred in 6% (n=6) of the HFNO group compared to 19% (n=17) of the standard treatment group. This reduction represents a relative risk of 0.31 (95% CI 0.13–0.76; P = 0.007)[8].

As the only RCT among the included trials classified as having a high risk of bias, Li et al. focused on postoperative complications in patients undergoing emergency surgery. The

study reported no significant differences between the intervention and control groups regarding: Nasopharyngeal complications (nasopharyngeal bleeding and pain) and Postoperative morbidity (pulmonary infection and postoperative nausea and vomiting[11].

Conclusion on safety outcomes collectively, across nearly all reported safety endpoints, neither NIMV nor HFNO therapies demonstrated an increased risk of adverse effects compared to standard treatment. Consequently, based on the available evidence, both methods can be considered safe and non-inferior to standard oxygen therapy with respect to these outcomes.

Articles indirectly related to the clinical question

Four randomized controlled trials (RCTs) involved oxygen administration during both the preoxygenation phase and the subsequent apneic period. Because this combined protocol precluded the isolation of effects attributable solely to the preoxygenation phase, these studies were deemed ineligible for the primary meta-analyses.

However, these trials merit separate qualitative discussion. They utilized oxygenation strategies similar to those in the included studies and provide valuable indirect evidence regarding the efficacy of continuous oxygen support throughout the intubation sequence.

Of these studies, two were assessed as having a low risk of bias, one a moderate risk of bias, and one a high risk of bias[13–16].

Conducted in the ED on 192 patients requiring rapid sequence intubation, the study by Chua et al. compared oxygenation strategies using HFNO against a non-rebreather face mask. In terms of efficacy, the median lowest SpO_2 values were calculated to be identical (100%) in both groups; although the incidence of hypoxia (SpO_2 < 90%) was numerically lower in the HFNO group compared to the control group (15.5% vs. 22.6%), this difference did not reach statistical significance (RR 0.68, 95% CI 0.37–1.25). Regarding safety outcomes, the incidence of ventilator-associated pneumonia and aspiration pneumonia was reported to be similar in both arms, leading the authors to conclude that the two methods are comparable with respect to all overall complications[13].

The multicenter study by Frat et al., conducted across 28 intensive care units involving 313 patients with acute hypoxemic respiratory failure, provides critical comparative data on high-flow nasal oxygen (HFNO) versus noninvasive ventilation (NIMV). While the analysis of the overall patient cohort indicated a similar incidence of severe hypoxemia (SpO_2 < 80%) between the two groups, subgroup analysis revealed a significant benefit for NIMV in patients with more profound respiratory failure. Specifically, among the 242 patients presenting with moderate-to-severe hypoxemia (defined as a PaO_2/FiO_2 ratio ≤ 200 mmHg), severe hypoxemia occurred significantly less frequently in the NIMV group compared to the HFNO group (24% vs. 35%; OR 0.56, 95% CI 0.32–0.99; p = 0.046), with no observed differences in serious adverse events between the treatment arms[14].

In the study by Karlupia et al., which enrolled patients undergoing rapid sequence intubation for abdominopelvic emergency surgery, oxygenation via HFNO was compared against standard face mask oxygenation. The analysis revealed no statistically significant differences between the two cohorts across a broad range of physiological and procedural outcomes, including post-intubation PaO_2

values, lowest SpO_2, apnea duration, number of laryngoscopy attempts, use of rescue maneuvers, or adverse effects ($p > 0.05$). Based on these findings, the authors concluded that the two modalities yielded comparable outcomes, specifically highlighting that HFNO demonstrated a safety profile at least equivalent to that of conventional face mask oxygenation[15].

Classified as the only randomized controlled trial among this subset with a high risk of bias, the study by Tarigonda et al. evaluated the comparative effectiveness of NIMV (specifically CPAP) versus nasal cannula oxygen administration in intensive care unit patients with hypoxemic type 1 respiratory failure. While the absolute lowest SpO_2 values observed during intubation were comparable between the groups, a significant difference was identified regarding the degree of desaturation—defined as the magnitude of the drop in oxygen saturation from the end of preoxygenation to the point of intubation. Specifically, this decline was significantly more pronounced in the nasal cannula group compared to the NIMV group (mean decline: 4.24 ± 3.67 vs. 2.10 ± 3.50; $p = 0.007$), whereas intubation duration and complication rates remained similar between the two cohorts[16].

In summary, findings from these four studies align closely with the broader body of evidence, demonstrating that both HFNO and NIMV offer efficacy comparable or superior to standard oxygen delivery via face mask or nasal cannula. Regarding safety, all modalities exhibit similar adverse event profiles, reinforcing the conclusion that these advanced preoxygenation methods are safe alternatives to standard care. While current evidence precludes a definitive declaration of superiority between the two advanced modalities, the data suggest a potential physiological advantage for NIMV, particularly in the subset of patients presenting with severe hypoxemia.

Conclusion and Clinical Recommendations

Based on the cumulative evidence, utilizing Non-Invasive Ventilation (NIMV) for preoxygenation instead of a standard face mask is associated with a significantly reduced risk of severe hypoxia. Given that no differences were observed in critical safety outcomes such as mortality and aspiration, prioritizing NIMV over standard face mask or bag-valve-mask (BVM) techniques—particularly for critically ill patients—emerges as a clinically sound strategy to mitigate the incidence of severe hypoxemia.

While current evidence remains insufficient to draw definitive conclusions regarding the superiority of HFNO over standard methods, the data suggest a potential therapeutic benefit. When viewed in conjunction with findings from Frat et al., which directly compared NIMV and HFNO, the plausibility of HFNO offering efficacy comparable to NIMV is reinforced. Furthermore, HFNO exhibits a safety profile equivalent to standard therapy and offers the distinct technical advantage of permitting continuous oxygen delivery during the apneic period (apneic oxygenation), thereby validating its role as a viable alternative.

In summary, the overall body of evidence indicates that for patients at high risk of hypoxia, preoxygenation with NIMV prior to emergency Rapid Sequence Intubation (RSI) yields a significant and clinically meaningful reduction in severe hypoxia and is safe with respect to adverse effects, specifically mortality and aspiration risk. Although HFNO demonstrates a similar physiological trend, the current evidence base is less robust than that

for NIMV. Consequently, taking into account resource availability and patient-specific characteristics, NIMV should be considered the first-line option in clinical practice, while HFNO may be considered a valuable alternative when NIMV is not feasible.

GRADE evidence classification tables detailing the certainty of evidence for the included studies are provided in (Supplementary File 4).

Research Gaps and Future Directions

The current evidence base regarding preoxygenation strategies is constrained by several methodological limitations. Most existing studies are single-center trials, and the inherent difficulty of blinding the intervention introduces a risk of performance bias; notably, blinding of outcome assessors was frequently either not implemented or not reported. Furthermore, the predominance of studies conducted in intensive care units limits the direct generalizability of these findings to the ED setting. Consequently, there is a critical need for high-quality RCTs specifically conducted in EDs that rigorously ensure outcome assessor blinding to minimize bias.

Future research should also prioritize targeted investigations into specific clinical subgroups to enable more precision in applying these interventions. Studies focusing on distinct patient phenotypes—such as hypoxic versus non-hypoxic patients, individuals with obesity, and those with concurrent heart failure or respiratory failure—would provide valuable data for personalized care. Additionally, given the practical ease of application associated with HFNO and the current paucity of definitive data, there is a pressing need for robust studies specifically evaluating the effectiveness of this modality.

Finally, while both HFNO and NIMV appear to be safe based on current data, caution is warranted regarding the interpretation of aspiration risk. The absence of statistically significant differences between groups may be attributable to insufficient statistical power resulting from small sample sizes or methodological heterogeneity rather than a true lack of risk. Therefore, further evaluation through large-scale, high-quality RCTs is essential to definitively assess whether positive pressure techniques, such as BVM and NIMV, increase the risk of aspiration compared to standard methods.

SCENARIO-2: In patients undergoing rapid sequence intubation in the emergency department, does the addition of apneic oxygenation to standard preoxygenation reduce the incidence of severe hypoxia (SpO_2<80%) or improve the lowest SpO_2 values?

2. APNEIC OXYGENATION	
Strength of Recommendation and Recommendations	**Level of Evidence**
Moderate	
The routine use of apneic oxygenation in addition to preoxygenation during rapid sequence intubation in the emergency department is not recommended.	Moderate
Expert Opinion: In patients at high risk of hypoxemia who receive high-flow nasal oxygen therapy during the preoxygenation phase, continuing high-flow nasal oxygen during the apneic period may be considered.	

Rationale and background

Hypoxemia During RSI Hypoxemia represents the most critical complication during Rapid Sequence Intubation (RSI) in the ED, particularly among critically ill patients, where it is a significant driver of mortality[17–20]. Conventionally, preoxygenation is employed prior to induction to maximize oxygen reserves and buffer against desaturation during the procedural apnea[20,21]. However, in critically ill populations—especially those with profound respiratory failure—standard preoxygenation alone may prove insufficient, thereby contributing to increased morbidity and mortality[21]. To mitigate this risk, recent research has focused on the efficacy of maintaining oxygen delivery during the apneic period—defined as the interval from induction until the passage of the endotracheal tube through the vocal cords. This technique, termed apneic oxygenation, is not entirely new; it has historically been applied using standard nasal cannula. However, the concept has experienced a resurgence in popularity with the widespread availability and adoption of HFNO devices. Despite this renewed interest, a review of the current literature reveals conflicting findings and varying expert opinions regarding its utility[22–28].

Consequently, the objective of this guideline is to provide evidence-based recommendations regarding the implementation of apneic oxygenation as an adjunct to preoxygenation for emergency physicians managing critically ill patients requiring intubation.

Study selection

Due to the significant semantic overlap in keywords between preoxygenation and apneic oxygenation studies, compounded by the lack of standardized terminology in the existing literature, a unified literature search strategy was employed for both topics. Following this combined search, the retrieved articles were stratified into two primary categories through a preliminary screening of abstracts. This systematic process, utilizing the specified keywords (Supplementary File 1) identified a total of 89 articles relevant to apneic oxygenation. Of these, 79 studies were subsequently excluded; exclusion criteria included non-randomized study designs—deemed unnecessary given the sufficiency of available randomized controlled trials—lack of direct relevance to the clinical question, or the enrollment of populations outside the ED or critical care settings. Consequently, the remaining 10 randomized controlled trials were included in the final evaluation (Supplementary File 2).

In the risk of bias assessment conducted using the Cochrane RoB-2 tool for the included randomized clinical trials, five articles were determined to have a low risk of bias, four were classified as having a moderate risk, and one was identified as having a high risk of bias (Figure 4). Detailed summaries of the characteristics and findings of these studies are provided in Supplementary File 3.

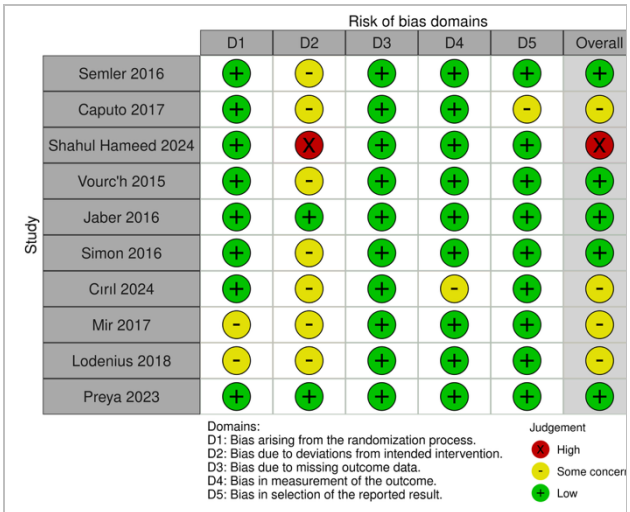


Figure 4. Traffic light plots of randomized clinical trials evaluating apneic oxygenation applied in addition to standard preoxygenation during rapid sequence intubation in the emergency department (Rob-2 risk of bias assessment).

Overview of the studies and outcome measures

An examination of the clinical settings across the included trials reveals distinct patient populations: three studies were conducted among critically ill patients requiring rapid sequence intubation in the ED [22-24], while four studies enrolled patients with similar indications within the intensive care unit[25-28]. The remaining three trials focused on patient populations requiring intubation specifically due to emergency surgical indications[29-31].

Regarding the efficacy outcomes within the ED and intensive care unit cohorts, all studies universally reported the lowest SpO_2 values observed during the intubation procedure as a primary measure. Furthermore, with the sole exception of the study by Shahul Hameed et al.[24] , the incidence of severe desaturation was documented in the remaining six trials. Despite the frequent designation of the lowest SpO_2 value as the primary endpoint in the original literature, the guideline panel elected to base its recommendations primarily on the "incidence of severe hypoxia." This decision reflects the consensus that preventing critical hypoxic events is of greater clinical significance than optimizing mean saturation values alone. Accordingly, effect sizes for both outcomes were pooled via meta-analysis for nearly all included studies.

Although the primary objective of the included studies was to evaluate the additive effect of apneic oxygenation, the utilization of divergent preoxygenation techniques in four of the trials[25-28] introduced a potential confounding factor that could obscure the isolated impact of the intervention. To mitigate this heterogeneity, stratification was employed during the meta-analysis: three studies utilizing consistent preoxygenation protocols were clustered into one subgroup[22-24], while the four studies employing variable preoxygenation methods were analyzed as a distinct subgroup. Regarding the specific modalities, preoxygenation involved bag-valve-mask (BVM), non-rebreather face masks, or noninvasive ventilation; for the apneic phase, while HFNO served as the predominant method, other techniques such as nasopharyngeal oxygen and standard nasal cannula oxygen were also utilized.

In the majority of studies involving patients with emergency surgical indications, the presence of respiratory distress or low

baseline SpO_2 levels served as an exclusion criterion. Consequently, these trials offer only indirect evidence regarding the specific clinical question at hand. Furthermore, because these studies predominantly utilized PaO_2 rather than SpO_2 as the primary outcome measure, they were ineligible for inclusion in the quantitative meta-analysis; instead, their findings are reviewed separately in a qualitative discussion.

While none of the studies focusing on emergency surgical indications reported instances of severe hypoxia (defined as SpO_2 < 80%), Lodenius et al. observed that five patients (12.5%) in the control group desaturated below 93%, whereas no desaturation events occurred in the group receiving apneic oxygenation via HFNO[30]. In contrast, Mir et al. reported that no patients in either study arm experienced desaturation below 90%[29].

Incidence of severe hypoxia (SpO_2 < 80%) during intubation

Upon examination of the meta-analysis results, which pooled data from 693 patients across six studies reporting this specific outcome[22,23,25–28], it was determined that the implementation of apneic oxygenation as an adjunct to preoxygenation failed to yield a statistically significant reduction in the incidence of severe hypoxia when compared to the control group receiving preoxygenation alone (OR 1.14, 95% CI 0.70–1.86; p = 0.59). Furthermore, subgroup analyses, stratified according to the homogeneity of preoxygenation techniques, consistently corroborated these findings, demonstrating that the addition of apneic oxygenation did not provide a significant benefit in reducing the incidence of severe hypoxia relative to preoxygenation alone (Figure 5).

Lowest SpO_2 recorded during intubation (Lowest SpO_2)

When the results of the meta-analysis—pooling data from 769 patients across seven studies reporting this outcome—were examined, it was observed that the use of apneic oxygenation in addition to preoxygenation did not result in a significant difference in the lowest SpO_2 values recorded during intubation compared with preoxygenation alone (mean difference 0.10, 95% CI −1.02 to 1.22; p = 0.87). Subgroup analyses, stratified based on the similarity of preoxygenation techniques, consistently demonstrated that apneic oxygenation failed to produce a statistically significant improvement in the lowest SpO_2 values observed during the rapid sequence intubation procedure relative to preoxygenation alone (Figure 6).

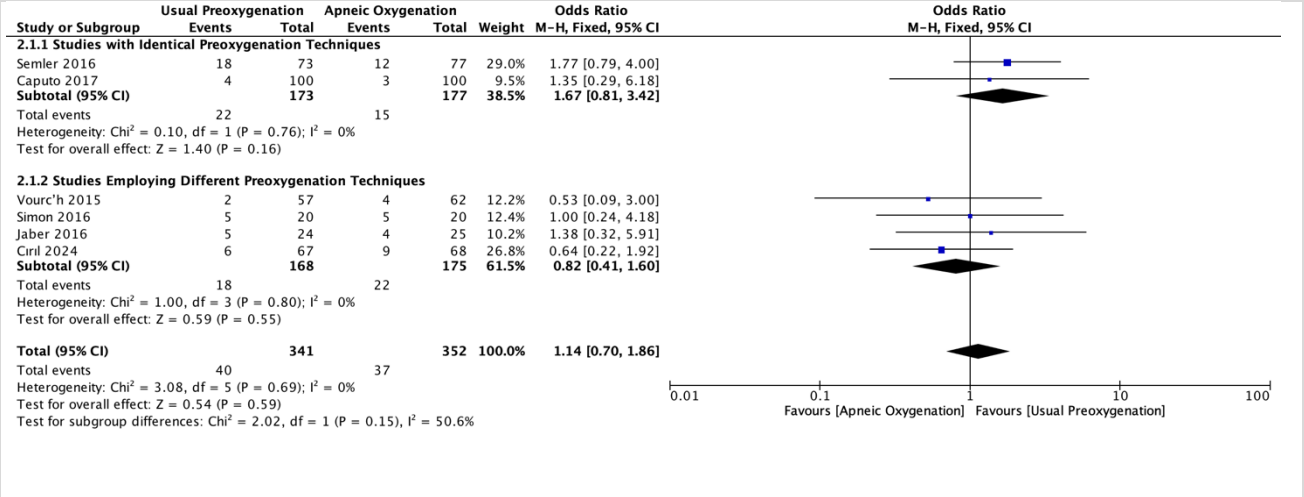


Figure 5. Forest plot showing the meta-analysis results of randomized clinical trials comparing apneic oxygenation applied in addition to standard preoxygenation with preoxygenation alone, in terms of the incidence of severe hypoxia (SpO_2 < 80%) during rapid sequence intubation in the emergency department.

Among the studies conducted on patients undergoing intubation for emergency surgical indications, reporting practices and findings varied significantly. Only the study by Lodenius et al. documented the lowest SpO_2 values, demonstrating no statistically significant difference between the treatment arms[30]. Conversely, Preya et al. did not report the lowest SpO_2 values; instead, they focused on arterial blood gas analysis, revealing that the lowest arterial PaO_2 measured during the apneic period was significantly higher in the group receiving apneic oxygenation via HFNO compared to the group receiving preoxygenation alone[31].

Mortality and other adverse outcome measures

Due to the heterogeneity in reported adverse events and safety outcomes across the evaluated studies, a pooled analysis of effect sizes was deemed inappropriate; instead, selected outcomes were reviewed individually.

Regarding mortality, while Caputo et al. assessed 24-hour outcomes[23], our other studies evaluated mortality over a 20–30-day period[22,25,26,28]; significantly, none of these investigations demonstrated a statistically significant difference between the treatment arms. In four studies, first-pass intubation success was compared, and no significant difference was shown between the two treatment arms[22,23,25,29]. Cırıl et al. investigated intubation duration as a secondary outcome and reported no significant difference[28].

Collectively, across the spectrum of reported secondary and safety outcomes, the data indicate that the addition of apneic oxygenation to standard preoxygenation does not yield a statistically distinguishable difference compared to preoxygenation alone.

Conclusion

In conclusion, a synthesis of the available randomized controlled trials evaluating the efficacy of apneic oxygenation as an adjunct to preoxygenation during Rapid Sequence Intubation (RSI) procedures—specifically among critically ill patients in the ED—demonstrates that the addition of apneic oxygenation does not yield a statistically significant difference regarding the incidence of severe hypoxia or the lowest measured SpO_2 values.

Similarly, the data indicate that this intervention does not lead to any deterioration in secondary outcomes, including mortality rates, first-pass intubation success, and intubation duration. However, the interpretation of these findings requires nuance; notably, four of the studies included in the meta-analysis employed divergent preoxygenation methodologies, thereby introducing a potential confounding factor. Given that the remaining studies—those isolating the pure effect of apneic oxygenation using identical preoxygenation protocols—possessed limited total sample sizes, there remains a compelling need for larger-scale investigations utilizing uniform preoxygenation strategies to provide definitive guidance.

GRADE evidence classification tables detailing the certainty of evidence for the

included studies are provided in Supplementary File 4.

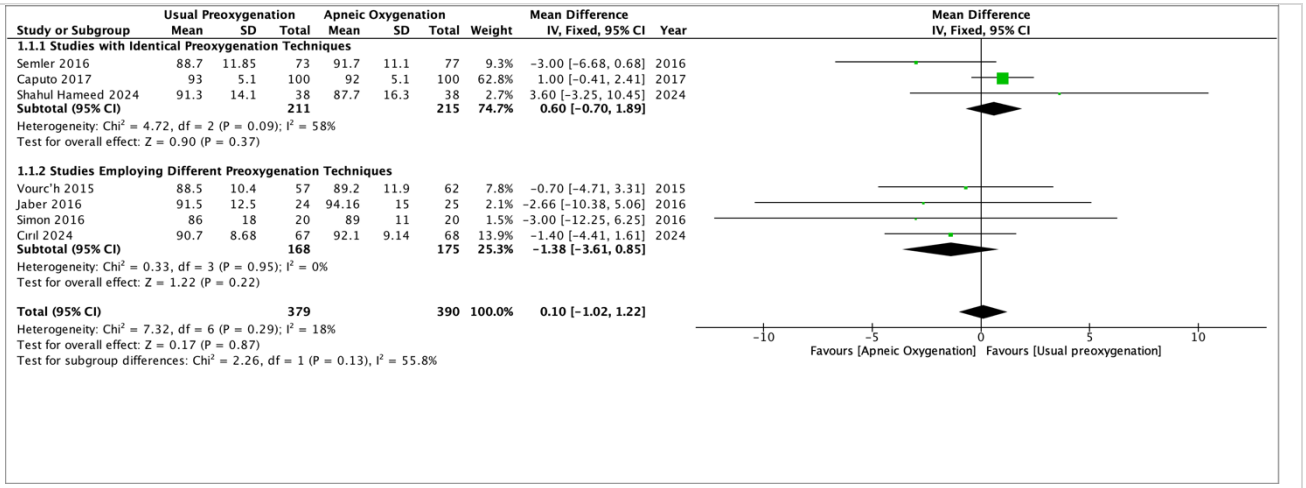


Figure 6. Forest plot presenting the meta-analysis results of randomized clinical trials comparing apneic oxygenation applied in addition to standard preoxygenation with preoxygenation alone, in terms of the lowest SpO_2 values recorded during the procedure during rapid sequence intubation in the emergency department.

Research Gaps and Future Directions

The current landscape of evidence is significantly limited by the predominance of single-center trials with restricted sample sizes, compounded by a general lack of standardization in preoxygenation methodologies across studies. Consequently, to establish definitive clinical guidelines, there is a critical need for large-scale, multicenter investigations that rigorously control for confounding variables by employing identical preoxygenation protocols in both the intervention and control arms. In particular, given its inherent ease of applicability and potential physiological benefits, future research should prioritize the specific evaluation of HFNO therapy as the primary modality for apneic oxygenation.

SCENARIO-3: In patients undergoing intubation in the emergency department, does the use of a gum elastic bougie, compared with standard intubation (with or without a stylet), increase first-pass intubation success or affect intubation duration?

3. COMPARISON OF GUM ELASTIC BOUGIE AND STANDARD INTUBATION	
Strength of Recommendation and Recommendations	**Level of Evidence**
Moderate	
In adult patients with a predicted difficult airway in the emergency department, the use of a gum elastic bougie is recommended over standard intubation (with or without a stylet).	Low
Weak	
The routine use of a gum elastic bougie may be considered during the intubation of adult patients in the emergency department.	Low

Rationale and background

In the high-stakes environment of ED airway management, first-pass success in endotracheal tube placement serves as a vital quality metric, given that multiple attempts are independently linked to severe adverse events such as hypoxemia, aspiration, and cardiac arrest. While the malleable stylet remains the standard adjunct in many institutions, the gum elastic bougie (GEB) has increasingly emerged as a preferred primary or rescue device among emergency physicians. Distinguished by its narrow diameter and a specific 35–40 degree distal angulation—often referred to as a Coudé tip—the GEB is designed to navigate the glottic opening even during scenarios of limited laryngeal visualization. Yet, the critical question remains whether these mechanical advantages translate into tangible clinical benefits within the volatile context of the ED, a setting defined by variable operator expertise and physiologically unstable patients. Consequently, this clinical policy guideline aims to rigorously evaluate the evidence comparing GEB-assisted intubation against standard methods, specifically focusing on its impact on first-pass success rates and procedural duration.

Study selection

A systematic literature search utilizing the relevant keywords (Supplementary File 1) initially yielded 942 articles. From this pool, 186 articles were identified as directly relevant to the research question; among these, 18 employed a randomized controlled trial (RCT) design, while the remainder were observational in nature. Given the sufficiency of high-quality randomized evidence, observational studies were excluded from further consideration (Supplementary File 2). From the initial set of 18 RCTs, strict exclusion criteria were applied to remove manikin, animal, and cadaver studies, as well as trials utilizing modified stylets, tracheal tubes, or mixed procedures involving mandatory additional adjunctive devices such as video laryngoscopy. However, studies in which additional adjunctive methods were utilized at the clinician's discretion rather than by protocol mandate were retained, resulting in the final inclusion of 11 RCTs for evaluation[32–43].

In the methodological quality assessment conducted using the Cochrane RoB-2 tool, significant variability was observed among the included randomized controlled trials; specifically, six studies were classified as having a high risk of bias, one study demonstrated a moderate risk, and four studies were determined to have a low risk of

bias (Figure 7). Detailed summaries of the characteristics and findings of these included studies are provided in Supplementary File-3.

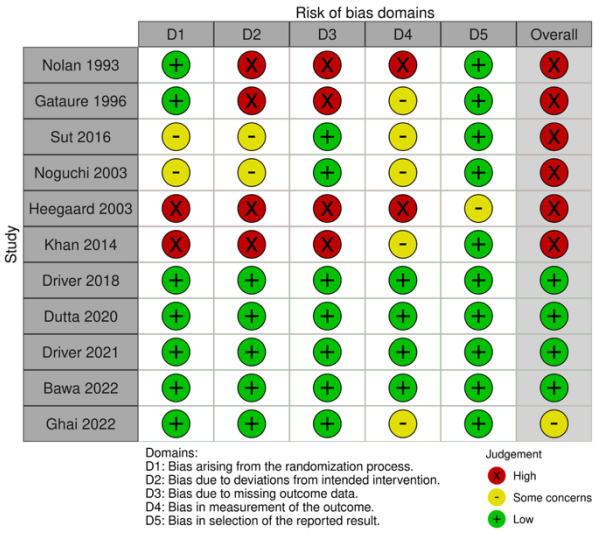


Figure 7. Traffic light plot of randomized controlled trials comparing the use of a gum elastic bougie with standard intubation (with or without a stylet) during intubation in the emergency department (Rob-2 risk-of-bias assessment).

Overview of the Studies and Outcome Measures

An analysis of the clinical environments across the included trials reveals a patient population predominantly situated within the operating room, with a smaller subset of studies conducted in ED (ED), intensive care unit (ICU), and prehospital settings. Regarding the study protocols, the GEB was universally utilized in the intervention arm. In the comparator arm, the use of a stylet was explicitly reported in six studies, while in the remaining five, the specific use of a stylet was not defined; instead, these were described generally as receiving "standard treatment" or "standard intubation." Consequently, for the purposes of analysis, all such comparator groups were aggregated into a single cohort representing standard intubation, irrespective of stylet usage.

When stratifying by methodological quality, distinct patterns emerge regarding study location. Among the trials classified as having a low or moderate risk of bias, three were conducted under controlled operating room conditions[32,35,37]. Notably, the 2018 investigation by Driver et al. was performed exclusively in the ED, whereas their subsequent 2021 study expanded to include both ED and ICU patient populations[33,34]. Conversely, among the studies deemed to have a high risk of bias, five were conducted in the operating room[36,39-42], while the study by Heegaard et al. stood alone as the only trial conducted in the prehospital setting[38].

First-attempt intubation success

Among the four studies classified as having a low or moderate risk of bias that evaluated first-attempt intubation success, three found no statistically significant difference, while only the 2021 investigation by Driver et al. reported a significant result favoring the GEB[33]. In the specific meta-analysis of these four studies, although the pooled effect size numerically trended toward the GEB, the association was not statistically significant (OR 1.36, 95% CI 0.49–3.76). Conversely, among the six studies characterized by a high risk of bias, three—specifically those by Gataure et al., Sut et al., and Khan et al.—identified a statistically significant benefit supporting GEB use, whereas the remaining studies reported no significant difference; notably, the pooled effect derived exclusively from these high-risk-of-bias studies demonstrated a marked benefit in favor of the GEB (OR 4.18, 95% CI 2.39–7.29). When the cumulative data from all 10 randomized controlled trials were synthesized, regardless of bias risk, the use of a GEB was

associated with a statistically significantly higher rate of first-attempt intubation success (OR 2.34, 95% CI 1.14–4.80) (Figure 8). However, it is imperative to note that while the overall pooled effect favors the GEB, this outcome is largely driven by the results from studies with a high risk of bias, as the pooled analysis restricted to studies with low risk of bias did not demonstrate a statistically significant difference.

In the stratified meta-analysis conducted according to clinical settings, the aggregate pooled effect across all strata consistently indicated higher first-attempt intubation success favoring the GEB (OR 2.03, 95% CI 1.10–3.74).

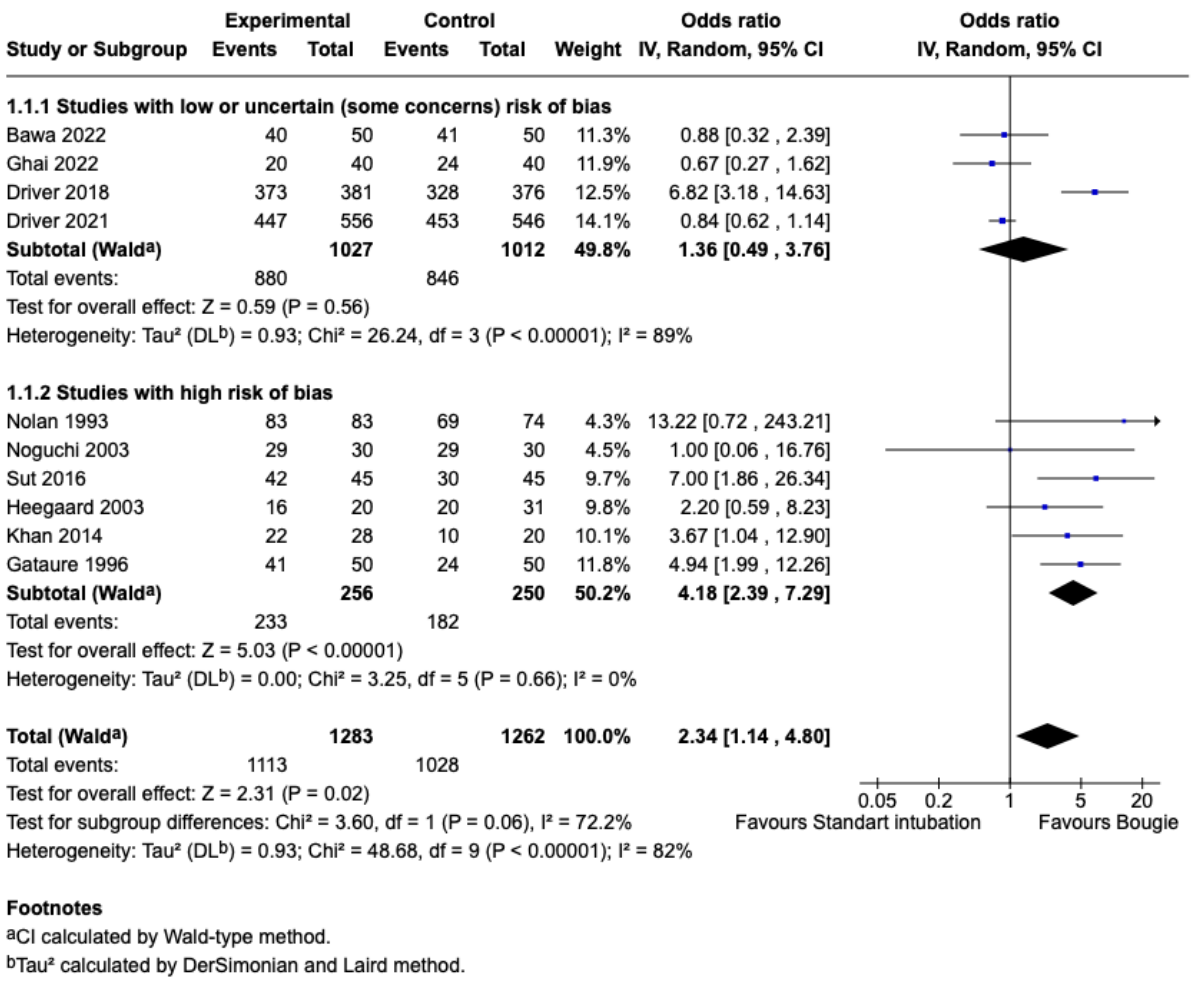


Figure 8. Forest plot showing the meta-analysis results of first-attempt intubation success in randomized clinical trials comparing the use of a gum elastic bougie with standard intubation (with or without stylet) during emergency department intubation; stratified according to the risk of bias of the studies.

However, upon stratifying studies by clinical environment, it became evident that the observed benefit attributable to the GEB was predominantly derived from prehospital and operating room investigations, the majority of which were characterized by a high risk of bias (Figure 9). Conversely, studies possessing a low or moderate risk of bias conducted within the

ED or intensive care unit ICU failed to demonstrate a consistent benefit favoring the GEB, with data from the ED proving particularly conflicting. Specifically, while the 2018 trial by Driver et al. identified a statistically significant advantage associated with GEB use (98% vs. 87%)[34], the subsequent 2021 study by the same investigators reported no significant difference between treatment arms (80% vs. 83%) and noted that intubation duration was, on average, 12 seconds longer in the GEB group[33]. Although the overall meta-analysis suggests a trend favoring the GEB, the presence of wide confidence intervals and substantial heterogeneity warrants caution. In this context, while a potential benefit of the GEB regarding first-attempt intubation success remains plausible, it must be emphasized that findings from randomized controlled trials of high methodological quality and low risk of bias do not definitively support this conclusion. Furthermore, methodological disparities and specific limitations across studies may have influenced these outcomes. In both the 2018 and 2021 trials by Driver et al., the utilization of video laryngoscopy (VL) was not standardized but rather left to clinician discretion. In the 2018 study, VL was employed significantly less frequently in the GEB arm compared to the control group, representing a notable methodological limitation; such unequal distribution of a confounder like VL usage could potentially skew results. However, it is noteworthy that despite the less frequent use of VL, outcomes still favored the GEB, suggesting that the intrinsic beneficial effect of the device may potentially exceed the reported effect size.

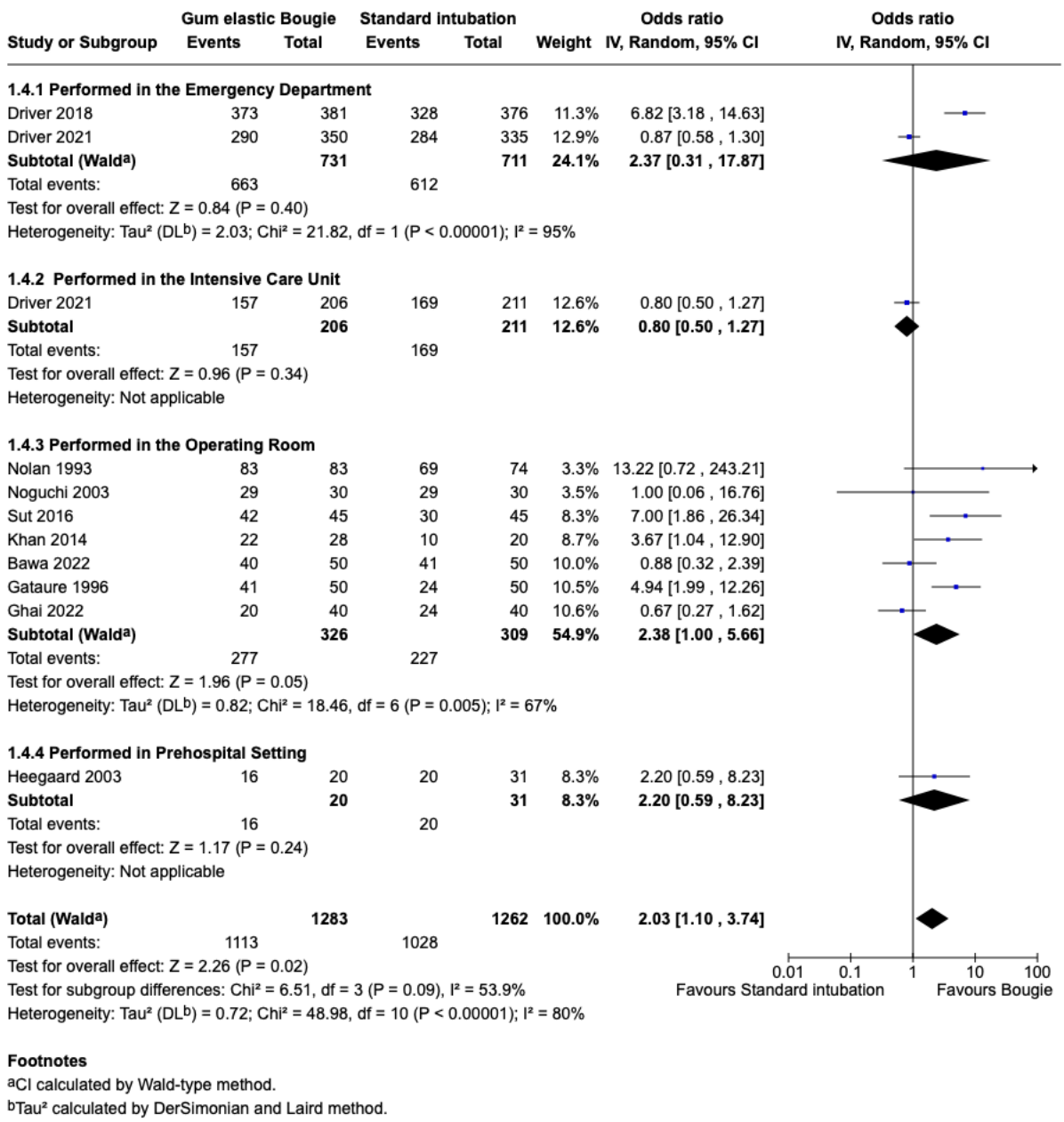


Figure 9. Forest plot showing the results of a stratified meta-analysis of randomized clinical trials comparing the use of a gum elastic bougie with standard intubation (with or without a stylet) during intubation in the ED, stratified by clinical setting, for first-attempt intubation success rates.

When the analysis is restricted exclusively to studies conducted involving patients with a difficult airway, the statistically significant and pronounced benefit associated with the GEB becomes particularly noteworthy. Across the spectrum of study quality—encompassing those with low or moderate as well as high risk of bias—both stratified analyses and the overall pooled effect consistently demonstrate that the use of a GEB significantly increases the likelihood of first-attempt intubation success (OR 2.11, 95% CI 1.47–3.01) (Figure 10).

In conclusion, although the aggregate data suggest that the GEB may be associated with a statistically significant improvement in

first-attempt intubation success across the general patient population, large-scale studies characterized by a low risk of bias fail to definitively corroborate this finding. Consequently, while a potential benefit of routine GEB use remains plausible, the evidence supporting its universal application is currently equivocal. However, when the focus is narrowed to the specific subgroup of patients presenting with a difficult airway, the approximate twofold increase in the odds of first-attempt intubation success represents a substantial clinical advantage, thereby allowing the benefit of the GEB in this specific context to be asserted with a significantly higher degree of confidence.

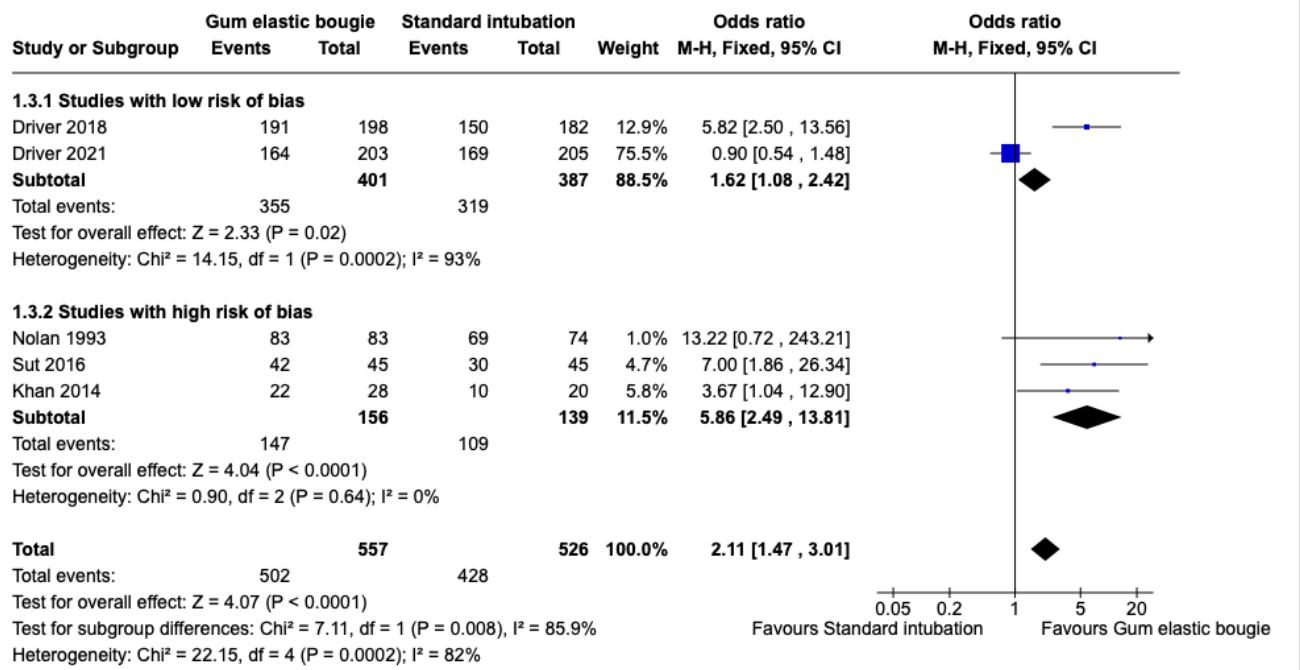


Figure 10. Forest plot showing the results of a meta-analysis of randomized clinical trials comparing the use of a gum elastic bougie with standard intubation (with or without a stylet) for first-attempt intubation success in difficult airway cases in the emergency department.

Overall intubation failure

The majority of the included literature primarily designated first-attempt intubation success or the cumulative number of attempts as their principal outcome measures. Within the limited subset of studies that explicitly reported overall intubation failure, this endpoint was generally defined as the inability to achieve successful intubation after two attempts and/or a procedural duration exceeding 60 seconds; consequently, this guideline adopted a concordant definition for the assessment of overall intubation failure. Regarding the methodological quality of the investigations reporting overall failure rates, the study conducted by Ghai et al. was determined to have a moderate risk of bias, whereas the remaining three studies were classified as having a high risk of bias[32–35].

In the meta-analysis, the investigation by Ghai et al. (2022)—characterized by a low or moderate risk of bias—revealed no discernible difference between treatment arms (OR 2.11, 95% CI 0.36–12.24). Conversely, the pooled results derived from the three studies identified as having a high risk of bias demonstrated a statistically significantly lower rate of overall intubation failure within the GEB

group (OR 0.21, 95% CI 0.06–0.68). When the cumulative pooled effect across all studies was evaluated, although a numerical trend favoring the GEB was observed, this potential benefit did not reach the threshold for statistical significance (OR 0.39, 95% CI 0.09–1.62) (Figure 11).

Beyond the aggregate data provided by the meta-analysis, an examination of study-specific outcomes reveals compelling granular findings regarding rescue strategies. Specifically, in the investigation by Gataure et al., every patient in the standard treatment cohort who experienced intubation failure after two attempts was subsequently and successfully intubated utilizing a gum elastic bougie as a rescue intervention[36]. Similarly, in the 2018 study by Driver et al., A parallel trend was observed in the 2018 study by Driver et al.; among a cohort of 56 patients exhibiting first-attempt failure across both trial arms—comprising 48 patients from the standard intubation group and 8 from the gum elastic bougie group—49 were successfully rescued via bougie-assisted intubation[34]. In both instances, the preferential deployment of the gum elastic bougie as a salvage strategy following failed attempts, coupled with the high rate of subsequent successful intubation associated with its use, underscores its critical utility in the management of the difficult airway.

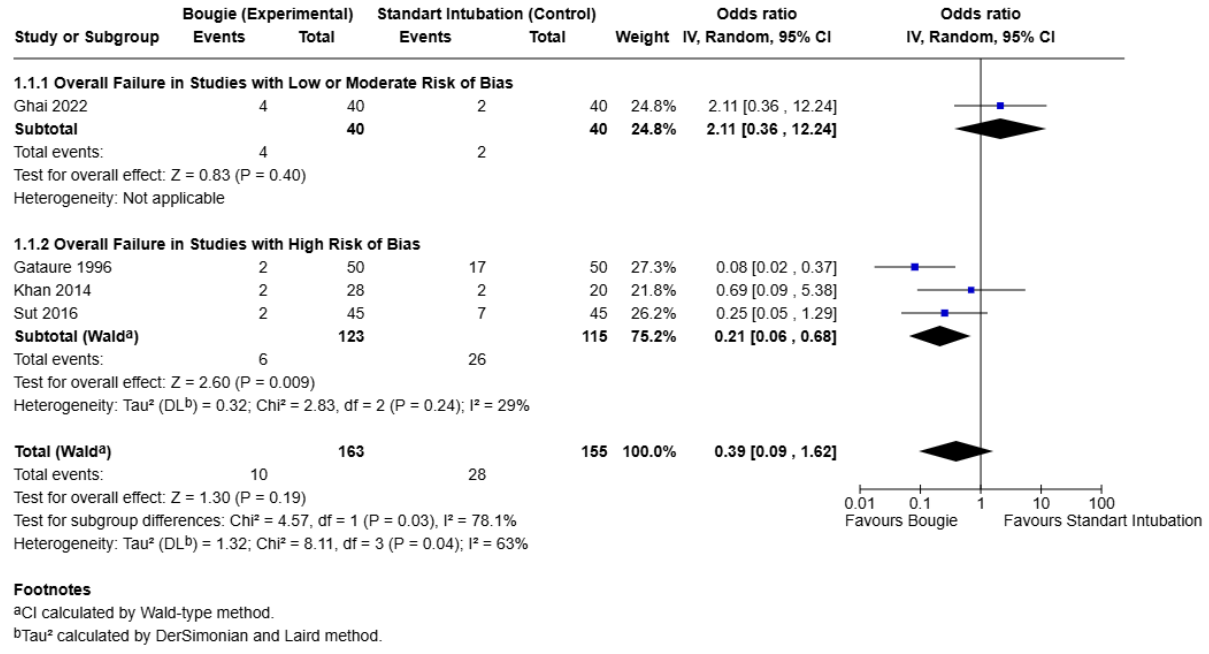


Figure 11. Forest plot showing the results of a meta-analysis of randomized clinical trials comparing the use of a gum elastic bougie with standard intubation (with or without a stylet) for overall intubation failure rates during intubation in the emergency department.

Endotracheal intubation time

Although first-attempt intubation success represents the paramount outcome within rapid sequence intubation (RSI) protocols in the ED, the duration of the intubation procedure constitutes a secondary yet vital quality indicator, given that prolonged intubation times have been demonstrably associated with increased risks of hypoxemia and peri-resuscitative arrest. Among the randomized controlled trials selected for analysis, eight studies provided comparative

data on intubation times between the GEB and standard intubation cohorts. In six of these investigations, the data were presented as means with standard deviations. However, the two studies conducted by Driver et al., published in 2018 and 2021, reported these metrics as medians with interquartile ranges (IQR). Despite attempts to contact the authors via email to obtain the raw data in mean and standard deviation format, no response was forthcoming. Consequently, to facilitate a unified meta-analysis, the intubation times for these two specific studies were statistically reconstructed as means and standard deviations utilizing the transformation formula proposed by Luo et al. [43].

Notable disparities in reported intubation times across the included studies are evident and are hypothesized to stem from the absence of a standardized definition for this metric. In the majority of investigations, precise methodological details regarding the measurement of procedural duration were not explicitly delineated. Among the eight studies providing data, five were classified as having a low or moderate risk of bias; an analysis of the pooled effect from this specific subset revealed a statistically significant reduction in intubation time within the standard intubation arm. Although the pooled analysis of the three studies characterized by a high risk of bias failed to demonstrate a significant divergence between the groups, their inclusion in the aggregate assessment of all eight studies resulted in an overall pooled effect indicating a statistically significantly shorter intubation time favoring standard intubation (mean difference 3.7 s, 95% CI 1.02–6.38). However, when the 95% confidence interval is taken into account, this temporal disadvantage—ranging between 1 and 6 seconds—bears debatable clinical implications and may be interpreted as a marginal drawback associated with the GEB. While this differential may hold relevance for deeply hypoxemic patients, it is likely to be clinically tolerable within the general patient population (Figure 12).

Complications

A diverse array of outcomes was evaluated as complications across the included studies, although several failed to report any relevant safety data. Due to the heterogeneity of these outcomes, which precluded a valid meta-analysis, the findings are herein discussed on a qualitative, study-by-study basis. Specifically, four studies assessed the incidence of esophageal intubation, with all reporting comparable rates between the treatment arms[32,37–39]

In the 2021 study by Driver et al., a critical safety signal was observed regarding hemodynamic stability: the rate of cardiovascular collapse within one hour of the procedure was reported to be statistically significantly higher in the standard intubation arm (91 patients [16.7%]) compared to the gum elastic bougie group (68 patients [12.2%]), representing an absolute risk difference of 4.4% (95% CI 0.1–8.8)[33]

Due to the significant heterogeneity in how complication-related outcomes were defined across the included literature, there was a paucity of studies reporting overlapping safety data suitable for pooled analysis. However, when the investigations were examined individually, the treatment groups were consistently reported to demonstrate similar profiles with respect to a broad spectrum of adverse events, including laryngospasm, stridor, airway obstruction, and airway mucosal trauma. Furthermore, no significant disparities were observed between the cohorts regarding the incidence of severe

desaturation (SpO_2 < 80%), witnessed aspiration, newly developed pneumothorax, sore throat, hoarseness, lip laceration, dental trauma, or other hypoxemia-related complications.[32,35,36,38-40]

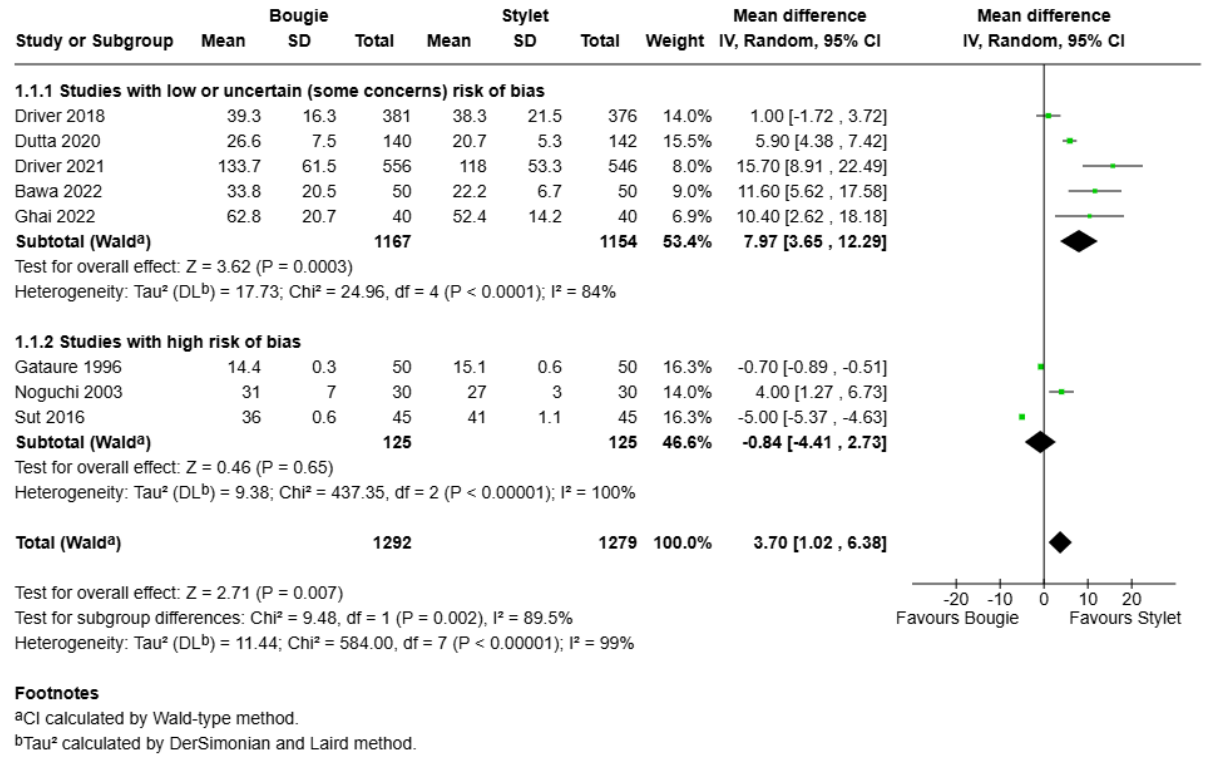


Figure 12. Forest plot showing the results of a meta-analysis of randomized clinical trials comparing the use of a gum elastic bougie with standard intubation (with or without a stylet) for endotracheal intubation time during intubation in the emergency department.

Conclusion

Current evidence suggests that GEB offers a statistically significant advantage in first-attempt intubation success over standard intubation, particularly for difficult airways, albeit with a slight prolongation of intubation time. However, these results should be interpreted with caution due to study heterogeneity—especially regarding first-attempt success—which affects the sensitivity of the meta-analyses. This potential benefit appears to be driven largely by prehospital and operating room studies. GRADE evidence classification tables summarizing the certainty of evidence are provided in Supplementary File 4.

In patients with a difficult airway (defined as a Cormack–Lehane grade III view or obscured anatomy due to vomitus, bleeding, deformity, etc.), GEB offers a distinct advantage. Therefore, the use of GEB during RSI should be preferred over standard intubation (with or without a stylet) in this cohort. Additionally, when standard intubation is selected as the initial approach but fails, GEB may be utilized as an effective rescue intervention.

While data suggest a benefit in first-attempt success rates favoring GEB, current evidence is insufficient to mandate its routine use for all patients. However, clinical context is critical; unlike the controlled environments of the operating room or ICU—where most studies

were conducted—patients in the ED often present with rapidly evolving clinical scenarios. Consequently, virtually every ED patient warrants consideration as a potential difficult airway case. Given this reality, alongside the favorable safety profile of GEB, we recommend prioritizing GEB over standard intubation across the entire patient population. Nevertheless, for GEB to be adopted routinely during RSI, it is imperative that personnel in these clinical settings receive adequate training in its application.

Research Gaps and Future Directions

There is a critical need for multicenter, ED-focused RCTs to further investigate differences in first-attempt tracheal tube passage success. A notable limitation in existing literature is the lack of a standardized definition for "tube placement time"; establishing a uniform metric for this concept is essential for future comparisons between GEB and standard intubation. Furthermore, targeted RCTs focusing on specific populations—such as obese patients, trauma patients, and the physiologically critically ill—are necessary to facilitate robust subgroup analyses and refine clinical recommendations.

SCENARIO-4: In adult emergency department patients who are hypotensive or at high risk of hypotension, does the administration of a push-dose vasopressor (e.g., phenylephrine, epinephrine) during or immediately before rapid sequence intubation, added to standard care, reduce the incidence of peri-intubation hypotension and improve clinical outcomes?

PUSH-DOSE VASOPRESSOR ADMINISTRATION DURING RAPID SEQUENCE INTUBATION
RECOMMENDATION RATIONALE
As the available evidence is indirect, of low quality, and insufficient to conclusively answer this question, the panel makes **no recommendation** for or against this intervention.
Expert Opinion: Although the panel refrained from making a formal recommendation on this issue, it acknowledges that push-dose vasopressor therapy is utilized in certain clinical practices. Consequently, the panel suggests that each institution determine via local clinical protocols whether push-dose vasopressors should be administered during rapid sequence intubation in critically ill adult patients who are hypotensive or at risk of hypotension.

Rationale and background

Rapid sequence intubation in critically ill ED patients is frequently associated with a high risk of hemodynamic instability. The sedative and paralytic agents administered during the procedure can precipitate abrupt decreases in blood pressure, potentially impairing organ perfusion and increasing morbidity and mortality—particularly in patients predisposed to hypotension.

In clinical practice, some clinicians utilize push-dose vasopressors (VP) during or immediately prior to RSI to mitigate these risks. Agents such as phenylephrine and epinephrine are commonly preferred due to their rapid onset of action and feasibility for peripheral administration. However, literature regarding the efficacy and safety of this approach remains limited. A recent meta-analysis of 24 RCTs demonstrated that prophylactic push-dose VP prior to orotracheal intubation was associated with higher post-intubation mean arterial and systolic pressures (mean difference: 7.6 mmHg, 95% CI 4.3–10.8). Nevertheless, that study focused exclusively on elective intubations in ASA I–II patients within operating room settings; thus, it provides only limited indirect evidence for the use of this strategy during RSI in critically ill, hypotensive patients.

This guideline aims to provide evidence-based recommendations for emergency physicians managing critically ill patients in the ED who are hypotensive, or at high risk of hypotension, and require RSI.

Study selection

A systematic literature search using relevant keywords identified a total of 98 studies (Supplementary File 1). From these, seven studies evaluating the use of push-dose VP during the peri-intubation period in critically ill patients who were hypotensive or at risk of hypotension were included for assessment. Phenylephrine was the most frequently utilized vasopressor in these trials. However, since this agent is unavailable in our country, three additional observational studies were included to broaden the evidence base. These supplemental studies evaluated the efficacy of push-dose VP in clinical scenarios outside the peri-intubation period and assessed epinephrine—which is more readily available locally—alongside phenylephrine. These studies were incorporated into the

recommendation development process as they provided essential comparative data on the efficacy and safety profiles of sympathomimetic agents Supplementary File 2).

All included studies were observational in design. No separate tool was utilized for risk-of-bias assessment; instead, given that the majority were single-arm observational studies, they were collectively categorized as having a high risk of bias. Summaries of these studies are presented in Supplementary File 3.

Overview of the studies and outcome measures

There are currently no randomized controlled trials (RCTs) directly comparing the use of push-dose VP during RSI in critically ill patients at risk of hypotension. Consequently, the evidence base primarily comprises observational studies and secondary analyses of previously conducted RCTs.

Studies evaluating the effectiveness of push-dose vasopressors during the peri-intubation period

Of the seven studies evaluating the effectiveness of push-dose VP during the RSI procedure, five were single-arm observational studies with limited sample sizes[49-53]. These studies primarily assessed changes in vital signs—most notably blood pressure—before and after push-dose VP administration. The findings generally indicated that clinically meaningful increases in blood pressure (approximately 10–20 mmHg) were achieved post-administration compared to baseline. However, adverse events such as arrhythmias and rebound hypertension were also reported at varying frequencies. Because these studies lacked comparator arms, it is not possible to determine with certainty whether these adverse event rates—or the observed clinical efficacy—were specifically attributable to push-dose VP administration.

One of the remaining two studies was a secondary analysis reported by Fuchita et al. in 2018, based on cohorts from two previously conducted RCTs[54]. In this study, propensity score matching was utilized to compare groups that did and did not receive push-dose VP. The authors reported that hypotension occurred more frequently in the group where a VP infusion was initiated following push-dose VP, compared to the group that received no VP (53% vs. 41%, p=0.02). However, as the authors acknowledged, this finding may primarily reflect substantial selection bias. In both underlying RCTs, no standardized protocol for VP use was defined; instead, the decision to initiate therapy was left to clinician discretion. Therefore, despite the use of propensity score matching to mitigate this bias, it is probable that patients who received VP were inherently more severely ill, which may have driven these results.

The final study evaluating the effectiveness of push-dose VP during RSI was a retrospective analysis by Schmitt et al., based on two years of intubation registry data[55]. In this study, propensity score matching was used to compare three groups: bolus only, infusion only, and combined (bolus + infusion) VP administration. The authors reported that the rate of poor outcomes was significantly lower in the bolus VP group compared to the other two groups (80% vs. 88%; $p < 0.01$).

In the majority of the evaluated studies, phenylephrine was the primary agent used. Regarding dosing and administration frequency, phenylephrine was generally prepared by adding 1,000 mcg of the drug to a 10-mL syringe to achieve a concentration of 100 mcg/mL. The most frequently described approach in the literature involves

administering an initial bolus of 100–200 mcg (1–2 mL of the prepared solution), with repeat doses every 1–2 minutes as clinically indicated.

However, as this agent is not widely available in Türkiye, the effectiveness of push-dose epinephrine—which serves as the primary alternative locally—was further evaluated by incorporating the additional studies summarized below.

Studies evaluating the use of push-dose epinephrine and phenylephrine in non-peri-intubation scenarios

In two separate studies evaluating data from ICU and ED patients who were hypotensive and critically ill, both push-dose phenylephrine and epinephrine were reported to produce significant increases in blood pressure. However, in both studies, the magnitude of this effect was greater with epinephrine than with phenylephrine[56-57]. In the study by Singer et al., epinephrine was associated with a higher incidence of adverse effects, such as hypertensive episodes and tachycardia[56]. Similarly, Nam et al. reported that dosing errors occurred more frequently with epinephrine compared with phenylephrine[57]. Finally, in the study by Nawrocki et al., epinephrine administered as bolus therapy in critically ill hypotensive patients increased blood pressure to a clinically acceptable extent, with a lower rate of adverse events (approximately 2%) compared with other studies[58].

When the dosages were evaluated, all studies reported the administration of a 10–20 mcg (1:100,000) epinephrine bolus every two minutes as needed.

Conclusion

The current literature provides insufficient evidence to definitively confirm the efficacy and safety of push-dose VP use. Consequently, the panel has chosen not to issue a formal recommendation on this topic; however, it recognizes that push-dose VP therapy remains a part of clinician-dependent practice in certain settings. Given this context, the panel concludes that for critically ill patients who are hypotensive or at high risk of hypotension, the decision to administer push-dose vasopressors during RSI should be determined by each institution in accordance with its local clinical policies.

If an institution adopts a policy to administer push-dose VP, the route of administration and specific dosing protocols must be clearly defined. Although recommended dosages vary by agent, the available literature utilizes ranges of 100–200 mcg for phenylephrine and 10–20 mcg for epinephrine. Since phenylephrine is not widely available in Türkiye, low-dose epinephrine—which elicits a similar hemodynamic response—may be utilized as an alternative. If this approach is implemented, the panel recommends the intravenous administration of epinephrine at a push-dose of 10 mcg over 1 minute.

SCENARIO-5: In adult emergency department patients at risk of increased intracranial pressure, is the use of ketamine during rapid sequence intubation a safe option?

KETAMINE USE IN PATIENTS AT RISK OF INCREASED INTRACRANIAL PRESSURE	
Strength of Recommendation and Recommendations	**Level of Evidence**
Moderate Against	
Concerns that ketamine use during rapid sequence intubation causes an increase in intracranial pressure (ICP) in patients with acute brain injury at risk of elevated ICP are anecdotal, and current literature does not support this. Therefore, ketamine should not be avoided solely due to concerns regarding increased intracranial pressure.	Very Low

Rationale and background

Severe acute brain injury (ABI) is frequently encountered in the ED across conditions such as traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, acute ischemic stroke, and hypoxic brain injury. Due to the potential for increased intracranial pressure, there is a constant risk of secondary cerebral injury and poor prognosis in this patient population[59]. In the emergency management of patients with severe ABI, RSI is often required both to secure the airway and to mitigate secondary brain damage.

Ketamine, an N-methyl-D-aspartate receptor antagonist, is among the induction agents commonly used during RSI in the ED. However, based on the findings of a few historically limited studies, the concern that ketamine may elevate intracranial pressure remains widespread among clinicians[60,61]. 60-61. Although several recent studies have reported findings to the contrary, differing opinions persist regarding the use of ketamine during RSI, particularly in the context of severe ABI[62,63].

This guideline aims to provide evidence-based recommendations for emergency physicians regarding the use of ketamine as an induction agent during RSI for patients with acute ABI. This guideline does not compare effectiveness across different clinical conditions.

Study selection

A systematic literature search using relevant keywords identified 85 articles (Supplementary File 1). Of these, 18 articles relevant to the research question were included for final evaluation; 7 were randomized controlled trials (RCTs), while the remaining 11 were observational studies (Supplementary File 2).

Although all observational studies were categorized as having a high risk of bias, the risk-of-bias assessment performed using the Cochrane RoB 2 tool for the RCTs demonstrated that majority of the trials also carried a high risk of bias (Figure 13). In addressing the clinical question, RCTs served as the primary evidence base. However, due to concerns regarding indirectness related to study populations and outcomes, the main findings of the observational studies were also taken into consideration. Summaries of the included studies are presented in Supplementary File 3.

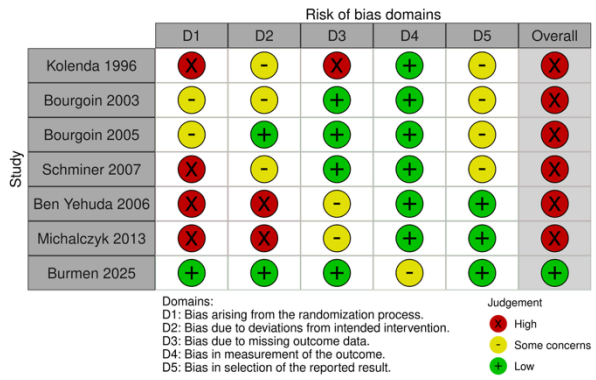


Figure 13. Traffic light plots of randomized clinical trials evaluating the use of ketamine during rapid sequence intubation in patients with acute brain injury at risk of increased intracranial pressure (Rob-2 risk-of-bias assessment).

Overview of the studies and outcome measures

None of the identified randomized controlled trials or observational studies fully address our specific research question. Specifically, no available RCT directly defined its study population as patients at risk of increased intracranial pressure (ICP) undergoing RSI. Instead, five RCTs evaluated the effects of ketamine administered as a continuous sedative infusion on ICP in already intubated patients with ICP elevation due to ABI [63-67]. In four of these five studies, continuous ketamine infusion for sedation was compared with opioid infusions (fentanyl or sufentanil) (Figure 14a). Similarly, four studies utilized and reported continuous ICP monitoring via intraventricular catheters in all patients. ICP and cerebral perfusion pressure (CPP) values measured at the end of the first day of infusion were utilized as common outcomes suitable for meta-analysis. Results of the meta-analysis indicated that ketamine infusion for sedation had no adverse effect on ICP or CPP compared with opioid infusion (for ICP: mean difference −0.78 mmHg, 95% CI −1.87 to 0.31; for CPP: mean difference −1.07 mmHg, 95% CI −7.95 to 5.80) (Figure 14b).

In the randomized controlled trial conducted by Burman et al., intubated patients with severe acute brain injury (GCS < 8) sedated with fentanyl and midazolam were randomized to receive either an additional ketamine infusion or a placebo[67] In both treatment arms, intracranial pressure (ICP) and cerebral perfusion pressure (CPP) were continuously monitored via an intraventricular catheter throughout a 36-hour infusion period. The authors reported that ICP values in the ketamine group generally tended to be lower than those in the placebo group, with the difference reaching statistical significance at the 4–6 hour intervals. Similarly, CPP values were generally higher in the ketamine group, also reaching statistical significance during the 4–6 hour period. Because the study did not report overall mean ICP and CPP values, these data could not be included in the meta-analysis.

Although their study populations do not directly represent patients with established intracranial hypertension, the results of two randomized controlled trials were considered in this guideline. Both studies involved direct measurement of intracranial pressure and reported early post-ketamine data in a manner analogous to the initial phase of an RSI procedure[68,69].

In the study by Ben Yehuda et al. (2006), 39 pediatric patients undergoing lumbar puncture (LP) for suspected meningitis were randomized to receive either ketamine + midazolam or midazolam alone for procedural sedoanalgesia[68]. The primary outcome was the opening pressure measured during the procedure. The ketamine + midazolam group demonstrated higher opening pressures

compared to the midazolam-only group (24.4 ± 8.87 mmHg vs. 20 ± 3.74 mmHg).

Similarly, in the randomized controlled trial conducted by Michalczyk et al. (2013), sedation regimens were compared in 25 pediatric oncology patients undergoing a total of 84 LP procedures as part of their diagnostic follow-up[69]. Patients were assigned to one of three sedation strategies: ketamine + midazolam, propofol + fentanyl, or ketamine alone. The primary outcome was again the opening pressure. In this study, the group receiving ketamine alone had significantly higher opening pressure values compared to the other two groups.

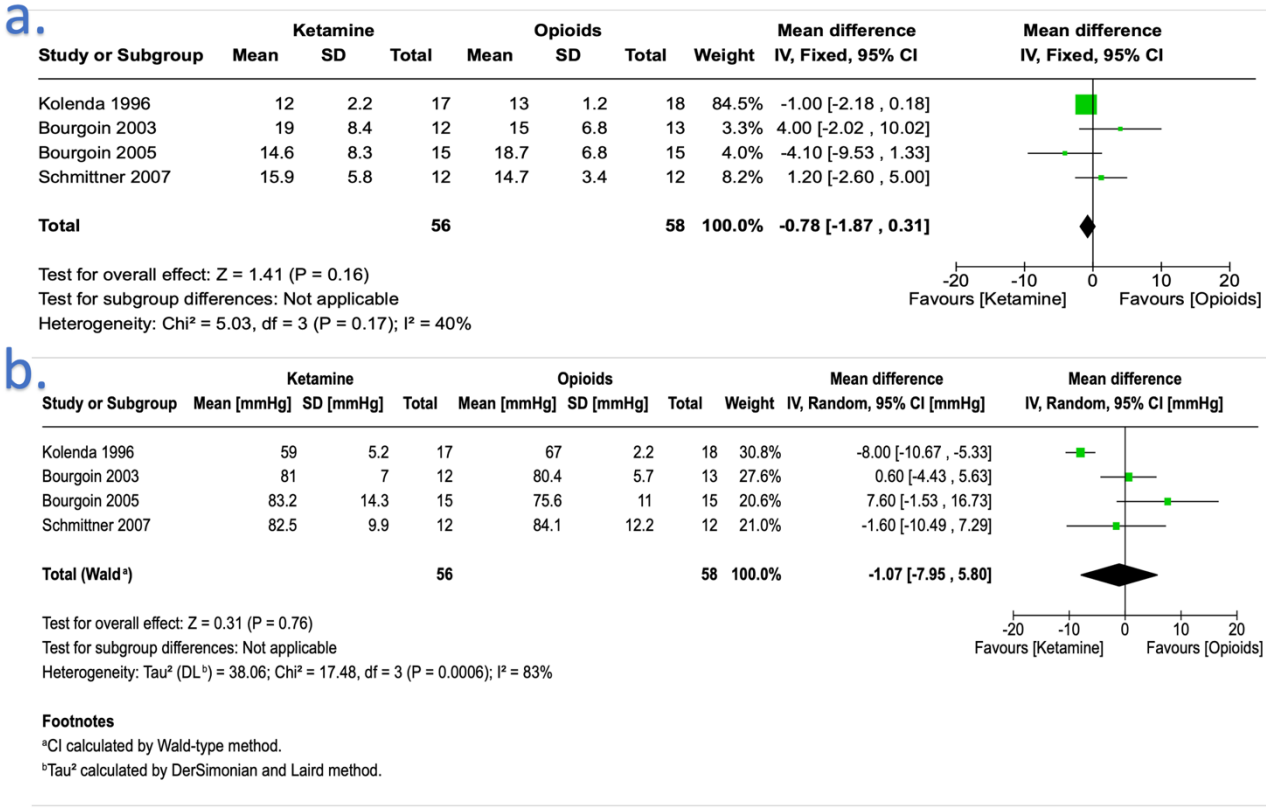


Figure 14. Forest plots showing the meta-analysis results of randomized clinical trials comparing the effects of ketamine infusion versus opioid infusion used for sedation on intracranial pressure (a) and cerebral perfusion pressure (b) in intubated patients with acute brain injury and elevated intracranial pressure.

Observational Studies

Eleven observational studies evaluating the effects of ketamine in patients with acute brain injury (ABI) and suspected increased intracranial pressure (ICP) were also assessed. In seven of these studies, the study population comprised patients with ABI who underwent RSI, with ketamine compared against other induction agents. Although ICP and cerebral perfusion pressure (CPP) were not defined as primary outcome measures in these studies, ketamine was reported to have no more adverse effects than other agents regarding mortality, neurological outcomes, first-pass intubation success, and hemodynamic parameters[70-75]. Only the study by Fouche et al. reported a higher incidence of post-intubation hypotension in the ketamine group[76].

n the remaining four observational studies, the focus was not specifically on patients undergoing RSI, but rather on the effects of ketamine used for sedation in already intubated ABI patients. These studies monitored ICP changes through continuous monitoring. The findings indicated either no significant changes in ICP and CPP values or a favorable effect, particularly regarding improved CPP[77-80]. (Supplementary File 3).

Conclusion

As discussed in detail above, while the available studies carry a high risk of bias and the majority were not conducted within an RSI scenario, there is no evidence to suggest that intravenous ketamine causes a greater increase in intracranial pressure (ICP) compared with other agents. Furthermore, ketamine does not appear to worsen neurological or other clinical outcomes in patients with acute brain injury (ABI) and suspected elevated ICP. Only two studies, conducted in a pediatric population without ABI, reported higher lumbar puncture opening pressures.

Consequently, we believe there is no specific clinical reason to avoid the use of ketamine as an induction agent during RSI in this patient population. However, clinicians should remain mindful that the existing evidence is highly indirect and that there are currently no randomized controlled trials with a low risk of bias conducted specifically in patients at risk of increased ICP undergoing RSI. GRADE evidence certainty tables for the included studies are presented in Supplementary File 4.

REFERENCES

1. Maia IWA, Besen BAMP, Silva LOJE, von Hellmann R, Hajjar LA, Sandefur BJ, Pedrollo DF, Nogueira CG, Figueiredo NMP, Miranda CH, Martins D, Baumgratz TD, Bergesch B, Costa D, Colleoni O, Zanettini J, Freitas AP, Moreira NP, Gaspar PL, Tambelli R, Costa MC, Silveira S, Correia W, de Maria RG, Filho UAV, Weber AP, da Silva Castro V, Dornelles CFD, Tabach BS, Guimarães HP, Stanzani G, Gava TF, Mullan A, Souza HP, Ranzani OT, Bellolio F, Alencar JCG; BARCO group. Peri-intubation adverse events and clinical outcomes in emergency department patients: the BARCO study. Crit Care. 2025 Apr 17;29(1):155. doi: 10.1186/s13054-025-05392-w.
2. Yang TH, Shao SC, Lee YC, Hsiao CH, Yen CC. Risk factors for peri-intubation cardiac arrest: A systematic review and meta-analysis. Biomed J. 2024 Jun;47(3):100656. doi: 10.1016/j.bj.2023.100656. Epub 2023 Sep 1.
3. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med. 2012 Mar;59(3):165-75.e1. doi: 10.1016/j.annemergmed.2011.10.002. Epub 2011 Nov 3.
4. Pitre T, Liu W, Zeraatkar D, Casey JD, Dionne JC, Gibbs KW, Ginde AA, Needham-Nethercott N, Rice TW, Semler MW, Rochwerg B. Preoxygenation strategies for intubation of patients who are critically ill: a systematic review and network meta-analysis of randomised trials. Lancet Respir Med. 2025 Jul;13(7):585-596. doi: 10.1016/S2213-2600(25)00029-3. Epub 2025 Mar 21.
5. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-382. doi:10.1016/j.jclinepi.2010.09.011
6. Mourad Ouzzani, Hossam Hammady, Zbys Fedorowicz, and Ahmed Elmagarmid. Rayyan — a web and mobile app for systematic reviews. Systematic Reviews (2016) 5:210, DOI: 10.1186/s13643-016-0384-4.
7. Baillard C, Prat G, Jung B, Futier E, Lefrant JY, Vincent F, et al. Effect of preoxygenation using non-invasive ventilation before intubation on subsequent organ failures in hypoxaemic patients: a randomised clinical trial. Br J Anaesth. Şubat 2018;120(2):361-7.
8. Guitton C, Ehrmann S, Volteau C, Colin G, Maamar A, Jean-Michel V, et al. Nasal high-flow preoxygenation for endotracheal intubation in the critically ill patient: a randomized clinical trial. INTENSIVE CARE Med. 2019;45(4):447-58.
9. Gibbs K, Semler M, Driver B, Seitz K, Stempek S, Taylor C, et al. Noninvasive Ventilation for Preoxygenation during Emergency Intubation. N Engl J Med. 2024;390(23):2165-77.
10. Baillard C, Fosse J, Sebbane M, Chanques G, Vincent F, Courouble P, et al. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. Am J Respir Crit CARE Med. 2006;174(2):171-7.
11. Li J, Liu B, Zhou Q, Ni H, Liu M, Deng K. Pre-oxygenation with high-flow oxygen through the nasopharyngeal airway compared to facemask on carbon dioxide clearance in emergency adults: a prospective randomized non-blinded clinical trial. Eur J TRAUMA Emerg Surg. 2024;50(3):1051-61.
12. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. Haziran 2018;27(6):1785-805.
13. Chua M, Ng W, Lu Q, Low M, Punyadasa A, Cove M, et al. Pre- and apnoeic high-flow oxygenation for rapid sequence intubation in the emergency department (the Pre-AeRATE trial): A multicentre randomised controlled trial. Ann Acad Med Singap. 2022;51(3):149-60.
14. Frat J, Ricard J, Quenot J, Pichon N, Demoule A, Forel J, et al. Non-invasive ventilation versus high-flow nasal cannula oxygen therapy with apnoeic oxygenation for preoxygenation before intubation of patients with acute hypoxaemic respiratory failure: a randomised, multicentre, open-label trial. LANCET Respir Med. 2019;7(4):303-12.
15. Karlupia D, Garg K, Jain R, Grewal A. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange Versus Conventional Facemask Breathing for Preoxygenation During Rapid Sequence Induction. CUREUS J Med Sci. 2023;15(8).
16. Tarigonda S, Nagaiah SK, Manem A, Krishnamurthy D. Comparison of Two Techniques of Peri-Intubation Oxygenation to Minimize the Degree of Desaturation in Patients with Hypoxemic Respiratory Failure in Intensive Care Unit. Med J Dr Patil Vidyapeeth. 2023;16(8):S222-7.
17. Jaber S, Amraoui J, Lefrant J-Y, Arich C, Cohendy R, Landreau L, Calvet Y, Capdevila X, Mahamat A, Eledjam J-J. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Crit Care Med 2006;34: 2355–2361.
18. Simpson GD, Ross MJ, McKeown DW, Ray DC. Tracheal intubation in the critically ill: a multi-centre

national study of practice and complications. Br J Anaesth 2012;108:792–799.

19. De Jong A, Molinari N, Terzi N, Mongardon N, Arnal J-M, Guitton C, Allaouchiche B, Paugam-Burtz C, Constantin J-M, Lefrant J-Y, et al.; AzuR´ea Network for the Frida-R´ea Study Group. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. Am J Respir Crit Care Med 2013;187:832–839.

20. Mort TC. Preoxygenation in critically ill patients requiring emergency tracheal intubation. Crit Care Med 2005;33: 2672–2675

21. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med 2012;59:165–75.e1.

22. Semler MW, Janz DR, Lentz RJ, Matthews DT, Norman BC, Assad TR, Keriwala RD, Ferrell BA, Noto MJ, McKown AC, Kocurek EG, Warren MA, Huerta LE, Rice TW; FELLOW Investigators; Pragmatic Critical Care Research Group. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. Am J Respir Crit Care Med. 2016 Feb 1;193(3):273-80. doi: 10.1164/rccm.201507-1294OC.

23. Caputo N, Azan B, Domingues R, Donner L, Fenig M, Fields D, Fraser R, Hosford K, Iuorio R, Kanter M, McCarty M, Parry T, Raja A, Ryan M, Williams B, Sharma H, Singer D, Shields C, Scott S, West JR; Lincoln Airway Group. Emergency Department use of Apneic Oxygenation Versus Usual Care During Rapid Sequence Intubation: A Randomized Controlled Trial (The ENDAO Trial). Acad Emerg Med. 2017 Nov;24(11):1387-1394. doi: 10.1111/acem.13274. Epub 2017 Sep 23.

24. Shahul Hameed IZ, Hazra D, Ganesan P, Prabhakar AKP. Does apneic oxygenation with nasopharyngeal cannula during intubation improve the oxygenation in patients with acute hypoxemic respiratory failure compared to the standard bag valve mask preoxygenation? An open-labeled randomized control trial. Turk J Emerg Med. 2024 Jan 8;24(1):33-40. doi: 10.4103/tjem.tjem_176_23.

25. Vourc'h M, Asfar P, Volteau C, Bachoumas K, Clavieras N, Egreteau PY, Asehnoune K, Mercat A, Reignier J, Jaber S, Prat G, Roquilly A, Brule N, Villers D, Bretonniere C, Guitton C. High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled clinical trial. Intensive Care Med. 2015 Sep;41(9):1538-48. doi: 10.1007/s00134-015-3796-z. Epub 2015 Apr 14.

26. Jaber S, Monnin M, Girard M, Conseil M, Cisse M, Carr J, Mahul M, Delay JM, Belafia F, Chanques G, Molinari N, De Jong A. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. Intensive Care Med. 2016 Dec;42(12):1877-1887. doi: 10.1007/s00134-016-4588-9. Epub 2016 Oct 11.

27. Simon M, Wachs C, Braune S, de Heer G, Frings D, Kluge S. High-Flow Nasal Cannula Versus Bag-Valve-Mask for Preoxygenation Before Intubation in Subjects With Hypoxemic Respiratory Failure. Respir Care. 2016 Sep;61(9):1160-7. doi: 10.4187/respcare.04413. Epub 2016 Jun 7.

28. Cırıl MF, Akarca M, Unal Akoglu E, Cimilli Ozturk T, Onur Ö. High-Flow Nasal Cannula versus Bag Valve Mask for Preoxygenation during Rapid Sequence Intubation in the Emergency Department: A Single-Center, Prospective, Randomized Controlled Trial. Prehosp Disaster Med. 2024 Feb;39(1):45-51. doi: 10.1017/S1049023X23006684. Epub 2023 Dec 18.

29. Mir F, Patel A, Iqbal R, Cecconi M, Nouraei SA. A randomised controlled trial comparing transnasal humidified rapid insufflation ventilatory exchange (THRIVE) pre-oxygenation with facemask pre-oxygenation in patients undergoing rapid sequence induction of anaesthesia. Anaesthesia. 2017 Apr;72(4):439-443. doi: 10.1111/anae.13799. Epub 2016 Dec 30.

30. Lodenius Å, Piehl J, Östlund A, Ullman J, Jonsson Fagerlund M. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) vs. facemask breathing pre-oxygenation for rapid sequence induction in adults: a prospective randomised non-blinded clinical trial. Anaesthesia. 2018 May;73(5):564-571. doi: 10.1111/anae.14215. Epub 2018 Jan 13.

31. Preya R, Ravishankar M, Sripriya R. Effectiveness of Face mask only oxygenation and apnoeic oxygenation in addition to face mask in sustaining PaO2 during rapid sequence induction - A randomized control trial. J Anaesthesiol Clin Pharmacol. 2023 Jul-Sep;39(3):366-371. doi: 10.4103/joacp.joacp_392_21. Epub 2023 Feb 16.

32. Bawa C, Raina J, Dureja M, Singh A, Yadav N, Kumar A. Intubation Performance with Stilet and Preloaded Bougie for Rapid Sequence Intubation in Patients Undergoing General Anaesthesia: A Randomised Clinical Trial. J Clin Diagn Res. 2022;16(7):UC15-9.

33. Driver BE, Semler MW, Self WH, Ginde AA, Trent SA, Gandotra S, et al. Effect of Use of a Bougie vs Endotracheal Tube With Stilet on Successful Intubation on the First Attempt Among Critically Ill Patients

Undergoing Tracheal Intubation: A Randomized Clinical Trial. JAMA. 2021;326(24):2488-97.

34. Driver BE, Prekker ME, Klein LR, Reardon RF, Miner JR, Fagerstrom ET, et al. Effect of Use of a Bougie vs Endotracheal Tube and Stilet on First-Attempt Intubation Success Among Patients With Difficult Airways Undergoing Emergency Intubation: A Randomized Clinical Trial. JAMA. 2018;319(21):2179-89.

35. Dutta A, Sethi N, Choudhary P, Gupta M, Malhotra S, Panday BC, et al. The impact of tracheal-tube introducer guided intubation in anticipated non-difficult airway on postoperative sore throat: a randomized controlled trial. Minerva Anestesiol. 2020;86(9):913-21.

36. Gataure PS, Vaughan RS, Latto IP. Simulated difficult intubation. Comparison of the gum elastic bougie and the stilet. Anaesthesia. 1996;51(10):935-8.

37. Ghai A, Bharti N, Jain M, Wadhera S, Singh AK, Wadhera R. Endotracheal Intubation with Laryngeal Mirror in Simulated Difficult Direct Laryngoscopy: Comparison of Gum Elastic Bougie Versus Stileted Endotracheal Tube. Indian J Otolaryngol Head Neck Surg Off Publ Assoc Otolaryngol India. 2022;74:5448-53.

38. Heegaard WG, Black C, Pasquerella C, Miner J. Use of the endotracheal tube introducer as an adjunct for oral tracheal intubation in the prehospital setting. Air Med J. 2003;22(1):28-31.

39. Khan R, Khan F, Azam M. Comparison of the stilet and the gum elastic bougie in tracheal intubation in a simulated difficult airway. Anaesth PAIN INTENSIVE CARE. 2014;18(3):256-9.

40. Noguchi T, Koga K, Shiga Y, Shigematsu A. The gum elastic bougie eases tracheal intubation while applying cricoid pressure compared to a stilet. Can J Anaesth J Can Anesth. 2003;50(7):712-7.

41. Nolan JP, Wilson ME. Orotracheal intubation in patients with potential cervical spine injuries. An indication for the gum elastic bougie. Anaesthesia. 1993;48(7):630-3.

42. Sut EY, Gunal S, Yazar MA, Dikmen B. [Comparison of effectiveness of intubation by way of "Gum Elastic Bougie" and "Intubating Laryngeal Mask Airway" in endotracheal intubation of patients with simulated cervical trauma]. Rev Bras Anestesiol. 2017;67(3):238-45.

43. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. Haziran 2018;27(6):1785-805.

44. Russotto V, Myatra SN, Laffey JG, Tassistro E, Antolini L, Bauer P, Lascarrou JB, Szuldrzynski K, Camporota L, Pelosi P, Sorbello M, Higgs A, Greif R, Putensen C, Agvald-Öhman C, Chalkias A, Bokums K, Brewster D, Rossi E, Fumagalli R, Pesenti A, Foti G, Bellani G; INTUBE Study Investigators. Intubation Practices and Adverse Peri-intubation Events in Critically Ill Patients From 29 Countries. JAMA. 2021 Mar 23;325(12):1164-1172. doi: 10.1001/jama.2021.1727.

45. Heffner AC, Swords D, Kline JA, Jones AE. The frequency and significance of postintubation hypotension during emergency airway management. J Crit Care. 2012 Aug;27(4):417.e9-13. doi: 10.1016/j.jcrc.2011.08.011. Epub 2011 Oct 26..

46. Weingart S. Push-dose pressors for immediate blood pressure control. Clin Exp Emerg Med. 2015 Jun 30;2(2):131-132. doi: 10.15441/ceem.15.010.

47. McPherson KL, Kovacic Scherrer NL, Hays WB, Greco AR, Garavaglia JM. A Review of Push-Dose Vasopressors in the Peri-operative and Critical Care Setting. J Pharm Pract. 2023 Aug;36(4):925-932. doi: 10.1177/08971900221096967. Epub 2022 Apr 22.

48. da Silveira F, de Oliveira LH, Nedel W, Lisboa TC. Effectiveness of prophylactic push-dose vasopressors for preventing arterial hypotension during elective orotracheal intubation: A systematic review and meta-analysis. J Crit Care. 2025 Sep 30;91:155275. doi: 10.1016/j.jcrc.2025.155275. Epub ahead of print.

49. Panchal AR, Satyanarayan A, Bahadir JD, Hays D, Mosier J. Efficacy of Bolus-dose Phenylephrine for Peri-intubation Hypotension. J Emerg Med. 2015;49(4):488-494. doi:10.1016/j.jemermed.2015.04.033

50. Schwartz MB, Ferreira JA, Aaronson PM. The impact of push-dose phenylephrine use on subsequent preload expansion in the ED setting. Am J Emerg Med. 2016 Dec;34(12):2419-2422. doi: 10.1016/j.ajem.2016.09.041. Epub 2016 Sep 22.

51. Swenson K, Rankin S, Daconti L, Villarreal T, Langsjoen J, Braude D. Safety of bolus-dose phenylephrine for hypotensive emergency department patients. Am J Emerg Med. 2018;36(10):1802-1806. doi:10.1016/j.ajem.2018.01.095

52. Rotando A, Picard L, Delibert S, Chase K, Jones CMC, Acquisto NM. Push dose pressors: Experience in critically ill patients outside of the operating room. Am J Emerg Med. 2019;37(3):494-498. doi:10.1016/j.ajem.2018.12.001

53. Davis DP, Olvera D, Selde W, Wilmas J, Stuhlmiller D. Bolus Vasopressor Use for Air Medical Rapid Sequence Intubation: The Vasopressor Intravenous Push to Enhance Resuscitation Trial. Air Med J. 2023;42(1):36-41. doi:10.1016/j.amj.2022.09.004

54. Fuchita M, Pattee J, Russell DW, et al. Prophylactic Administration of Vasopressors Prior to Emergency Intubation in Critically Ill Patients: A Secondary Analysis of Two Multicenter Clinical Trials. Crit Care Explor. 2023;5(7):e0946. Published 2023 Jul 12. doi:10.1097/CCE.0000000000000946

55. Schmitt CJ, Mattson AE, Brown CS, et al. The incidence of cardiovascular instability in patients receiving various vasopressor strategies for peri-intubation hypotension. Am J Emerg Med. 2023;65:104-108. doi:10.1016/j.ajem.2022.12.020

56. Singer S, Pope H, Fuller BM, Gibson G. The safety and efficacy of push dose vasopressors in critically ill adults. Am J Emerg Med. 2022;61:137-142. doi:10.1016/j.ajem.2022.08.055

57. Nam E, Fitter S, Moussavi K. Comparison of push-dose phenylephrine and epinephrine in the emergency department. Am J Emerg Med. 2022;52:43-49. doi:10.1016/j.ajem.2021.11.033

58. Nawrocki PS, Poremba M, Lawner BJ. Push dose epinephrine use in the management of hypotension during critical care tranSpOrt. Prehosp Emerg Care. 2020;24(2):188-195. doi:10.1080/10903127.2019.1588443

59. Chang LC, Raty SR, Ortiz J, Bailard NS, Mathew SJ. The emerging use of ketamine for anesthesia and sedation in traumatic brain injuries. CNS Neurosci Ther. 2013;19:390–5.

60. Shapiro HM, Wyte SR, Harris AB. Ketamine anaesthesia in patients with intracranial pathology. Br J Anaesth. 1972;44:1200–4

61. Gibbs JM. The effect of intravenous ketamine on cerebrospinal fluid pressure. Br J Anaesth. 1972;44:1298–302.

62. Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on ICP intraumatic brain injury. Neurocrit Care. 2014;21:163–73.

63. Schmittner MD, Vajkoczy SL, Horn P, Bertsch T, Quintel M, Vajkoczy P, et al. Effects of fentanyl and S(+)-ketamine on cerebral hemodynamics, gastrointestinal motility, and need of vasopressors in patients with intracranial pathologies: a pilot study. J Neurosurg Anesthesiol. 2007;19:257–62.

64. Bourgoin A, Albanèse J, Léone M, Sampol-Manos E, Viviand X, Martin C. Effects of sufentanil or ketamine administered in target-controlled infusion on the cerebral hemodynamics of severely brain-injured patients. Crit Care Med. 2005 May;33(5):1109-13. doi: 10.1097/01.ccm.0000162491.26292.98.

65. Bourgoin A, Albanèse J, Wereszczynski N, Charbit M, Vialet R, Martin C. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. Crit Care Med. 2003 Mar;31(3):711-7. doi: 10.1097/01.CCM.0000044505.24727.16.

66. Kolenda H, Gremmelt A, Rading S, Braun U, Markakis E. Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. Acta Neurochir (Wien). 1996;138(10):1193-9. doi: 10.1007/BF01809750. Erratum in: Acta Neurochir (Wien) 1997;139(12):1193.

67. Burman S, Chouhan RS, Kumar N, Mahajan C. Effect of Ketamine Analgosedation on Neurological Outcome in patients with Severe Traumatic Brain Injury: A Randomized Controlled Pilot Study. Neurocrit Care. 2025 May 13. doi: 10.1007/s12028-025-02274-5. Epub ahead of print.

68. Ben Yehuda Y, Watemberg N. Ketamine increases opening cerebrospinal pressure in children undergoing lumbar puncture. J Child Neurol. 2006 Jun;21(6):441-3. doi: 10.1177/08830738060210060601.

69. Michalczyk K, Sullivan JE, Berkenbosch JW. Pretreatment with midazolam blunts the rise in intracranial pressure associated with ketamine sedation for lumbar puncture in children. Pediatr Crit Care Med. 2013 Mar;14(3):e149-55. doi: 10.1097/PCC.0b013e31827204459.

70. Lyon RM, Perkins ZB, Chatterjee D, Lockey DJ, Russell MQ; Kent, Surrey & Sussex Air Ambulance Trust. Significant modification of traditional rapid sequence induction improves safety and effectiveness of pre-hospital trauma anaesthesia. Crit Care. 2015 Apr 1;19(1):134. doi: 10.1186/s13054-015-0872-2.

71. Cornelius BG, Webb E, Cornelius A, Smith KWG, Ristic S, Jain J, Cvek U, Trutschl M. Effect of sedative agent selection on morbidity, mortality and length of stay in patients with increase in intracranial pressure. World J Emerg Med. 2018;9(4):256-261. doi: 10.5847/wjem.j.1920-8642.2018.04.003.

72. Mudri M, Williams A, Priestap F, Davidson J, Merritt N. Comparison of drugs used for intubation of pediatric trauma patients. J Pediatr Surg. 2020 May;55(5):926-929. doi: 10.1016/j.jpedsurg.2020.01.041. Epub 2020 Jan 31.

73. Mazandi VM, Lang SS, Rahman RK, Nishisaki A, Beaulieu F, Zhang B, Griffis H, Tucker AM, Storm PB, Heuer GG, Gajjar AA, Ampah SB, Kirschen MP, Topjian AA, Yuan I, Francoeur C, Kilbaugh TJ, Huh JW. Co-administration of Ketamine in Pediatric Patients with Neurologic Conditions at Risk for Intracranial Hypertension. Neurocrit Care. 2023 Apr;38(2):242-253. doi: 10.1007/s12028-022-01611-2. Epub 2022 Oct 8.

74. Mansvelder FJ, Bossers SM, Loer SA, Bloemers FW, Van Lieshout EMM, Den Hartog D, Hoogerwerf N, van

der Naalt J, Absalom AR, Peerdeman SM, Bulte CSE, Schwarte LA, Schober P; BRAIN-PROTECT collaborators. Etomidate versus Ketamine as Prehospital Induction Agent in Patients with Suspected Severe Traumatic Brain Injury. Anesthesiology. 2024 Apr 1;140(4):742-751. doi: 10.1097/ALN.0000000000004894.

75. Loi MV, Lee JH, Huh JW, Mallory P, Napolitano N, Shults J, Krawiec C, Shenoi A, Polikoff L, Al-Subu A, Sanders R Jr, Toal M, Branca A, Glater-Welt L, Ducharme-Crevier L, Breuer R, Parsons S, Harwayne-Gidansky I, Kelly S, Motomura M, Gladen K, Pinto M, Giuliano J Jr, Bysani G, Berkenbosch J, Biagas K, Rehder K, Kasagi M, Lee A, Jung P, Shetty R, Nadkarni V, Nishisaki A; National Emergency Airway Registry for Children (NEAR4KIDS) Investigators, Pediatric Acute Lung Injury, Sepsis Investigators (PALISI) Network. Ketamine Use in the Intubation of Critically Ill Children with Neurological Indications: A Multicenter Retrospective Analysis. Neurocrit Care. 2024 Feb;40(1):205-214. doi: 10.1007/s12028-023-01734-0. Epub 2023 May 9.

76. Fouche PF, Meadley B, St Clair T, Winnall A, Jennings PA, Bernard S, Smith K. The association of ketamine induction with blood pressure changes in paramedic rapid sequence intubation of out-of-hospital traumatic brain injury. Acad Emerg Med. 2021 Oct;28(10):1134-1141. doi: 10.1111/acem.14256. Epub 2021 Apr 9.

77. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. J Neurosurg Pediatr. 2009 Jul;4(1):40-6. doi: 10.3171/2009.1.PEDS08319.

78. Caricato A, Tersali A, Pitoni S, De Waure C, Sandroni C, Bocci MG, Annetta MG, Pennisi MA, Antonelli M. Racemic ketamine in adult head injury patients: use in endotracheal suctioning. Crit Care. 2013 Nov 8;17(6):R267. doi: 10.1186/cc13097.

79. Dengler BA, Karam O, Barthol CA, Chance A, Snider LE, Mundy CM, Bounajem MT, Johnson WC, Maita MM, Mendez-Gomez PM, Seifi A, Hafeez S. Ketamine Boluses Are Associated with a Reduction in Intracranial Pressure and an Increase in Cerebral Perfusion Pressure: A Retrospective Observational Study of Patients with Severe Traumatic Brain Injury. Crit Care Res Pract. 2022 May 21;2022:3834165. doi: 10.1155/2022/3834165.

80. Laws JC, Vance EH, Betters KA, Anderson JJ, Fleishman S, Bonfield CM, Wellons JC 3rd, Xu M, Slaughter JC, Giuse DA, Patel N, Jordan LC, Wolf MS. Acute Effects of Ketamine on Intracranial Pressure in Children With Severe Traumatic Brain Injury. Crit Care Med. 2023 May 1;51(5):563-572. doi: 10.1097/CCM.0000000000005806. Epub 2023 Feb 21.

SUPPLEMENTARY FILES

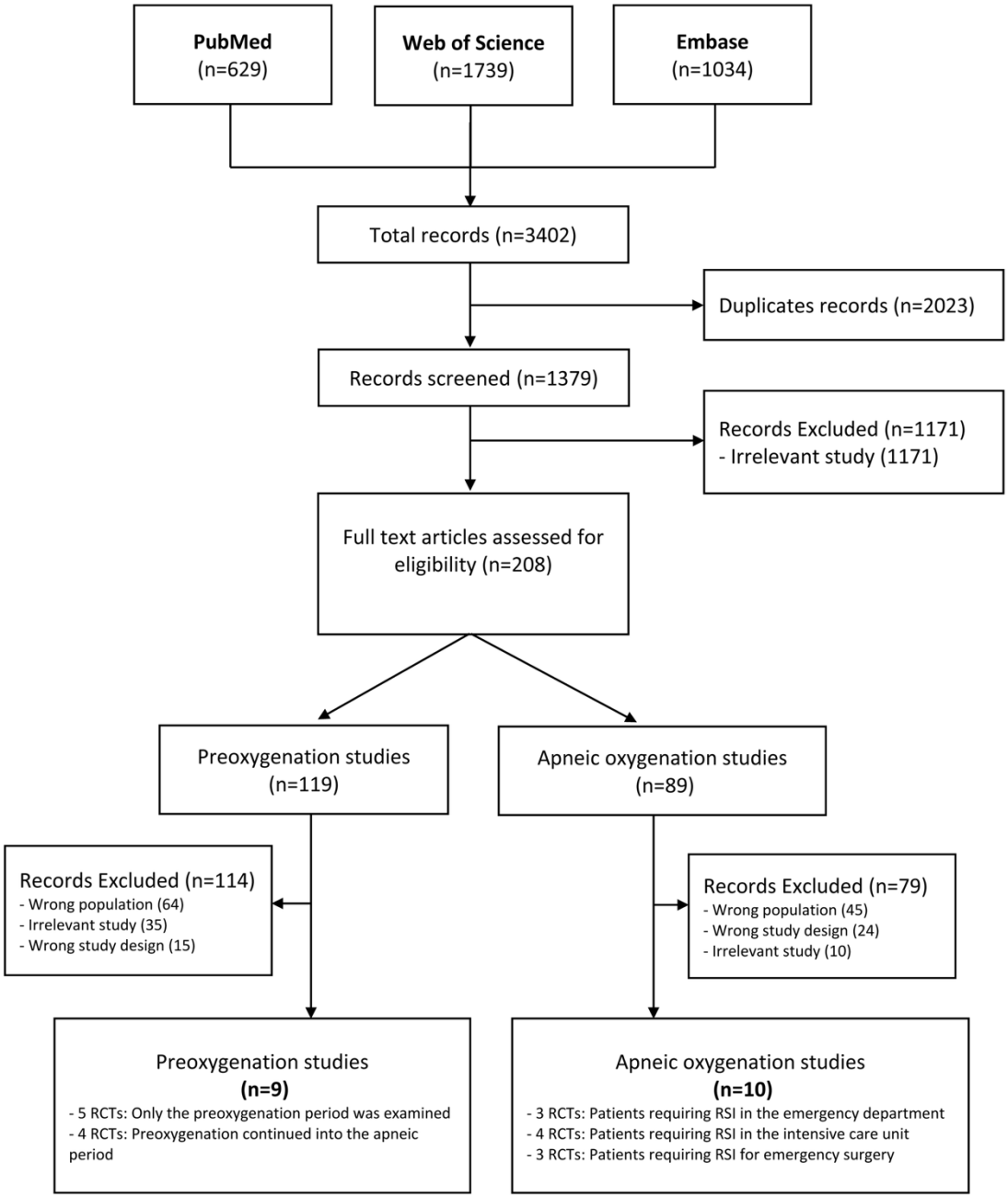
Supplementary File 1. Search queries (hedges) used in the systematic literature review

Search Queries	
Preoxygenation and Apneic Oxygenation	((((((((((Intubation[Title/Abstract]) OR (entubation[Title/Abstract])) OR (Intubation, Intratracheal[Title/Abstract])) OR (endotracheal intubation[Title/Abstract])) OR (tracheal intubation[Title/Abstract])) OR (infraglottic airway*[Title/Abstract])) OR (Anesthesia, General[Title/Abstract])) OR ((airway manag*[Title/Abstract]) OR (airway control[Title/Abstract])))) OR ((Rapid Sequence Intubation[Title/Abstract]) OR (Rapid Sequence Induction[Title/Abstract])))) AND ((((((((((((((((positive-pressure ventilation[Title/Abstract]) OR (bag mask[Title/Abstract])) OR (ambu[Title/Abstract])) OR (bag-assist technique[Title/Abstract])) OR (bag-mask ventilation[Title/Abstract])) OR (nonrebreather mask[Title/Abstract])) OR (non-rebreather mask[Title/Abstract])) OR (noninvasive ventilation[Title/Abstract])) OR (non-invasive ventilation[Title/Abstract])) OR (bilevel positive airway pressure[Title/Abstract])) OR (BiPAP[Title/Abstract])) OR (CPAP[Title/Abstract])) OR (high-flow nasal oxygen[Title/Abstract])) OR (Continuous Positive Airway Pressure[Title/Abstract])) OR (Biphasic Positive Airway Pressure[MeSH Terms])) OR ((((((((((High-flow Nasal Cannula[Title/Abstract]) OR (high flow nasal cannula oxygen therapy[Title/Abstract])) OR (HFNO[Title/Abstract])) OR (high-flow oxygen therapy[Title/Abstract])) OR (high flow nasal oxygen[Title/Abstract])) OR (HFNC[Title/Abstract])) OR (High-Flow Humidified Oxygen[Title/Abstract])) OR (High flow nasal cannula oxygenation[Title/Abstract])) OR (high flow oxygen[Title/Abstract])))) OR ((nasopharyngeal oxygen[Title/Abstract]) OR ((((apne* oxygen*[Title/Abstract]) OR (passive oxygen*[Title/Abstract])) OR (passive ventilation[Title/Abstract])) OR (apnoic oxygen*[Title/Abstract])))))) AND ((((Oxygenation[Title/Abstract]) OR (preoxygenat*[Title/Abstract])) OR (pre-oxygenat*[Title/Abstract])) OR (preoxygenated[Title/Abstract])))) NOT ((((review[Title]) OR (review[Publication Type])) OR ((Meta Analysis[Publication Type]) OR (Meta Analysis[Title])))) OR (Case reports[Publication Type]))
Gum Elastic Bougie	((((((Rapid Sequence Intubation[Title/Abstract]) OR (Rapid Sequence Induction[Title/Abstract])) OR (((((((Intubation[Title/Abstract]) OR (entubation[Title/Abstract])) OR (Intubation, Intratracheal[Title/Abstract])) OR (endotracheal intubation[Title/Abstract])) OR (tracheal intubation[Title/Abstract])) OR (infraglottic airway*[Title/Abstract])) OR (Anesthesia, General[Title/Abstract])))) OR (airway manag*[Title/Abstract])) AND ((((((((ETT introducer[Title/Abstract]) OR (gum elastic bougie[Title/Abstract])) OR (endotracheal tube introducer[Title/Abstract])) OR (tracheal tube introducer[Title/Abstract])) OR (bougie[Title/Abstract])) OR (Frova guide[Title/Abstract])) OR (Eschman introducer[Title/Abstract])) OR (bougie stylet[Title/Abstract])) OR (rigid stylet[Title/Abstract])))) NOT (((review[Title]) OR (review[Publication Type])) OR ((Meta Analysis[Publication Type]) OR (Meta Analysis[Title]))))) NOT (Case reports[Publication Type])
Push-Dose Vasopressor	((((((((((Intubation[Title/Abstract]) OR (entubation[Title/Abstract])) OR (Intubation, Intratracheal[Title/Abstract])) OR (endotracheal intubation[Title/Abstract])) OR (tracheal intubation[Title/Abstract])) OR (infraglottic airway*[Title/Abstract])) OR (Anesthesia, General[Title/Abstract])) OR (airway manag*[Title/Abstract])) AND ((((((((((((((((((((Vasoconstrictor Agents[Title/Abstract]) OR (Vasopressor Agent[Title/Abstract])) OR (Vasoactive Agonists[Title/Abstract])) OR (Epinephrine[Title/Abstract])) OR (norepinephrine[Title/Abstract])) OR (Adrenaline[Title/Abstract])) OR (Epitrate[Title/Abstract])) OR (Lyophrin[Title/Abstract])) OR (Epifrin[Title/Abstract])) OR (Catecholamines[Title/Abstract])) OR (Sympathin[Title/Abstract])) OR (Dobutamine[Title/Abstract])) OR (Dopamine[Title/Abstract])) OR (Intropin[Title/Abstract])) OR (Vasopressins[Title/Abstract])) OR (Ephedrine[Title/Abstract])) OR (Phenylephrine[Title/Abstract])) OR

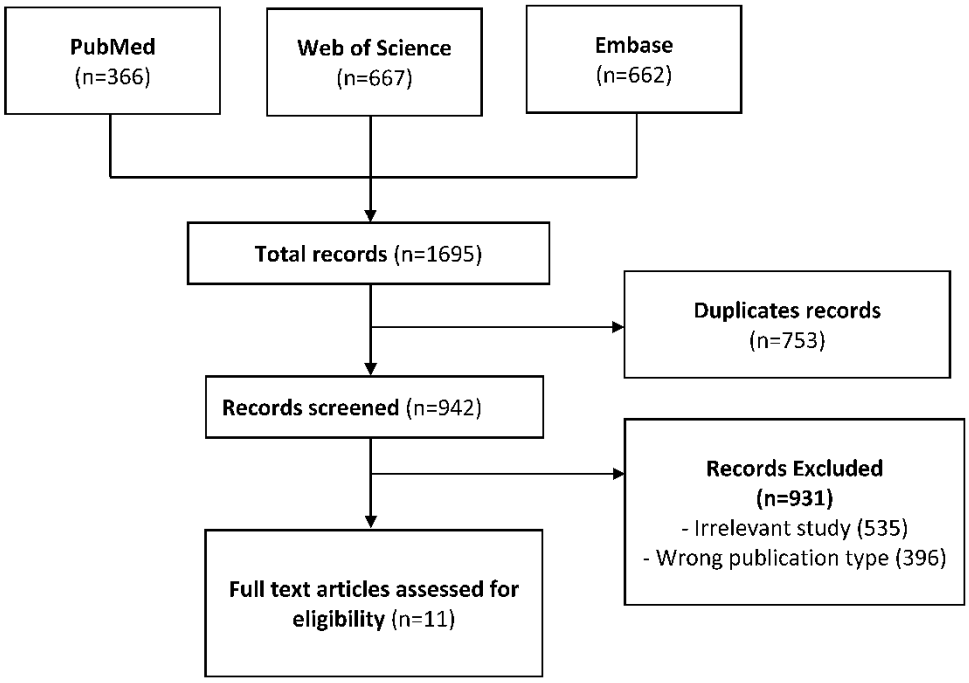
	(Metaoxedrin[Title/Abstract])) OR (Isoproterenol[Title/Abstract])) OR (pressor[Title/Abstract]))) NOT (((review[Title]) OR (review[Publication Type])) OR ((Meta Analysis[Publication Type]) OR (Meta Analysis[Title]))))) NOT (Case reports[Publication Type])
Ketamine	(((((Rapid Sequence Intubation[Title/Abstract]) OR (Rapid Sequence Induction[Title/Abstract])) OR (((((Intubation[Title/Abstract]) OR (entubation[Title/Abstract])) OR (Intubation, Intratracheal[Title/Abstract])) OR (endotracheal intubation[Title/Abstract])) OR (tracheal intubation[Title/Abstract]))) OR (airway manag*[Title/Abstract])) AND (("Ketamine"[MeSH Terms] OR ("Ketamine"[Title/Abstract] OR "Ketamine Hydrochloride"[Title/Abstract] OR "Ketalar"[Title/Abstract] OR "Ketaset"[Title/Abstract] OR "Ketanest"[Title/Abstract] OR "Ketaject"[Title/Abstract] OR "CI-581"[Title/Abstract] OR "2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone"[Title/Abstract]))))) AND ((((("Acute Brain Injury"[Title/Abstract] OR "Acute Cerebral Injury"[Title/Abstract] OR "Acute Brain Damage"[Title/Abstract] OR "Acute Cerebral Damage"[Title/Abstract] OR "Acute Brain Trauma"[Title/Abstract] OR "Acute Cerebral Trauma"[Title/Abstract])) OR ("Traumatic Brain Injury"[Title/Abstract] OR "Head Trauma"[Title/Abstract] OR "Head Injury"[Title/Abstract] OR "Cranial Trauma"[Title/Abstract] OR "Cranial Injury"[Title/Abstract] OR "Cerebral Trauma"[Title/Abstract] OR "Cerebral Injury"[Title/Abstract] OR "Brain Trauma"[Title/Abstract])) OR (("Intracranial Pressure"[MeSH Terms] OR ("Intracranial Pressure"[Title/Abstract] OR "Intracranial Hypertension"[Title/Abstract] OR "Raised Intracranial Pressure"[Title/Abstract] OR "Increased Intracranial Pressure"[Title/Abstract] OR "Intracranial Tension"[Title/Abstract] OR "Intracranial Hypertensive Syndrome"[Title/Abstract] OR "Cerebral Pressure"[Title/Abstract]))))

Supplementary File 2. Flow diagrams of the studies identified through the systematic literature search.

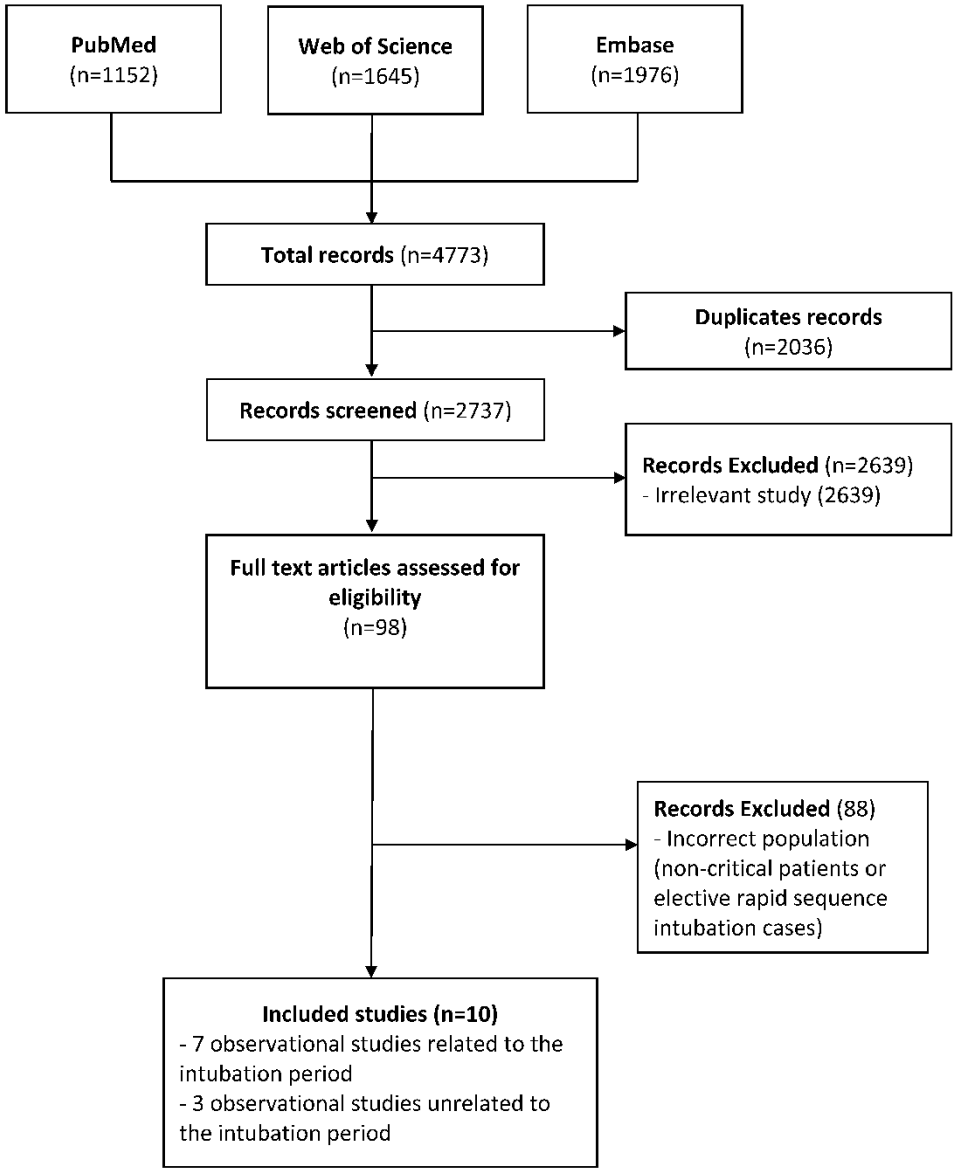
1. Flow diagram of the systematic literature search for studies evaluating preoxygenation methods and adjunctive apneic oxygenation during rapid sequence intubation in the emergency department.



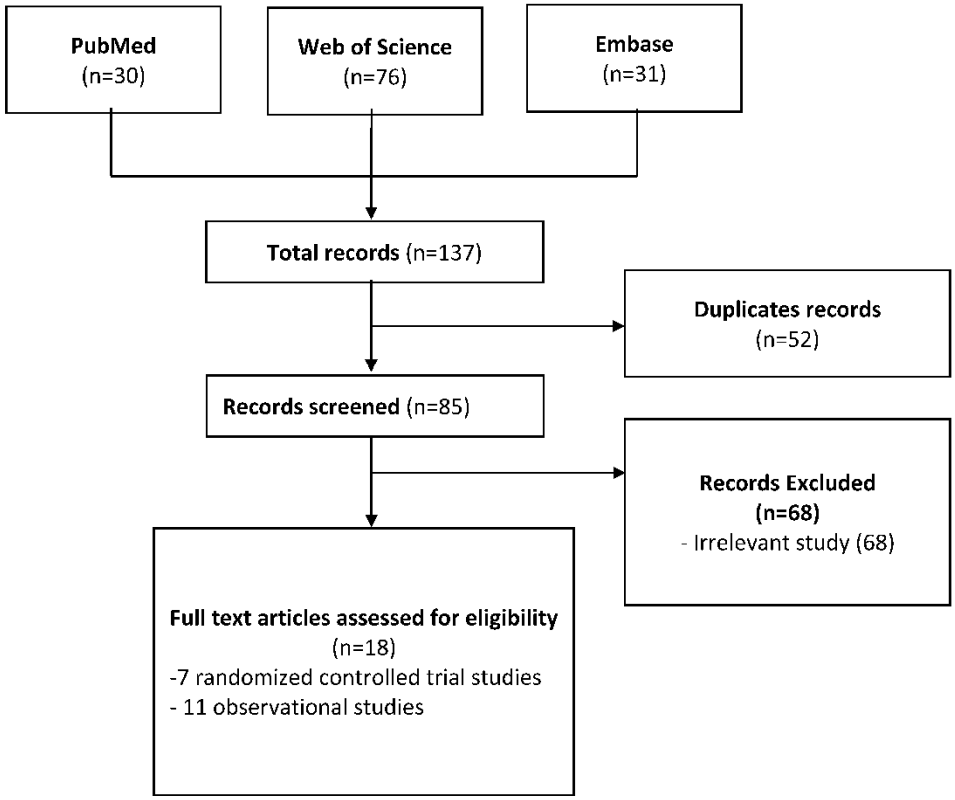
2. Flow diagram of the systematic literature search for studies comparing the use of a gum elastic bougie with standard intubation (with or without a stylet) during rapid sequence intubation in the emergency department.



3. Flow diagram of the systematic literature search for studies evaluating the use of push-dose vasopressors during or immediately before rapid sequence intubation in hypotensive adult patients or those at high risk of hypotension in the emergency department.



4. Flow diagram of the systematic literature search for studies evaluating ketamine use during rapid sequence intubation in patients with acute brain injury at risk of increased intracranial pressure.



Supplementary File 3. Summary tables of the studies (5 tables).

Table 1. Summaries of Studies Comparing Different Preoxygenation Methods in Patients Undergoing Rapid Sequence Intubation

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Studies in which oxygenation was not applied during the apneic period (pure preoxygenation studies)						
Baillard 2006	Single-center, open-label, randomized controlled trial.	**Inclusion Criteria:** Adult patients admitted to medical or surgical ICUs with acute respiratory failure and hypoxemia (PaO_2 <100 mmHg while receiving 10 L/min oxygen via face mask).. **Exclusion Criteria:** Encephalopathy, coma, cardiac resuscitation, hyperkalemia (≥5.5 mEq/L), and patients with a prior failed trial of NIMV.	**Group 1 (NIMV):** Preoxygenation with NIMV using an ICU ventilator via face mask (FiO_2 100%, PEEP 5 cmH_2O), with tidal volume set at 7–10 mL/kg. **Group 2 (BVM):** Preoxygenation with a non-rebreather bag-valve-mask at 15 L/min oxygen, allowing spontaneous breathing with intermittent assistance as needed.	**Primary outcome:** Mean decrease in SpO_2 during intubation. **Secondary outcomes:** PaO_2 measured at 5 and 30 minutes after intubation.	A total of 57 patients were included (29 in the NIMV group, 28 in the control group). After preoxygenation, SpO_2 increased significantly more in the NIMV group (from 89 ± 6% to 98 ± 2%) compared with the control group (from 90 ± 5% to 93 ± 6%) ($p < 0.05$). The lowest SpO_2 during intubation was higher in the NIMV group (93 ± 8% vs 81 ± 15%; $p < 0.001$), and fewer patients experienced SpO_2 < 80% (2 vs 12; $p < 0.01$). PaO_2 values at the end of preoxygenation and at 5 and 30 minutes after intubation were also significantly higher in the NIMV group ($p < 0.01$).	None

Baillard 2018	Multicenter, assessor-blinded, randomized controlled trial.	**Inclusion Criteria:** Adult ICU patients with acute hypoxemic respiratory failure requiring intubation (PaO_2/FiO_2 ≤300 mmHg and SpO_2 ≤95% on room air). **Exclusion Criteria:** Age <18 years, pregnancy, cardiac arrest, facial trauma or deformity, respiratory arrest, do-not-intubate decision, and need for urgent/emergent intubation.	**Group 1 (NIMV):** Preoxygenation for 3 minutes before intubation using NIMV via a face mask with 100% FiO_2 (pressure support 8 cmH_2O, PEEP 5 cmH_2O). **Group 2 (Face mask):** Preoxygenation for 3 minutes using a nonrebreather face mask with 100% oxygen at a flow rate of 15 L/min.	**Primary outcome:** Maximum Sequential Organ Failure Assessment (SOFA) score within 7 days after intubation. **Secondary outcomes:** Severe hypoxemia during intubation (SpO_2 <80%), adverse events (arrhythmia associated with hemodynamic deterioration, regurgitation, myocardial ischemia, failure of preoxygenation), number of organ failures, ICU-free and ventilator-free days within 28 days, ICU mortality within 28 days.	Total number of patients: 201 (NIMV: 99, Face mask: 102). Median maximum SOFA score within the first 7 days: NIMV group 9 [IQR 6–12], Face mask group 10 [IQR 6–12]; p=0.65. Number of organ failures per patient: 1 [0–2] in both groups; p=0.42. Severe hypoxemia during intubation (SpO_2 <80%): NIMV 18.4% vs Face mask 27.7%; p=0.10. Preoxygenation failure: 5 patients (4.9%) in the Face mask group, 0 in the NIMV group. Among patients previously receiving NIMV, intubation-related adverse events were more frequent in the Face mask group compared with the NIMV group (OR 5.2; 95% CI 1.4–19.5; p=0.006). There were no significant differences between groups in 28-day mortality, ventilator-free days, or ICU-free days.	None

Guitton 2019	Multicenter, open-label, randomized controlled trial.	**Inclusion** Criteria: Adult patients (≥18 years) admitted to the ICU who required endotracheal intubation and had a PaO_2/FiO_2 ≥200 within the 4 hours prior to enrollment. **Exclusion Criteria:** Anatomical nasopharyngeal obstruction, Cormack–Lehane grade 4 glottic view, patients under legal protection, pregnancy, lack of informed consent, prior endotracheal intubation in the ICU, intubation without rapid sequence induction (e.g., during cardiac arrest), fiberoptic intubation, and conditions requiring emergent airway management due to asphyxia.	**Group 1 (HFNO):** Preoxygenation using high-flow nasal oxygen therapy at a flow rate of 60 L/min. **Group 2 (BVM):** Standard preoxygenation using a disposable, self-inflating bag-valve-mask with reservoir, delivering 100% oxygen at 15 L/min.	**Primary outcome:** Median lowest SpO_2 measured during intubation. **Secondary outcomes:** SpO_2 levels from the start of preoxygenation to the end of intubation; episodes of SpO_2 dropping below 95%, 90%, and 80%; incidence of difficult intubation; adverse events and organ failure within the first 5 days; duration of mechanical ventilation; length of ICU stay; incidence of ventilator-associated pneumonia; 28-day mortality.	Total of 183 patients (HFNO: 94, BVM: 89). The median [IQR] lowest SpO_2 during intubation was 100% [97–100] in the HFNO group and 99% [95–100] in the BVM group, with no statistically significant difference between groups (p=0.30). In multivariable analysis, HFNO was associated with a lower frequency of desaturation below 90% and fewer intubation-related complications, as well as a trend toward reduced oxygen desaturation below 80% (p=0.058).	None .

Gibbs 2024	Multicenter, open-label, randomized controlled trial.	**Inclusion Criteria:** Critically ill patients aged ≥18 years undergoing tracheal intubation with sedation and laryngoscopy in 7 emergency departments and 17 intensive care units. **Exclusion Criteria:** Pregnant patients, prisoners, patients already receiving positive-pressure ventilation, presence of apnea/hypopnea, need for emergent intubation, and cases in which the operator deemed NIMV or an oxygen mask to be mandatory or contraindicated.	**Group 1 (NIMV):** NIMV delivered via a tight-fitting mask using a mechanical or dedicated NIMV ventilator; FiO_2 100%, EPAP ≥5 cmH_2O, IPAP ≥10 cmH_2O, respiratory rate ≥10/min; applied from the start of preoxygenation until laryngoscopy. **Group 2 (Oxygen Mask):** Supplemental oxygen via a non-rebreather mask or bag-valve-mask device (without manual ventilation); highest available oxygen flow (≥15 L/min); applied until laryngoscopy.	**Primary outcome:** Hypoxemia (SpO_2 <85%) from induction of anesthesia until the 2nd minute after intubation. **Secondary outcomes:** Lowest SpO_2 during the same interval; hemodynamic events (hypotension, vasopressor use, cardiac arrest); markers of aspiration (clinical, radiologic, physiologic).	Total of 1301 patients (645 NIMV, 656 oxygen mask). Hypoxemia occurred in 9.1% (57/624) of the NIMV group and 18.5% (118/637) of the oxygen mask group (absolute risk difference: −9.4%, 95% CI −13.2 to −5.6; P<0.001). Median lowest SpO_2: 99% [IQR 95–100] with NIMV versus 97% [IQR 89–100] with oxygen mask (median difference: 2%; 95% CI 1–3). The effect of NIMV was more pronounced in patients with higher BMI.	None

Li 2024	Single-center, open-label, randomized controlled trial.	**Inclusion Criteria:** Adults aged 18–60 years of either sex, requiring emergency surgery; fasting duration <8 hours and no fluid intake within the last <2 hours; body mass index (BMI) 18–35 kg/m²; ASA Physical Status I–III; NYHA functional class I–II. **Exclusion Criteria:** Pregnancy; high risk of aspiration (e.g., bowel obstruction, diaphragmatic hernia, altered mental status); presence of a gastric tube; contraindications to nasopharyngeal airway placement.	**Group 1 (HFNO):** 100% oxygen delivered via a nasopharyngeal airway at a flow rate of 30–60 L/min. **Group 2 (Mask Group):** 100% oxygen delivered via a face mask securely fixed with a four-point head strap at a flow rate of 8 L/min. Preoxygenation was applied for 3 minutes with instructions for deep breathing.	**Primary outcome:** Arterial partial pressure of carbon dioxide ($PaCO_2$) at T1, T2, and T3. **Secondary outcomes:** Arterial partial pressure of oxygen (PaO_2) at T1–T3; gastric antrum cross-sectional area (CSA) at T1 and T3; complication rate. Timeline: Preoxygenation (T0), post-induction (T1), post-intubation (T2), post-initiation of mechanical ventilation (T3).	Total of 115 patients (58 HFNO, 57 Mask). $PaCO_2$ was significantly lower in the HFNO group at all time points: T1 (32.3 vs 34.6 mmHg, P=0.045), T2 (45.0 vs 49.4 mmHg, P<0.001), T3 (47.9 vs 52.9 mmHg, P<0.001). PaO_2 was significantly higher in the HFNO group at T1 (median 404.5 vs 358.9 mmHg, P=0.007), T2 (343.0 vs 258.3 mmHg, P<0.001), and T3 (333.5 vs 149.8 mmHg, P<0.001). There was no significant difference between groups in CSA measurements. Hypoxemia occurred in 1 patient (1.7%) in the HFNO group and in 9 patients (15.8%) in the mask group (P=0.019). There were no significant differences between groups with respect to other complications.	None
Studies in which preoxygenation continued throughout the apneic period						

Frat 2019	Multicenter, open-label, randomized controlled trial.	**Inclusion Criteria:** Patients aged ≥18 years admitted to the ICU with acute hypoxemic respiratory failure requiring intubation. **Exclusion Criteria:** Intubation due to cardiac arrest, Glasgow Coma Scale <8, contraindications to NIMV, pregnant or breastfeeding women, and patients who refused participation.	**Group 1 (NIMV):** Preoxygenation was performed using a face mask connected to an ICU ventilator. Pressure support was adjusted to achieve an expiratory tidal volume of 6–8 mL/kg of predicted body weight; PEEP 5 cmH_2O, FiO_2 1.0. **Group 2 (HFNO):** Preoxygenation was performed by delivering continuous oxygen at a flow of 60 L/min via a bi-nasal cannula. High-flow oxygen provides oxygenation during preoxygenation, between induction and laryngoscopy, and throughout laryngoscopy (apneic oxygenation), but has a limited ventilatory effect.	**Primary outcome:** PaO_2 after tracheal intubation.	There were 142 patients in Group 1 and 171 patients in Group 2. The mean (SD) PaO_2 was 43.7 (15.2) kPa in the apneic oxygenation group and 41.9 (16.2) kPa in the control group (p=0.722); $PaCO_2$ values were 5.8 (1.1) kPa and 5.6 (1.0) kPa, respectively (p=0.631); arterial pH values were 7.36 (0.05) and 7.34 (0.06), respectively (p=0.447).	The study was not blinded, and the authors noted that the more controlled and careful laryngoscopy/intubation performed in the intervention group may have attenuated any potential superiority of the technique with respect to arterial blood gas outcomes. Because patients with pre-existing respiratory distress were excluded in this study, the degree of indirectness is high.

Chua 2022	Multicenter, open-label, randomized controlled trial.	**Inclusion Criteria:** Patients aged ≥21 years requiring RSI for any indication. **Exclusion Criteria:** Active do-not-resuscitate order; crash, awake, or delayed sequence intubations; need for NIMV; cardiac arrest; suspected or confirmed skull base fracture or severe facial trauma preventing nasal cannula placement; pregnancy; incarceration.	**Group 1 (NRB Group):** Preoxygenation with NRB mask at flush flow only, followed by apneic oxygenation via nasal cannula at ≥15 L/min HFNO. **Group 2 (HFNO):** The HFNO group received heated and humidified oxygen at 37 °C with a flow of 60 L/min and >90% FiO_2 during both the preoxygenation and apneic oxygenation phases.	**Primary outcome:** The lowest SpO_2 recorded during the first intubation attempt. **Secondary outcomes:** Incidence of SpO_2 dropping below 90% and safe apnea time (the duration until successful intubation while SpO_2 remained ≥90%).	There were 93 patients in the control group and 97 patients in the intervention group. There was no statistically significant difference between the intervention and control groups in terms of the lowest SpO_2 recorded during the first intubation attempt (median SpO_2 100% [96.0–100] vs 100% [91.0–100], p=0.138). In quantile regression analysis adjusting for significant covariates, the first quartile of the lowest SpO_2 achieved during the first intubation attempt was 5.5% higher in the intervention group compared with the control group (95% CI 1.5–9.5, p=0.007). The median safe apnea time was 10 minutes in the intervention group and 7 minutes in the control group, corresponding to a 3.0-minute longer duration in the intervention group (p=0.082).	The use of HFNO for preoxygenation and apneic oxygenation did not improve the median lowest SpO_2 achieved during the first intubation attempt compared with usual care. However, this approach may prolong the safe apnea time.

Tarigonda 2023	Randomized clinical trial	**Inclusion Criteria:** ICU-admitted patients aged 18–65 years with hypoxemic respiratory failure who were hemodynamically stable. **Exclusion Criteria:** Suspected difficult airway, contraindication to nasopharyngeal airway placement, contraindication to NIMV, pregnancy/breastfeeding.	**Group 1 (NIMV + NC):** Preoxygenation for 5 minutes with NIMV using FiO_2 100%, 5 cmH_2O PEEP, and 10 cmH_2O pressure support. Apneic oxygenation was provided using a nasal cannula at a flow rate of 15 L/min. **Group 2 (NIMV + NPA):** Preoxygenation again for 5 minutes with NIMV using FiO_2 100%, 5 cmH_2O PEEP, and 10 cmH_2O pressure support. Apneic oxygenation was provided via a nasopharyngeal airway connected to the ventilator circuit with 10 cmH_2O CPAP and FiO_2 100%.	**Primary outcome:** The decrease in SpO_2 between peri-intubation oxygenation techniques when oxygen is delivered via nasal cannula versus CPAP delivered via a nasopharyngeal airway. **Secondary outcomes:** Intubation difficulty assessed using the Intubation Difficulty Scale (IDS); incidence of adverse events such as bradyarrhythmia/tachyarrhythmia and cardiac arrest.	Twenty-five patients were included in each group. The lowest SpO_2 recorded after intubation was 93.96 ± 4.38 in Group 1 and 96.08 ± 4.6 in Group 2 (p = 0.104).	None
Karlupia 2023	Single-center, open-label, randomized controlled trial.	**Inclusion Criteria:** Adult patients requiring rapid sequence intubation (RSI) for emergency abdominopelvic surgery. **Exclusion Criteria:** Pregnancy, severe cardiopulmonary disease, laryngotracheal stenosis, suspected or confirmed skull base fracture or facial trauma preventing nasal cannula placement, hypopharyngeal obstruction, BMI ≥40 kg/m².	**Group 1 (HFNO):** Preoxygenation was performed using HFNO at a flow rate of 60 L/min and was continued throughout the apneic period and during laryngoscopy. **Group 2 (Face Mask):** Preoxygenation was performed using a face mask delivering oxygen at 12 L/min and was continued throughout the apneic period.	**Primary outcome:** PaO_2 measured immediately after intubation (ABG). **Secondary outcomes:** Lowest SpO_2 within the first 5 minutes after intubation, apnea duration, number of laryngoscopy attempts, use of rescue maneuvers, and adverse events such as desaturation (SpO_2 ≤90%) or hemodynamic instability.	A total of 80 patients were included (40 in each group). The mean PaO_2 was 258 ± 106 mmHg in Group 1 and 239 ± 107 mmHg in Group 2 (P > 0.05). There were no significant differences between the groups in terms of $PaCO_2$, pH, HCO_3, or lactate values. The median lowest SpO_2 was similar between groups (97% in Group 1 vs 97.5% in Group 2, P > 0.05). There were no significant differences with respect to adverse events or the use of rescue maneuvers.	None

RSI: Rapid sequence intubation, ICU: Intensive care unit, NC: Nasal cannula, NRB: Non-rebreather mask, BiPAP: Bilevel Positive Airway Pressure, BVM: Bag-valve-mask, HFNC: High-flow nasal cannula, SpO_2: Oxygen saturation, NIMV: Non-invasive mechanical ventilation, ASA: American Society of Anesthesiologists, NYHA: New York Heart Association, NPA: Nasopharyngeal airway.

Table 2. Summaries of Studies Investigating the Effectiveness of Apneic Oxygenation in Patients Undergoing Rapid Sequence Intubation

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Studies Using the Same Preoxygenation Techniques						
Semler 2016	Single-center, open-label, randomized controlled trial.	**Inclusion Criteria:** Patients aged ≥18 years who will undergo endotracheal intubation in the medical ICU. **Exclusion Criteria:** Planned awake intubation, cases requiring intubation too urgently to allow randomization, and situations in which the use of a specific intraprocedural oxygenation method or laryngoscopy device is mandatory.	**Control:** Usual preoxygenation method (NRB, BiPAP, BVM, or standard nasal cannula). **Apneic** Oxygenation arm: In addition to the usual preoxygenation method, HFNC (15 L/min) was initiated prior to induction.	**Primary outcome:** Lowest SpO_2 level at 0 minutes after intubation. **Secondary outcomes:** Rates of severe desaturation defined as SpO_2 <80% and SpO_2 <90%.	There were 73 patients in the control group and 77 patients in the apneic oxygenation group. The median lowest SpO_2 was measured as 90% (80–96%) in the control group and 92% (84–99%) in the intervention group; there was no statistically significant difference between the groups (p=0.16). Apneic oxygenation did not affect the proportion of patients who experienced oxygen saturation <90%, <80%, or a desaturation greater than 3% during the procedure.	The results of this clinical study show that, in critically ill adult patients, apneic oxygenation during endotracheal intubation does not increase the lowest arterial oxygen saturation compared with usual care. Routine use of apneic oxygenation during emergency intubations is not recommended.
Caputo 2017	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: All adult patients aged ≥18 years presenting to the emergency department who required endotracheal intubation were included in the study. Exclusion Criteria: Patients who did not undergo 3 minutes of preoxygenation with 100% FiO_2 according to standard RSI protocol (via BVM, BiPAP, or NRB), patients in cardiac or traumatic arrest, and patients	Control: Usual preoxygenation method (NRB, BiPAP, or BVM). Apneic Oxygenation: In addition to the usual preoxygenation method, HFNO (>15 L/min) was started simultaneously and continued until the end of intubation (apneic phase).	Primary outcome: Lowest SpO_2 during the RSI procedure. Secondary outcomes: SpO_2 <80% (severe desaturation), SpO_2 <90% desaturation, and first-attempt intubation success rate.	There were 102 patients in the control group and 104 patients in the intervention group. The mean lowest SpO_2 was 93% (SD 5.1) in the control group and 92% (SD 5.1) in the apneic oxygenation group, with no statistically significant difference between groups (p=0.08). Severe desaturation (SpO_2 <80%) occurred in 4 patients in the control group and 3 patients in the apneic oxygenation group.	This study demonstrated that, in patients who received adequate preoxygenation during rapid sequence intubation in the emergency department, the use of apneic oxygenation did not result in a significant difference in mean lowest oxygen saturation, rates of

		intubated without an apneic period were excluded from the study.				desaturation, or successful intubation without hypoxemia.
Shahul Hameed 2024	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Patients aged ≥18 years presenting to the emergency department with acute hypoxemic respiratory failure requiring RSI were included in the study. Exclusion Criteria: Patients whose relatives did not provide consent, pregnancy, contraindication to nasopharyngeal cannula placement, and patients assessed as having a difficult airway were excluded from the study.	Control: Standard preoxygenation using a BVM. Apneic Oxygenation: In addition to preoxygenation via BVM, nasopharyngeal oxygen therapy (>15 L/min) was initiated simultaneously and continued until the completion of intubation (apneic phase).	Primary outcome: Lowest SpO_2 levels immediately after intubation (0 minute).	There were 38 patients in the control group and 38 patients in the intervention group. The median SpO_2 was 89% (76–98%) in the control group and 95% (80–99%) in the intervention group, with no statistically significant difference between groups (p=0.27).	In the intervention group, there was no significant difference in the incidence of hypoxemia during intubation or in the prevention of post-intubation adverse events.
Studies Using Different Preoxygenation Techniques						
Vourc'h 2015	Multicenter, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients aged ≥18 years with acute hypoxemic respiratory failure requiring endotracheal intubation. Exclusion Criteria: Contraindication to orotracheal intubation; intubation without rapid sequence induction (RSI); pregnancy or lack of informed consent.	Control: Preoxygenation using only a face mask with 15 L/min oxygen. Apneic Oxygenation: Preoxygenation and apneic oxygenation using HFNO at a flow rate of 60 L/min.	Primary outcome: Lowest SpO_2 during the RSI procedure. Secondary outcome: SpO_2 <90% (desaturation).	A total of 62 patients were included in the intervention group and 57 patients in the control group. The median lowest SpO_2 was 89.5% (81–95) in the control group and 91.5% (80–96) in the intervention group, with no significant difference between groups (p=0.44). Severe desaturation (SpO_2 <90%) occurred in 2 patients (3.5%) in the control group and 4 patients (6.5%) in the intervention group (p=0.49).	Despite its theoretical advantages, HFNO therapy in acutely severely hypoxemic patients was not found to be more effective than a high-FiO_2 face mask in preventing desaturation during endotracheal intubation.
Jaber 2016	Single-center, double-blind, randomized controlled trial.	Inclusion Criteria: Patients admitted to the intensive care unit requiring mechanical ventilation via an orotracheal tube were included in the study.	Control: Preoxygenation for 4 minutes in a 30° head-up position using NIMV alone (PS 10 cmH_2O, PEEP 5 cmH_2O, FiO_2 100%).	Primary outcome: Lowest SpO_2 during the RSI procedure. Secondary outcomes: SpO_2 <80% (severe desaturation),	A total of 25 patients were included in the apneic oxygenation group and 24 patients in the control group. The mean lowest SpO_2 was 91.5% (SD 12.5) in the control group and 94.6% (SD	The results did not indicate any safety concerns and suggest that this novel approach may be more

		Exclusion Criteria: Patients under 18 years of age, pregnant or breastfeeding women, individuals under legal protection, patients in cardiocirculatory arrest, nasopharyngeal obstruction preventing HFNO use, and patients with standard contraindications to NIMV were excluded.	Apneic Oxygenation: In addition to NIMV, HFNO (60 L/min) was started simultaneously with preoxygenation and continued until the completion of intubation (apneic phase).	intubation-related complications, and ICU morbidity.	15) in the intervention group; the difference was not statistically significant (p=0.08). Severe desaturation (SpO_2 <80%) occurred in 5 patients (21%) in the control group and 4 patients (16%) in the intervention group.	effective than the reference method using NIMV alone in increasing the minimal SpO_2 values during intubation in critically ill patients with severe hypoxemic respiratory failure.
Simon 2016	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients (≥18 years) admitted to the ICU with acute hypoxemic respiratory failure (PaO_2/FiO_2 ≤300 mmHg) requiring endotracheal intubation. Exclusion Criteria: Contraindications to HFNO or BVM, nasopharyngeal obstruction, need for emergent intubation, and difficult or known difficult airway.	Control: Standard preoxygenation method using BVM with 10 L/min oxygen. Apneic Oxygenation: Preoxygenation and apneic oxygenation using HFNO at a flow rate of 50 L/min.	Primary outcome: Lowest SpO_2 during the RSI procedure. Secondary outcomes: Intubation-related complications and severe desaturation (SpO_2 <80%).	Each group consisted of 20 patients. The mean lowest oxygen saturation (SpO_2) was 86% in the control group and 89% in the apneic oxygenation (AO) group; this difference was not statistically significant (p=0.56). Severe desaturation (SpO_2 < 80%) was observed in 5 patients (25%) in both groups (p=0.99). No adverse events were reported.	None
Cırıl 2024	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients (≥18 years) presenting to the emergency department who required RSI. Exclusion Criteria: Patients with a "do-not-resuscitate" order, trauma patients, cardiac arrest, delayed or crash intubation, history of facial trauma or surgery, prior use of HFNO or NIMV, need for a surgical airway, pregnancy, or missing 30-day mortality data.	Control: Preoxygenation using BVM with 15 L/min oxygen. Apneic Oxygenation: Preoxygenation and apneic oxygenation using HFNO at 60 L/min.	Primary outcome: Lowest SpO_2 during RSI. Secondary outcomes: SpO_2 <90% (desaturation), SpO_2 <80% (severe hypoxemia), intubation duration, rate of failed intubation, 30-day mortality.	A total of 135 patients were included (HFNO group: 68, BVM group: 67). The median lowest SpO_2 was 92% (86–98) in the control group and 96% (89–99) in the apneic oxygenation group; the difference was not statistically significant (p=0.16). Severe desaturation (SpO_2 <80%) occurred in 6 patients (9%) in the control group and 9 patients (13.2%) in the apneic oxygenation group (p=0.4).	None
Studies Evaluating the Effectiveness of Apneic Oxygenation in Patients Intubated for Emergency Surgery						

Mir 2017	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Patients aged >16 years requiring rapid sequence induction (RSI) for general anesthesia in emergency surgery were included. Exclusion Criteria: Patients under 16 years of age, those unable to provide informed consent due to language barriers, or patients with severe respiratory disease were excluded.	Control: Patients in the face mask group received preoxygenation via face mask at an oxygen flow rate of 12 L/min for 3 minutes. Apneic Oxygenation: Preoxygenation was performed using HFNO at 30 L/min, and apneic oxygenation was provided using HFNO at 70 L/min.	Primary outcome: PaO_2 at the end of tracheal intubation.	Primary outcome: PaO_2 measured after intubation. A total of 40 patients were included in the study (20 in each group). The mean (SD) PaO_2 was 43.7 (15.2) kPa in the apneic oxygenation group and 41.9 (16.2) kPa in the control group (p=0.722). $PaCO_2$ values were 5.8 (1.1) kPa and 5.6 (1.0) kPa, respectively (p=0.631), and arterial pH values were 7.36 (0.05) and 7.34 (0.06) (p=0.447).	The study was not blinded, and the authors noted that this may have led to more controlled and careful laryngoscopy and intubation in the intervention group, potentially attenuating any advantage of the method with respect to arterial blood gases. Because patients with pre-existing respiratory distress were excluded, the level of indirectness in this study is high.
Lodenius 2018	Single-center, open-label, randomized controlled trial.	Inclusion Criteria: Adult patients (≥18 years) requiring rapid sequence induction (RSI) under anesthesia for emergency surgery during daytime hours. Exclusion Criteria: BMI >35 kg/m², pregnancy, need for non-invasive ventilation to maintain oxygenation, or inability to provide consent.	Control: Preoxygenation was performed via a face mask for at least 3 minutes using 100% oxygen delivered at 10 L/min from a circle system. Apneic Oxygenation: Preoxygenation was performed using HFNO at 40 L/min, increased to 70 L/min during the apneic phase. The nasal cannula was left in place during intubation.	Primary outcome: Lowest SpO_2 during the RSI procedure.	A total of 79 patients were included in the study (39 in the control group, 40 in the apneic oxygenation group). The median lowest SpO_2 was 99% (range: 70–100) in the control group and 99% (range: 96–100) in the apneic oxygenation group; the difference was not statistically significant (p=0.09).	None

Preya 2023	Single-center, open-label, randomized controlled trial	Inclusion Criteria: Patients aged 18–60 years, ASA Physical Status I–III, requiring emergency laparotomy, and who provided written consent were included in the study. Exclusion Criteria: Patients with anatomically difficult airway, SpO_2 <95% on room air, hemoglobin <8 g/dL, hemodynamic instability (systolic blood pressure <90 mmHg and on vasopressor support), or coronary artery disease were excluded.	Control: Patients received preoxygenation via face mask at an oxygen flow rate of 5 L/min for 3 minutes. Apneic Oxygenation: In addition to preoxygenation via face mask, nasopharyngeal oxygen therapy (>10 L/min) was started simultaneously and continued until the completion of intubation (throughout the apneic phase).	Primary outcome: Decrease in the partial pressure of oxygen (PaO_2) after 90 seconds of apnea.	Primary outcome: Magnitude of decrease in partial pressure of oxygen (PaO_2) after 90 seconds of apnea. During the 90-second apneic period following preoxygenation, PaO_2 decreased by 38% in the control group and by 12% in the intervention group (P<0.001).	In this study, patients with pre-existing respiratory distress and baseline SpO_2 <95% were excluded, resulting in a high degree of indirectness.

RSI: Rapid Sequence Intubation, ICU: Intensive Care Unit, NRB: Non-rebreather Mask, BiPAP: Bilevel Positive Airway Pressure, BVM: Bag-Valve-Mask, HFNO: High-Flow Nasal Oxygen, SpO_2: Oxygen Saturation, NIMV: Non-invasive Mechanical Ventilation

Table 3. Summary of Studies Comparing Gum Elastic Bougie with Standard Intubation (with or without Stylet) in Tracheal Intubation

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Ghai 2022	Randomized clinical trial	Participants: 80 patients undergoing elective surgery. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: Success rate of intubation. Secondary outcomes: Intubation duration, complications.	Results: First-attempt success: Bougie 50% (20 of 40 patients), standard intubation 60% (24 of 40 patients). Duration: Bougie 62.80 ± 20.74 seconds, standard intubation 52.44 ± 14.23 seconds (p=0.01). Overall success within two attempts was similar (Bougie 90% vs Standard 95%, p=0.55).	Randomization was reported, but the allocation concealment was not described. No serious adverse events were reported.
Bawa 2022	Randomized clinical trial	Participants: 100 patients (50 per group) undergoing elective or emergency surgery, ASA Physical Status I–II. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: Intubation duration. Secondary outcomes: Number of attempts, hemodynamic changes, sore throat.	Results: First-attempt success: Bougie 80% (40 of 50 patients), Stylet 82% (41 of 50 patients) (p=0.196). Duration: Bougie 33.78 ± 20.49 seconds, standard intubation 22.16 ± 6.65 seconds (p<0.05).	Sore throat was more frequent in the Stylet group (12 vs 6 patients, p=0.02). Desaturation: 0 vs 1; esophageal intubation: 1 vs 0. Randomization was reported.
Driver 2021	Randomized clinical trial	Participants: 1,102 critically ill patients undergoing emergency intubation. Study setting: Emergency department and ICU (7 emergency departments and 8 ICUs).	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: First-attempt success rate. Secondary outcomes: Hypoxemia, esophageal intubation, trauma.	First-attempt success: Bougie 80.4% (447/556), Stylet 83% (453/546) (p=0.27). Absolute risk difference: −2.6% [95% CI, −7.3 to 2.2]. Median time from induction to intubation: Bougie 124 sec (IQR 97–180), Stylet 112 sec (IQR 85–157). Mean ± SD time: Bougie 133.7 ± 61.5 sec; Stylet 118 ± 53.3 sec.	Severe hypoxemia: Bougie 11.0% (58/556), Stylet 8.8% (46/546). Esophageal intubation: Bougie 0.7% (4), Stylet 0.9% (5). Pneumothorax: Bougie 2.5% (14), Stylet 2.7% (15). Oral, glottic, or thoracic injury: Bougie 0%, Stylet 0.5% (3). No significant differences were observed in complications.

Driver 2018	Randomized clinical trial	Participants: 757 patients (>17 years) undergoing intubation in the emergency department, including both difficult and non-difficult airways. Study setting: Emergency department.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: First-attempt success rate. Secondary outcomes: Duration, hypoxemia, esophageal intubation.	Results: First-attempt success: Bougie 98% (373/381), Stylet 87% (328/376) (absolute difference 11% [95% CI, 7–14], p<0.001). No differences were observed regarding hypoxemia or trauma. Subgroups: Difficult airway: Bougie 96% (191/198), Stylet 82% (150/182). Non-difficult airway: Bougie 99% (182/183), Stylet 92% (178/194). First-attempt durations: Bougie 38 sec (29–51), Stylet 36 sec (25–54). Mean ± SD: Bougie 39.3 ± 16.3 sec; Stylet 38.3 ± 21.5 sec.	The incidence of hypoxemia was similar (13% vs 14%). This is a multicenter, methodologically robust randomized controlled trial.

Dutta 2020	Randomized clinical trial (3-arm).	Participants: 450 patients aged 18–65 years, ASA Physical Status I–II, undergoing laparoscopic or open general surgery. Study setting: Operating room.	Intervention 1: Intubation assisted by a rigid tracheal tube introducer (TTI). Intervention 2: Intubation assisted by a flexible (non-rigid) TTI (gum elastic bougie). Control: Standard intubation (use of stylet not specified).	Primary outcome: Postoperative sore throat (POST) scored from 0–3. Secondary outcomes: Laryngoscopy quality, number of attempts, intubation duration, minor complications (airway obstruction, stridor).	Results: POST incidence was lowest in the rigid TTI group (29%), significantly lower than standard intubation (45.1%, p=0.005); no significant difference was observed between the rigid TTI and non-rigid TTI (bougie) groups (37.9%, p=0.117). Intubation duration: Standard 20.7 ± 5.3 sec, rigid TTI 25.7 ± 4.6 sec, bougie (non-rigid TTI) 26.6 ± 7.5 sec (p=0.000). Patients requiring more than one attempt: Standard 8.5%, rigid TTI 1.4%, bougie 1.4% (p=0.011).	First-attempt success rate was not reported. No differences were observed in complications such as laryngospasm or stridor. Analysis was conducted per protocol.

Sut 2016	Randomized clinical trial (3-arm).	Participants: Elective surgical patients aged 18–65 years, ASA Physical Status I–II, with a cervical collar applied to simulate a difficult airway.	Intervention 1: Gum elastic bougie. Intervention 2: ILMA (intubating laryngeal mask). Control: Standard intubation (use of stylet not specified).	Primary outcome: Intubation success. Secondary outcomes: Intubation duration, number of attempts, Cormack–Lehane classification. (The study does not clearly specify which outcome was primary.)	Results: First-attempt success: Bougie 93%, ILMA 45%, standard intubation 60% (p<0.001). Mean intubation duration: Bougie 36.0 ± 0.6 sec, Standard 41.0 ± 1.1 sec, ILMA 92.0 ± 1.0 sec (all comparisons p<0.05). Intraoperative complications: Bougie 6%, Standard 13%, ILMA 34% (p=0.02). Postoperative sore throat: Bougie 73%, Standard 64%, ILMA 50% (p=0.07).	No differences were observed between groups in systolic/diastolic blood pressure, heart rate, SpO_2, or $EtCO_2$ values.
Khan 2014	Randomized clinical trial	Participants: 56 patients aged >11 years, ASA Physical Status I–II, with a rigid Philadelphia cervical collar applied to simulate a difficult airway. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: Overall success rate. Secondary outcomes: Number of attempts, need for alternative airway, complications.	Results: Overall success: Bougie 100%, standard intubation 71.4% (p=0.002). Fewer attempts were required in the Bougie group. First-attempt success: Bougie 78.5% (22/32), standard 50% (10/20). First-attempt duration was not measured.	Due to the small sample size, the statistical power was limited. No adverse events were reported.
Heegaard 2003	Randomized clinical trial	Participants: 51 critically ill patients aged >11 years requiring emergency intubation. (Criteria for "critically ill" were not explicitly defined.) Study setting: Prehospital environment.	Treatment group: Gum elastic bougie. Control group: Standard intubation (use of stylet not specified).	Primary outcome: First-attempt intubation success. Secondary outcomes: Intubation duration, number of attempts, complications.	Results: First-attempt success: Bougie 70% (16/20), standard 65% (20/31) (p=0.67). No differences were observed in complications. Mean total intubation duration was 62 seconds (no difference between groups, p=0.4).	Complications: One esophageal intubation occurred in the Bougie group, and two in the standard group.

Noguchi 2003	Randomized clinical trial	Participants: 60 patients undergoing elective surgery, ASA Physical Status I–III. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: First-attempt intubation success. Secondary outcomes: Intubation duration, ease of intubation, failure rate.	Results: Intubation success: Bougie 96.7% (29/30), Stylet 96.7% (29/30). (It is not specified whether this represents first-attempt or overall success.) Mean duration: Bougie 31 ± 7 sec, Stylet 27 ± 3 sec (p=0.09).	No adverse events were reported.
Gataure 1996	Randomized clinical trial	Participants: 100 elective surgical patients, ASA Physical Status I–II. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Stylet.	Primary outcome: First-attempt intubation success. Secondary outcomes: Intubation duration, complications.	Results: Overall success within two attempts: Bougie 96%, standard intubation 66% (p<0.001). First-attempt success: Bougie 82%, Stylet 48%. First-attempt duration: Bougie 14.4 ± 0.3 sec, Stylet 15.1 ± 0.6 sec.	No adverse events were reported.
Nolan 1993	Randomized clinical trial	Participants: 157 elective surgical patients with cervical spine immobilization using a cervical collar. Study setting: Operating room.	Treatment group: Gum elastic bougie. Control group: Standard intubation (use of stylet not specified).	Primary outcome: Intubation duration. Secondary outcomes: Success rate, complications, number of failed attempts.	Results: Success: Bougie 100% (83/83), standard intubation 93% (69/74). Mean duration: Bougie 26 sec (range 15–45), standard 20 sec (range 13–95).	The study demonstrates that bougie use increases intubation success in patients with cervical spine injuries. No adverse events were reported.

ASA: American Society of Anesthesiologists classification, ICU: Intensive Care Unit, CI: Confidence Interval, IQR: Interquartile Range, SD: Standard Deviation, TTI: Tracheal Tube Introducer, POST: Postoperative Sore Throat, ILMA: Intubating Laryngeal Mask Airway, SpO_2: Oxygen Saturation, $EtCO_2$: End-tidal Carbon Dioxide.

Table 4. Summary of Studies Evaluating Bolus Dose Vasopressor Use During Rapid Sequence Intubation in Critically Ill or Hypotensive Patients

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Studies on Bolus Dose Vasopressor Use During RSI or the Peri-Intubation Period						
Panchal 2015	Retrospective observational study (single-arm).	Participants: 20 adult patients in the emergency department requiring intubation with systolic blood pressure (SBP) <90 mmHg; received a bolus dose of phenylephrine during the 30-minute period before or after intubation. Mean age: 64 ± 16 years; 50% male. Diagnoses: Respiratory failure, pneumonia, sepsis, trauma.	Intervention: Bolus phenylephrine (100 mcg/mL, IV). Thirteen patients (65%) received more than one dose; median administration time was 2 minutes after intubation (range −18 to +29 minutes). Seventy percent additionally received other vasopressors (norepinephrine, dopamine, etc.).	Outcome measures: Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) before and after the first phenylephrine bolus; data were recorded up to 60 minutes post-intubation.	Results: Mean SBP increased from 73 to 93 mmHg ($p < 0.01$). Mean DBP increased from 42 to 52 mmHg ($p < 0.01$). Heart rate did not change (114 → 115 bpm, $p > 0.05$). No arrhythmias or adverse events were reported.	Bolus phenylephrine during RSI produced a significant increase in blood pressure. The application was not standardized; in most patients, it served as a bridge to continuous vasopressor infusion. This supports the rapid effect of phenylephrine but highlights the need for standardization and further research.
Schwartz 2016	Retrospective observational study (single-arm).	Participants: 73 adults in the emergency department receiving bolus-dose phenylephrine for acute hypotension (71.2% received vasopressors around RSI). Median age: 65 years. Diagnoses: Septic shock (45.2%), respiratory failure (19.2%), stroke, cardiac arrest, pulmonary embolism.	Intervention: IV phenylephrine 100–200 mcg administered from prefilled syringes. Timing relative to intubation (±60 minutes) was recorded. Administration was assessed in the context of at least 30 mL/kg fluid resuscitation prior to phenylephrine.	Primary outcome: Initiation rate of continuous vasopressor infusion (CVI) within 30 minutes after the first phenylephrine dose. Secondary outcomes: Hemodynamic response (SBP, HR), number of doses administered, adverse events.	Results: Continuous vasopressor infusion (CVI) was initiated within 30 minutes in 46.5% of patients. Sixty-seven point one percent received fluids prior to phenylephrine; patients with adequate fluid resuscitation required fewer doses (1.5 vs 2.3 doses, $p=0.01$). SBP increased from 56.5 to 79.3 mmHg ($p < 0.05$). Adverse events occurred in 20.5% of patients: bradycardia 9.6%, reactive hypertension 8.2%, ventricular tachycardia (VT) 2.7%.	Highlights the relationship between fluid status and vasopressor response: inadequate fluid resuscitation is associated with higher vasopressor requirements. Hypotension related to RSI occurred in 71.2% of patients. The study is limited by its retrospective design and generalizability.

Swenson 2018	Retrospective observational study (single-arm).	Participants: 181 adults in the emergency department receiving bolus-dose phenylephrine, 62 (34%) administered around RSI. Mean age: 53.6 years; 59% male. Diagnoses: Sepsis, respiratory failure, trauma, cardiac arrest, drug overdose.	Intervention: Prefilled 1000 mcg/10 mL phenylephrine syringes; doses 10–500 mcg IV at the clinician's discretion. Repeated dosing was administered in 81 patients. Vital signs were recorded 30 minutes before and after administration.	Primary outcome: Adverse events: SBP >180 mmHg, DBP >110 mmHg, HR <50 bpm within 30 minutes. Secondary outcomes: Changes in MAP, SBP, DBP, HR; dose-response relationship.	Results: MAP increased in all dose groups; the greatest increase occurred in the 200–500 mcg group (+12 mmHg, p = 0.02). Five patients (2.8%) met the adverse event threshold: 3 with high SBP, 2 with bradycardia; no serious adverse events (SAE) occurred. Phenylephrine increased MAP even in patients with HR <50 bpm.	Phenylephrine is safe and produces a short-term effect in hypotensive emergency patients, including those undergoing RSI. Adverse events were rare and clinically insignificant. Limitations include the absence of a control group and a standardized dosing protocol.
Fuchita 2018	Secondary analyses of two multicenter RCTs (BOUGIE and PREPARE II) using propensity score matching.	Participants: 1,798 critically ill patients undergoing emergency intubation in the ED or ICU. 187 patients (10%) received prophylactic vasopressors and were matched 1:1 with 187 controls. Patients in cardiac arrest prior to intubation were excluded.	Intervention: Prophylactic vasopressor administration before intubation or during induction (bolus or infusion dose titration). The intervention was non-randomized; agent and dose were at the clinician's discretion.	Primary outcome: Development of SBP <90 mmHg within 2 minutes after intubation (peri-intubation hypotension). Secondary outcomes: ΔSBP, need for new vasopressors, cardiac arrest within 1 hour, 30-day mortality, ventilator-free and ICU-free days.	Results: In 374 matched patients, incidence of hypotension: Vasopressor 41% vs Control 32% (p = 0.08). ΔSBP: −12 vs −11 mmHg (p = 0.66). 30-day mortality: Vasopressor 57% vs Control 47% (p = 0.08). Need for new vasopressors: 40% vs 29% (p = 0.03). Low SBP was associated with increased mortality risk (OR 1.08 per 10 mmHg decrease, p = 0.001).	This represents the largest analysis conducted in RSI patients. Although non-randomized, it closely reflects clinical practice. Prophylactic vasopressor use did not reduce peri-intubation hypotension. Findings are limited by confounding variables, heterogeneity of agents used, and short follow-up duration.
Rotando 2019	Prospective observational study (single-arm).	Participants: 146 adults in the emergency department receiving bolus-dose phenylephrine or ephedrine for hypotension. 43% received the drug around RSI, 37% before procedures such as cardioversion, 20% for spontaneous hypotension.	Intervention: Phenylephrine (50–200 mcg IV) or ephedrine (5–10 mg IV) at the clinician's discretion. No standardized dilution protocol was used. Doses related to RSI were administered during or immediately after induction.	Outcomes: Changes in SBP before and after drug administration; adverse events (reactive hypertension, arrhythmia, ischemic events).	Results: Mean SBP increased from 80 to 106 mmHg (+26 mmHg, p < 0.001). Adverse events occurred in 11.6% of patients: reactive hypertension 7.5%, arrhythmia 4.1%, ischemia 0%.	This ED-based study includes 43% of cases associated with RSI. Both agents produced consistent increases in SBP. Although limited by lack of randomization and standardized protocol, it provides

						valuable real-world data.
Schmitt 2021	Retrospective matched cohort (propensity score matching).	Participants: 105 adults in the emergency department who developed peri-intubation hypotension (SBP <90 mmHg). Bolus-dose phenylephrine (PDPE), norepinephrine (NE), or PDPE + NE were administered within 30 minutes before or after intubation.	Groups: 1.PDPE (100 mcg/mL bolus) 2.NE infusion (0.02–0.1 mcg/kg/min) 3.PDPE + NE combination Agent selection and timing were at the clinician's discretion. RSI was mostly performed using etomidate and rocuronium.	Primary outcome: Cardiovascular instability within 2 hours after vasopressor initiation (SBP <90 mmHg, HR <60 bpm, cardiac arrest, or death).	Results: Composite outcome frequency: NE 88.6%, PDPE 80.0%, PDPE + NE 88.6% (p = 0.50). Hypotension 83.7%, bradycardia 19.4%, cardiac arrest 4.9%. In the sepsis subgroup, adverse events were more frequent (p = 0.045); bradycardia was notable in the NE group (p = 0.048).	Despite the high rate of instability, there were no differences among the three strategies. PDPE and NE were commonly used, yet clinical outcomes were similar. The small sample size and retrospective design are limitations, but the findings remain applicable to emergency intubation practice.
Davis 2023	Prospective observational study (multicenter).	Participants: 523 critically ill patients with hypotension during RSI in the air ambulance setting. 344 received arginine-vasopressin (aVP) for trauma, 179 received phenylephrine (PI) for non-trauma indications.	Intervention: Bolus-dose vasopressors during RSI: aVP 2 U IV/IO (every 5 min in trauma patients) or PI 200 mcg IV/IO (every 5 min in non-trauma patients). Administered according to protocol; repeat doses allowed.	Outcomes: Changes in SBP after drug administration, resolution of hypotension, need for repeat dosing, rebound hypertension, or cardiac arrest within 20 minutes.	Results: SBP increased from 61 → 109 mmHg (aVP) and 64 → 107 mmHg (PI). Hypotension resolution: aVP 79.1%, PI 82.1%. Recurrent hypotension: aVP 50.6%, PI 60.9%. Reactive hypertension 4.5%, cardiac arrest approximately 15%.	This is a large, field-based study focusing on RSI-related hypotension. Both agents rapidly increased SBP. However, being single-arm, the effects on clinically significant outcomes such as cardiac arrest remain unclear.
Studies Evaluating Bolus-Dose Vasopressor Efficacy in Hypotensive Situations Outside of RSI						
NAWROCKI 2019	Retrospective observational study (single-arm).	Participants: 52 critically ill patients transported by air ambulance who received bolus-dose adrenaline for hypotension (total 94 doses). Average age ~65.5 years.	Intervention: Adrenaline 10–20 mcg/dose (1:100,000), IV every 2 minutes as needed. Used as a bridge while preparing continuous infusion. Administered by nurse–nurse teams according to protocol.	Primary outcome: Changes in mean arterial pressure (MAP) and heart rate (HR). Secondary outcomes: Adverse events (tachycardia, arrhythmia, hypertension, cardiac arrest).	Results: MAP increased by +13 mmHg (IQR 5–34); HR increased by +2 bpm. Hypotension resolved in 58.5% of patients. Repeat doses were 50% effective; sequential doses 70% effective. Three post-bolus cardiac arrests were considered	Adrenaline is effective as a bridge to infusion in prehospital care. Most patients were intubated. Adverse event rates were low, and administration protocols were clear. This is not specific to RSI

					expected clinical events.	but is contextually relevant.
SINGER 2022	Retrospective observational study (single-arm).	Participants: A total of 2,183 bolus-dose vasopressor administrations in critically ill patients in ICU or emergency department settings (2,041 phenylephrine, 142 adrenaline). Both agents were not used concurrently in the same patient; operating room administrations were excluded.	Intervention: Phenylephrine (100–200 mcg) or adrenaline (10–20 mcg) IV bolus using prefilled syringes. No bedside dilution was performed.	Primary outcome: ≥25% increase in SBP (defined as response). Secondary outcomes: Changes in MAP/DBP, adverse events (hypertension, bradycardia, tachycardia), cardiac arrest within 60 minutes, need for infusion, ICU/hospital length of stay, in-hospital mortality.	Results: Response rate: Phenylephrine 55.9%, Adrenaline 71.8% ($p < 0.001$). SBP increase: Phenylephrine +45 mmHg, Adrenaline +60 mmHg. Adverse events: Hypertension 6.5% (PE) vs 12% (Epi), tachycardia 35% vs 45%. ICU length of stay longer in PE responders ($p = 0.007$). Mortality ≈ 28% (no difference).	This represents the largest series of bolus-dose vasopressors to date. Adrenaline is more effective but has a higher rate of adverse events. Use of prefilled syringes improved safety. This is not specific to RSI but provides important real-world data on hypotension management.
NAM 2022	Retrospective observational study (single-arm).	Participants: 135 adults in the emergency department with SBP < 90 mmHg or MAP < 65 mmHg, including both intubated and non-intubated patients. Each patient received only one agent; those receiving both agents were excluded.	Intervention: Phenylephrine (100–200 mcg) or adrenaline (10–20 mcg) IV bolus, using prefilled syringes.	Primary outcome: Heart rate (HR) change within 30 minutes after drug administration. Secondary outcomes: SBP, DBP, MAP, shock index, adverse events, ICU/hospital length of stay, mortality, dosing errors.	Results: No significant change in HR ($p = 0.139$). SBP increase was greater with epinephrine: 33 vs 26 mmHg ($p = 0.049$). Percentage change in SBP was also higher with epinephrine ($p = 0.039$). Dosing errors: epinephrine 12.8%, phenylephrine 2.1% ($p = 0.021$). No differences in adverse events, ICU stay, or mortality.	Epinephrine produces a stronger SBP increase but carries a higher risk of dosing errors. Its use emphasizes the need for careful administration and standardization . Findings are not HAE-specific but provide comparative insights for managing hypotension in the emergency department.

HAE: Rapid Sequence Intubation, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, HR: Heart Rate, ICU: Intensive Care Unit, RCT: Randomized Controlled Trial, PDPE: Push-Dose Phenylephrine, NE: Norepinephrine, aVP: Arginine Vasopressin, Post-Intubation (PI), PDP: Push-Dose Vasopressor, PE: Phenylephrine, Epi: Epinephrine, LOS: Length of Stay.

Table 5. Summary of Studies Evaluating the Efficacy of Ketamine in Patients with Acute Brain Injury

Study	Study Design	Population	Interventions	Outcomes	Main Results	Comments
Randomized controlled trials conducted in patients with acute brain injury						
Burman 2025	Randomized controlled trial	Inclusion criteria: Patients with severe traumatic brain injury, Glasgow Coma Scale (GCS) score between 3–8, aged 18–49, under mechanical ventilation, and with an intracranial pressure (ICP) monitoring probe in place were included in the study.	Both groups received fentanyl (1 µg/kg/h) and midazolam (0.05–1 mg/kg/h). Treatment group: Ketamine infusion (3 mg/kg/h for 36 hours). Control group: 0.9% saline infusion (for 36 hours).	Primary outcome: Neurologic outcomes at 3 months. Secondary outcomes: Intracranial and systemic pressure dynamics in severe TBI patients.	Main findings: ICP values in the ketamine group remained lower over the 36-hour observation period. Statistically significant ICP reductions were observed at the 4th and 6th hours compared to the control group. Similarly, CPP values in the ketamine group were generally higher, with a significant difference observed between the 4th and 6th hours. There was no difference in 3-month neurological outcomes.	None
Bourgoin 2005	Randomized controlled trial	Inclusion criteria: Severe traumatic brain injury patients aged 18–75 years with Glasgow Coma Scale (GCS) <9 after resuscitation, and with cerebral perfusion pressure (CPP) monitoring.	Treatment group: Target plasma concentration: Ketamine 1.0 µg/mL + Midazolam 100 ng/mL. Control group: Target plasma concentration: Sufentanil 0.3 ng/mL + Midazolam 100 ng/mL.	Outcomes: Cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP) were continuously measured.	Main Findings: Total 30 patients (15 per group). On day 1, mean ICP: Ketamine group 14.6 ± 8.3 mmHg, Sufentanil group 18.7 ± 6.8 mmHg. Mean CPP: Ketamine group 83.2 ± 14.3 mmHg, Sufentanil group 75.6 ± 11 mmHg. No statistically significant differences between groups.	None
Bourgoin 2003	Randomized, double-blind, placebo-controlled study	Inclusion Criteria: Patients with traumatic brain injury, aged 16–75 years, post-resuscitation GCS score 3–8, requiring mechanical ventilation and ICP monitoring. Patients with high ICP risk based on computed tomography (CT) were included. Treatment Group: Midazolam 1	Control Group: Midazolam 1 µg/kg/min + sufentanil 0.005 µg/kg/min infusion.	Outcomes: Continuous measurement of cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP).	Main Findings: Total 25 patients (12 ketamine, 13 sufentanil). Day 1 average ICP: Ketamine group 19 ± 8.4 mmHg, Sufentanil group 15.7 ± 6.8 mmHg. Day 2 average CPP: Ketamine 81 ± 7 mmHg, Sufentanil 80.4 ± 5.7 mmHg. No significant difference observed. Due to uncontrolled intracranial hypertension, additional sedation was required in 4/12 ketamine patients and 4/13 sufentanil patients.	None

		µg/kg/min + ketamine 50 µg/kg/min infusion.				
Kolenda 1996	Randomized controlled trial	Inclusion Criteria: Patients aged 16–72 years with moderate or severe head trauma, undergoing ICP, MAP, and CPP monitoring.	Treatment Group: Midazolam 6.5 mg/kg/day + Ketamine 65 mg/kg/day. Control Group: Midazolam 6.5 mg/kg/day + Fentanyl 65 µg/kg/day.	Outcomes: Continuous monitoring of SPB, IKB, and mean arterial pressure (MAP). Additionally, neurological examinations were performed twice daily according to the Glasgow Coma Scale (GCS).	Main Findings: Total 24 patients (12 per group). Day 1 mean IKB: Ketamine 12 ± 2.2 mmHg, Fentanyl 13 ± 1.2 mmHg. Mean SPB: Ketamine 59 ± 5.2 mmHg, Fentanyl 67 ± 2.2 mmHg. No significant difference between groups. SPB was higher in the ketamine group compared to fentanyl due to increases in MAP.	Ketamine provided a supportive effect on cerebral perfusion pressure (CPP) due to its blood pressure–increasing properties.
Schmittner 2007	Randomized controlled trial	Inclusion Criteria: Patients diagnosed with severe traumatic brain injury (TBI) (Glasgow Coma Scale <9) or aneurysmal subarachnoid hemorrhage (Hunt-Hess > II).	Treatment Group: Ketamine 0.5 mg/kg IV bolus, followed by continuous infusion. Control Group: Fentanyl 3 µg/kg IV bolus, followed by continuous infusion. Doses were individually titrated to achieve adequate sedation.	Outcomes: Cerebral perfusion pressure (CPP), intracranial pressure (ICP), and mean arterial pressure (MAP) were continuously monitored.	Main Findings: Total 24 patients (12 per group). Day 1 mean ICP: Ketamine 15.9 ± 5.8 mmHg, Fentanyl 14.7 ± 3.4 mmHg. Mean CPP: Ketamine 82.5 ± 9.9 mmHg, Fentanyl 84.1 ± 12.2 mmHg. No significant differences between groups.	None
Michalczyk 2013	Randomized controlled trial	Inclusion Criteria: Pediatric patients with oncologic diagnoses scheduled for sedation prior to lumbar puncture.	Groups: Group A: Midazolam 0.1 mg/kg (max 4 mg) + ketamine 1 mg/kg Group B: Ketamine 1 mg/kg only Group C: Propofol + fentanyl combination	Outcome: Lumbar puncture opening pressure.	Main Findings: Total 25 patients, 84 procedures (Group A: 35, B: 39, C: 10). Mean opening pressures: A: 22 ± 7.56 mmHg B: 26.5 ± 8.03 mmHg C: 17.3 ± 6.92 mmHg The ketamine groups had significantly higher opening pressures.	Groups A and B were randomized, while the randomization method for Group C was not specified.
Yehuda 2006	Randomized controlled trial	Inclusion criteria: Pediatric patients undergoing lumbar puncture for suspected aseptic meningitis; sedation was administered prior to the procedure.	Groups: Group A: Ketamine 1 mg/kg + Midazolam 0.05 mg/kg Group B: Midazolam 0.1 mg/kg only	Outcome: Opening pressure measured after lumbar puncture.	Main Results: Total 39 patients (A: 26, B: 13). Mean opening pressures: A: 24.4 ± 8.87 mmHg, B: 20 ± 3.74 mmHg (p = 0.011).	None

Observational Studies on Ketamine Use						
Observational Studies Demonstrating the Effect of Ketamine in Patients with Acute Brain Injury Under Continuous ICP Monitoring						
Bar-Joseph 2009	Prospective, open-label clinical study	Inclusion Criteria: Children aged 1–16 years with sustained intracranial hypertension (ICP > 18 mmHg), unresponsive to first- and usually second-line treatments, currently under sedation and receiving mechanical ventilation.	Treatment Groups: Group 1: Patients receiving ketamine to prevent ICP increases during painful procedures. Group 2: Patients receiving ketamine as an additional intervention to reduce markedly elevated ICP.	Outcomes: Changes in ICP and CPP, hemodynamic stability.	Main Results: In 30 patients, a total of 82 ketamine administrations were evaluated. Overall, ICP decreased by 30% (25.8 ± 8.4 → 18.0 ± 8.5 mmHg, p < 0.001), CPP increased (54.4 ± 11.7 → 58.3 ± 13.4 mmHg, p <0.005). · Group 1 (n=17): During intervention, only one case showed an ICP increase >2 mmHg. · Group 2: Ketamine administered for refractory intracranial hypertension resulted in a 33% decrease in ICP (26.0 ± 9.1 → 17.5 ± 9.1 mmHg, p < 0.0001).	This study directly challenges historical concerns that ketamine increases ICP. The results demonstrate that ketamine lowered ICP without causing hemodynamic adverse effects, suggesting it may be a potentially safe option in pediatric patients with TBI and intracranial hypertension.
Caricato 2013	Prospective observational study	Inclusion Criteria: Patients aged 18–75 years with closed head trauma within 72 hours post-injury, Glasgow Coma Scale (GCS) ≤ 8; patients with ICP monitoring in place receiving sedation with propofol + remifentanil targeting a Ramsay score of 5–6.	Treatment Arms: ·Control Phase: Endotracheal suctioning (ETS) under propofol + remifentanil infusion. ·Intervention Phase: In patients exhibiting a cough reflex, a 10-minute racemic ketamine infusion at 100 µg/kg/min was administered in addition to the existing sedation before ETS.	Outcomes: ICP, CPP, jugular venous oxygen saturation (SjO_2), mean flow velocity of the middle cerebral artery (mVMCA), cough reflex score, hemodynamic changes.	Main Findings: In the control group after ETS, mean arterial pressure (MAP) increased (89.0 ± 11.6 → 96.4 ± 13.1 mmHg, p < 0.001), intracranial pressure (ICP) increased (11.0 ± 6.7 → 18.5 ± 8.9 mmHg, p < 0.001), jugular venous oxygen saturation (SjO_2) increased (82.3 ± 7.5 → 89.1 ± 5.4, p = 0.01), and mean middle cerebral artery velocity (mVMCA) increased (76.8 ± 20.4 → 90.2 ± 30.2 cm/s, p = 0.04), while cerebral perfusion pressure (CPP) remained unchanged. Median cough score was 2 [IQR 1–2]. In the ketamine group, only ICP increased (11.0 ± 6.4 → 15.1 ± 9.4 mmHg, p < 0.05); other parameters did not change significantly. The cough score was significantly lower compared to the control group (p < 0.0001).	None
Dengler 2022	Retrospective observational study	Inclusion Criteria: Patients with severe traumatic brain injury (TBI) who had invasive ICP monitoring, were intubated and mechanically	Treatment Arm: In 43 patients, a total of 216 administrations of ketamine were given as 2 mg/kg IV bolus; used as	Outcomes: Changes in ICP and CPP; proportion of administrations achieving both ICP reduction and CPP increase.	Main Findings: 44 patients (median age 30 years, median GCS 5). A total of 216 ketamine boluses were administered. Both ICP decrease and CPP increase were observed in 46% of administrations.	None

		ventilated, and received at least one bolus of ketamine.	rescue therapy for elevated ICP.		Median ICP change: −3.5 mmHg (IQR −9 to +1, p < 0.001). Median CPP change: +2 mmHg (IQR −5 to +12, p < 0.001).	
Laws 2023	Retrospective observational study	Inclusion Criteria: Pediatric patients under 18 years old, admitted to the intensive care unit, with severe traumatic brain injury (sTBI) and invasive ICP monitoring.	Treatment Arms: Ketamine group: Patients receiving ketamine bolus (subgroups: for ICP management and not for ICP management). Non-ketamine group: 17 patients with ICP > 20 mmHg treated with non-ketamine strategies.	Outcomes: Changes in ICP and MAP after ketamine administration; comparison of measured MAP values against age-specific thresholds; analysis of ICP and MAP trends over time.	Main Findings: A total of 33 pediatric patients; 127 ketamine boluses were administered to 22 patients. In the 18 ICP-targeted applications (11 patients, ICP > 20 mmHg for ≥5 min), mean ICP decreased significantly (−5.00 ± 7.44 mmHg, p = 0.046) and MAP increased. In applications given solely for sedation purposes, ICP or MAP did not change. Within the first 5 minutes, the MAP difference was not significant.	This study demonstrates, using high-frequency physiological data, that ketamine does not increase ICP in children and may reduce ICP during crisis periods.
Observational studies evaluating the effect of ketamine during rapid sequence intubation (RSI) in patients with acute brain injury.						
Lyon 2015	Comparative cohort study	Inclusion Criteria: All consecutive trauma patients who underwent prehospital rapid sequence intubation (RSI) during the defined study periods.	Treatment Groups: Group 1: Etomidate + Succinylcholine Group 2: Fentanyl + Ketamine + Rocuronium (Doses of fentanyl and ketamine were reduced in hemodynamically unstable patients.)	Outcomes: Intubation success, acute hemodynamic response, laryngoscopic view, survival until hospital discharge.	Main Results: Group 1: 116 patients, Group 2: 145 patients. Group 2 had better laryngoscopic view (p = 0.013) and higher first-attempt success (100% vs 95%, p = 0.007). Hypertensive response was less frequent (37% vs 79%, p < 0.0001). Hypotension was rare in both groups (1% vs 6%, p = 0.05). Mean arterial pressure (p = 0.148) and systolic blood pressure (p = 0.257) did not change.	None
Cornelius 2018	Retrospective observational study	Inclusion Criteria: Patients over 18 years old with suspected increased intracranial pressure (ICP) who required intubation.	Treatment Arms: Etomidate, midazolam, and ketamine were used for induction or sedation during rapid sequence intubation (RSI).	Outcomes: Mortality rate, time of death, discharge rate, and Glasgow Coma Scale (GCS).	Main Results: There were no significant differences between the groups for any of the outcomes.	None
Mudri 2020	Retrospective observational study	Inclusion Criteria: Pediatric trauma patients aged 0–17 years with traumatic brain injury; rapid sequence intubation (RSI) performed.	Treatment Arms: Propofol, ketamine, midazolam, and etomidate (used alone or in combination), administered with or without neuromuscular blockers.	Outcomes: Mortality rate, Hemodynamic stability measured by Pediatric Adjusted Shock Index (PASI), First-attempt intubation success.	Main Results: A total of 107 pediatric trauma patients. First-attempt intubation success was 88.5%, overall survival 87%. Mean hospital stay 21 days, ICU stay 7.5 days. Midazolam was the most frequently used agent;	When ketamine was used alone, no change in blood pressure was observed; however, no direct statistical comparison was made between induction agents.

					ketamine used alone in 7 patients. Propofol was associated with post-intubation hypotension. Blood pressure decrease observed with propofol or ketamine/midazolam combination; no change in blood pressure when ketamine used alone. No statistically significant hemodynamic differences were found between agents.	An increase in PASI scores was also observed in the ketamine group, but the highest increase occurred in patients receiving propofol or propofol/midazolam.
Fouche 2021	Retrospective observational study	Inclusion Criteria: Patients aged ≥12 years with suspected traumatic brain injury (TBI) by paramedics, who underwent prehospital rapid sequence intubation (RSI).	Intervention Groups: Pre-Ketamine period (before January 2015): RSI primarily performed using fentanyl and midazolam. Ketamine period (after January 2015): Ketamine (1.5 mg/kg) used as the primary induction agent for RSI.	Outcomes: Incidence of hypotension after RSI, changes in systolic blood pressure (SBP), shock index.	Main Results: A total of 1,619 patients were analyzed (792 pre-ketamine period, 827 ketamine period). After transitioning to ketamine use, post-HAE hypotension increased by 5% (p = 0.046) with an additional 0.5% rise per quarter (p = 0.004). Mean SBP decreased by 7.8 mmHg (p = 0.04) and showed a quarterly downward trend. In sensitivity analysis, the adjusted increase in hypotension was 5.6% (p = 0.02). Intubation success remained stable at 97.5%.	None
Mazandi 2023	Retrospective observational study	Inclusion Criteria: Pediatric patients <18 years old with a risk of intracranial hypertension due to neurological conditions (e.g., TBI, hydrocephalus, intracranial hemorrhage) requiring tracheal intubation.	Intervention Arms: Ketamine as the primary induction agent for intubation was compared with non-ketamine agents (e.g., etomidate or propofol).	Outcomes: Assessment of whether ketamine administration in this patient group increased the risk of neurological, hemodynamic, or respiratory events within 5 hours after induction.	Main results: A total of 143 patients (70 ketamine, 73 non-ketamine). No increase in neurological, hemodynamic, or respiratory adverse events was observed with ketamine. No mortality occurred within 24 hours. In the subgroup with ICP monitoring (n = 23), no ICP increase was observed; MAP remained stable. In 3 patients with elevated ICP, ketamine administration followed by intubation resulted in improvement of ICP.	None
Mansvelder 2024	Retrospective observational study	Inclusion criteria: Prehospital patients with Glasgow Coma Scale (GCS) ≤ 8 and suspected severe traumatic brain injury (TBI) based on trauma	Intervention groups: Comparison between etomidate and S(+)-ketamine.	Outcomes: Relationship between induction agent and 30-day mortality; Systolic blood pressure after induction;	Main results: A total of 1,451 patients (955 etomidate, 496 ketamine). No significant difference in 30-day mortality (32.9% vs 33.8%, p = 0.716). No differences were observed in post-	None

		mechanism or clinical findings, who received prehospital advanced airway management using etomidate or S(+)-ketamine.		Glasgow Coma Scale (GCS) at discharge; ICU length of stay and hospital length of stay.	induction blood pressure, ICU length of stay, or functional outcomes at discharge. In adjusted analysis, hospital length of stay was slightly longer in the ketamine group. No significant differences were found in definitive or isolated traumatic brain injury subgroups.	
Loi 2024	Retrospective observational study	Inclusion criteria: Children under 18 years old who were intubated for a primary neurological indication in pediatric intensive care units (PICU), pediatric cardiac ICU, or emergency department.	Intervention arms: Patients who received ketamine as the induction agent for tracheal intubation were compared with those who received other induction agents.	Outcomes: Association of ketamine use with combined adverse events (SpO_2 < 80% hypoxemia, hemodynamic instability) occurring within 20 minutes after intubation.	Main results: A total of 2,073 intubations (495 ketamine, 1,578 other agents). Combined adverse events: 17% (ketamine) vs 13% (other agents) (p = 0.026); however, in the adjusted analysis, not statistically significant (aOR 1.34, 95% CI 0.99–1.81, p = 0.057). No difference in first-attempt intubation success. In the traumatic brain injury (TBI) subgroup, adverse event rates were similar between ketamine and non-ketamine groups.	None

TBI: Traumatic Brain Injury, sTBI: Severe Traumatic Brain Injury, ICP: Intracranial Pressure, CPP: Cerebral Perfusion Pressure, MAP: Mean Arterial Pressure, SBP: Systolic Blood Pressure, GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, ICU: Intensive Care Unit, PICU: Pediatric Intensive Care Unit, ETS: Endotracheal Suctioning, SjO_2: Jugular Venous Oxygen Saturation, mVMCA: Middle Cerebral Artery Mean Flow Velocity, PASI: Pediatric Adjusted Shock Index, $PbtO_2$: Brain Tissue Oxygen Pressure, aOR: Adjusted Odds Ratio, RSI: Rapid Sequence Intubation, IQR: Interquartile Range.

Supplementary File 4. "GRADE" evidence level classification tables for the studies..

Question 1A: In adult patients undergoing rapid sequence intubation in the emergency department, does the choice of preoxygenation technique (noninvasive mechanical ventilation or conventional techniques) affect the incidence of severe hypoxemia?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Face Mask]	[NIMV]	Relative (95% CI)	Absolute (95% CI)		
Severe Hypoxia												
3	randomised trials	not serious	not serious	not serious	not serious	none	42/750 (5.6%)	98/765 (12.8%)	OR 0.40 (0.28 to 0.58)	73 fewer per 1.000 (from 89 fewer to 50 fewer)	⨁⨁⨁⨁ High	
Lowest SPO2												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	672	682	-	MD 6.76 higher (-2.28 lower to 15.81 higher)	⨁⨁⨁◯ Moderate[a]	

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. A wide confidence interval is present.

Question 1B: In adult patients undergoing rapid sequence intubation in the emergency department, does the choice of preoxygenation technique (high-flow nasal oxygen or conventional techniques) affect the incidence of severe hypoxemia?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Face Mask]	[HFNO]	Relative (95% CI)	Absolute (95% CI)		
Severe Hypoxia												
1	randomised trials	serious	not serious	not serious	serious [a]	none	7/89 (7.9%)	2/95 (2.1%)	**OR 0.25** (0.05 to 1.25)	**16 fewer per 1.000** (from 20 fewer to 5 more)	⨁⨁◯◯ Low[a]	
Lowest SPO2												
1	randomised trials	serious [a]	serious[b]	not serious	serious [a]	none	89	95	-	MD **2 higher** (0.69 lower to 4.69 higher)	⨁◯◯◯ Very low[a,b]	

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. A wide confidence interval is present.
b. There is only one study conducted on this topic.

Question 2: In patients undergoing rapid sequence intubation in the emergency department, does the addition of apneic oxygenation to standard preoxygenation reduce the incidence of severe hypoxia (SpO_2 < 80%) or improve the lowest SpO_2 values?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Apneic oxygenation]	[No apneic oxygenation]	Relative (95% CI)	Absolute (95% CI)		
Severe Hypoxemia												
6	randomised trials	not serious	not serious	serious	not serious	none	40/341 (11.7%)	37/352 (10.5%)	**OR 1.14** (0.70 to 1.86)	**13 more per 1.000** (from 29 fewer to 74 more)	⊕⊕⊕◯ Moderate	
Lowest SPO2												
7	randomised trials	not serious	not serious	serious	not serious	none			-	MD **0.1 higher** (-1.02 lower to 1.22 higher)	⊕⊕⊕◯ Moderate	
Advers Effects												
10	randomised trials	not serious	not serious	serious	not serious	none					⊕⊕⊕◯ Moderate	

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Question 3: In patients undergoing intubation in the emergency department, does the use of a gum elastic bougie, compared with standard intubation (with or without a stylet), increase first-pass intubation success or affect intubation duration?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Gum Elastic Bougie]	[standart entubation]	Relative (95% CI)	Absolute (95% CI)		
First-pass intubation success												
10	randomised trials	serious	serious[a]	not serious	not serious	none	1113/1283 (86.7%)	1028/1262 (81.5%)	OR 2.34 (1.14 to 4.80)	97 more per 1.000 (from 19 more to 140 more)	⨁⨁◯◯ Low[a]	
Intubation time												
8	randomised trials	not serious	not serious	not serious	not serious	none	1292	1279	-	MD 3.7 higher (1.02 higher to 6.38 higher)	⨁⨁⨁⨁ High	

Question 4: In adult emergency department patients who are hypotensive or at high risk of hypotension, does the administration of a push-dose vasopressor (e.g., phenylephrine, epinephrine) during or immediately before rapid sequence intubation, added to standard care, reduce the incidence of peri-intubation hypotension and improve clinical outcomes?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Push Dose Vasopressor]	[Placebo or infusion vasopressor]	Relative (95% CI)	Absolute (95% CI)		
Systolic Blood Pressure												
7	non-randomised studies	very serious	not serious	serious [a]	not serious	none					⨁◯◯◯ Very low[a]	
Adverse Effect												
10	non-randomised studies	very serious [a]	not serious	serious [a]	not serious	none					⨁◯◯◯ Very low[a]	

CI: confidence interval

Explanations

a. All studies do not have a comparison group.

Question 5: In adult emergency department patients at risk of increased intracranial pressure, is the use of ketamine during rapid sequence intubation a safe option?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Ketamine]	[Others]	Relative (95% CI)	Absolute (95% CI)		
ICP by using direct catheterization												
6	randomised trials	very serious	serious[a]	very serious	serious[b]	none	56	58	-	MD **0.78 lower** (1.87 lower to 0.31 higher)	⨁◯◯◯ Very low[a,b]	
CPP by using direct catheterization												
6	randomised trials	very serious	serious[a]	very serious	serious[b]	none	56	58	-	MD **1.07 lower** (7.95 lower to 5.8 higher)	⨁◯◯◯ Very low[a,b]	
ICP measurement in LP procedure												
2	randomised trials	very serious	not serious	very serious	serious	none					⨁◯◯◯ Very low	
Poor clinical outcome or ICP increase in observational studies												
11	non-randomised studies	very serious	not serious	serious	not serious	none	No study has reported that ketamine use is associated with an extra ICP increase or poor clinical outcome				⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. Although the I2 value was 40% for ICP outcome and 83% for CCP outcome, it was reported that there was no statistically significant difference in the majority of studies in terms of these outcomes.
b. The confidence intervals of the effect sizes were wide.