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Review Article

REVIEW ARTICLE

Apnoeic oxygenation during paediatric tracheal intubation: a systematic review and meta-analysis

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Abstract

Background: Supplemental oxygen administration by apnoeic oxygenation during laryngoscopy for tracheal intubation is intended to prolong safe apnoea time, reduce the risk of hypoxaemia, and increase the success rate of first-attempt tracheal intubation under general anaesthesia. This systematic review examined the efficacy and effectiveness of apnoeic oxygenation during tracheal intubation in children.

Methods: This systematic review and meta-analysis included randomised controlled trials and non-randomised studies in paediatric patients requiring tracheal intubation, evaluating apnoeic oxygenation by any method compared with patients without apnoeic oxygenation. Searched databases were MEDLINE, Embase, Cochrane Library, CINAHL, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), Scopus, and Web of Science from inception to March 22, 2023. Data extraction and risk of bias assessment followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendation.

Results: After initial selection of 40 708 articles, 15 studies summarising 9802 children were included (10 randomised controlled trials, four pre-post studies, one prospective observational study) published between 1988 and 2023. Eight randomised controlled trials were included for meta-analysis (n=1070 children; 803 from operating theatres, 267 from neonatal intensive care units). Apnoeic oxygenation increased intubation first-pass success with no physiological instability (risk ratio [RR] 1.27, 95% confidence interval [CI] 1.03–1.57, P=0.04, I^2=0), higher oxygen saturation during intubation (mean difference 3.6%, 95% CI 0.8–6.5%, P=0.02, I^2=63%), and decreased incidence of hypoxaemia (RR 0.24, 95% CI 0.17–0.33, P<0.01, I^2=51%) compared with no supplementary oxygen administration.

Conclusion: This systematic review with meta-analysis confirms that apnoeic oxygenation during tracheal intubation of children significantly increases first-pass intubation success rate. Furthermore, apnoeic oxygenation enables stable physiological conditions by maintaining oxygen saturation within the normal range.

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Clinical trial registration: Protocol registered prospectively on PROSPERO (registration number: CRD42022369000) on December 2, 2022.

Keywords: airway; apnoea; apnoeic oxygenation; paediatric anaesthesia; supplemental oxygen; tracheal intubation

Editor's key points

- Supplemental oxygen administration by apnoeic oxygenation during laryngoscopy for tracheal intubation could prolong safe apnoea time, reduce the risk of hypoxaemia, and increase the success rate of first attempt tracheal intubation under general anaesthesia.
- This systematic review examined the efficacy of apnoeic oxygenation in facilitating tracheal intubation in children.
- Apnoeic oxygenation increased intubation first-pass success, increased oxygen saturation during intubation, and decreased incidence of hypoxaemia compared with no supplementary oxygen.
- However, the included studies were heterogeneous, and more high-quality randomised controlled trials are warranted with well-defined outcome variables.

Tracheal intubation aims to establish a patent airway to ensure ventilation of the lungs during surgery, procedures, or respiratory insufficiency. It is lifesaving for children with severe acute respiratory failure. The number of tracheal intubation attempts is associated with an increased incidence of severe complications.[1,2] Interventions to improve first-attempt intubation success rate and increase safety are pivotal.[3] Tracheal intubation in the operating theatre is associated with an incidence of difficult airway of ~0.9% in children up to 16 yr old,[4] but alarmingly this is 5.8% in neonates,[1] and is mostly unanticipated. Furthermore, the incidence of haemoglobin desaturation appears to be as high as 40%, potentially leading to severe adverse events in neonates.[1] Prolonged severe desaturation can lead to hypoxic encephalopathy,[5] cardiac arrest,[6,7] or death.[8]

Facemask preoxygenation in children can be difficult because of lack of cooperation leading to improper mask seal,[9] and is relatively ineffective, especially in infants, considering hypoxaemia occurs within seconds after cessation of spontaneous or assisted ventilation.[10] Safe apnoea time is generally described as the time from cessation of breathing or ventilation until a patient attains a critical level of peripheral arterial oxygen saturation.[11] Beyond this point, oxygenation decreases rapidly to critically low blood and tissue oxygen levels endangering vital functions.[12]

Apnoeic oxygenation to reduce the risk of hypoxaemia and extend safe apnoea time was initially described in the early 1900s.[13,14] It consists of administering a constant stream of oxygen 100% while the patient is not breathing. The physiological requirements for adequate apnoeic oxygenation are a patent upper and lower airway, diffusion of highly concentrated oxygen into the alveoli, minimal pulmonary shunting, and presence of cardiac function. Low-flow oxygen with different delivery techniques achieves this objective, and mounting evidence supports the possible advantages of high-flow nasal oxygen administration.[15] However, apnoeic oxygenation is currently not a routine practice during tracheal intubation in most institutions.[2,16,17] This systematic review evaluates the efficacy of apnoeic oxygenation on first-attempt intubation success, oxygen saturation, and adverse effects during paediatric tracheal intubation.

Methods

The review protocol for this systematic review and meta-analysis was registered with PROSPERO (registration number: CRD42022369000) on December 2, 2022. We report our findings according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA).[18]

Eligibility criteria

We included peer-reviewed randomised controlled trials (RCTs) and non-randomised studies (non-RCTs, interrupted time series, controlled before-and-after studies, and cohort studies) in paediatric patients (age <16 yr) requiring tracheal intubation. Included studies compared apnoeic oxygenation by any method or device with a control group without apnoeic oxygenation. Apnoeic oxygenation was defined as any passive insufflation of oxygen of any flow into the nose or mouth without ventilation. Unpublished studies, case series, conference abstracts, trial protocols, duplicates, and unretrievable articles were excluded.

Searched databases and search strategy

A literature search strategy was devised for the following databases: MEDLINE, Embase, Cochrane Library, CINAHL, Web of Science Core Collection, Scopus, ClinicalTrials.gov, and International Clinical Trials Registry Platform (ICTRP). A medical information specialist (MvG) developed an initial search strategy in MEDLINE with a test against a list of core references to ensure that key publications were included. After refinement, the information specialist set up the search strategy for each information source based on database-specific index terms and free text. The free text search included synonyms, acronyms, and similar terms. No database-provided limits have been applied in any sources considering study types, languages, publication years, or any other formal criteria. The search was finalised on March 22, 2023. The detailed final search strategies were published,[19] and additional information about the systematic search is available in the Supplementary material.

Study selection and assessment

After identifying relevant publications, all were imported into EndNote (EndNote20, Clarivate, Philadelphia, PA, USA). We used Deduklick (Risklick AG, Bern, Switzerland) for

deduplication (MvG). An equal number of titles and abstracts were distributed to four groups with two study researchers (ND and ACL, AF and GK, TR and JA, RB and CSR). The researchers independently screened all titles and abstracts using the blinded mode in Rayyan[20] for systematic reviews. Disagreements were resolved through discussion or consulting a third senior researcher (RG). All available data were extracted (GK, CSR), including study characteristics, design, interventions, populations, study methods, and outcomes of significance to the review question and specific objectives (Table 1). Any discrepancies were resolved through discussion or consultation with a senior researcher (RG).

The risk of bias was assessed by five authors (AA, AF, CSR, GK, RB) using Version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) for randomised trials,[21] Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) for observational studies,[22] and the checklist from the National Institutes of Health (NIH) quality assessment tool for before-after studies.[23] Disagreements were resolved by consensus or discussion with a senior researcher (RG). If information from included studies was not available to answer our primary and secondary outcomes or assess the overall quality of the studies, the corresponding authors were approached.

Three authors (AF, GK, MH) independently assessed the certainty of evidence with Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[24] Any disagreements that arose were resolved through consensus. Six clinically relevant outcomes were defined and included in the GRADE table of certainty of evidence (Table 2).

Outcomes

The primary outcome was the incidence of successful first-pass tracheal intubation. Secondary outcomes were: number of intubation attempts; incidence of life-threatening events during tracheal intubation (i.e. cardiac arrest, failed intubation, failed ventilation, or both, emergency front of neck access, severe hypoxaemia (SpO_2 <80%), severe bradycardia (<60 bpm), or death); barotrauma (i.e., pneumothorax or pneumomediastinum confirmed with ultrasound or chest radiography); hypoxaemia (SpO_2 <90%), bradycardia (<80 beats min^{-1} or <100 beats min^{-1}), injury of the upper airway (e.g. bleeding or swelling), or unplanned admission to the intensive care unit secondary to tracheal intubation attempt.

Statistical methods

Only RCTs were considered for meta-analysis. Effect sizes (risk ratios [RRs] for binary outcomes and mean differences for continuous outcomes) were calculated when at least two RCTs reported data for an outcome.

As considerable between-study heterogeneity was detected, a random-effects model was used for analysis of effect sizes. We chose to apply the inverse variance method for continuous outcomes, and Mantel–Haenszel for binary outcomes. When median and inter-quartile ranges were reported as summary statistics for continuous outcomes, a quantile estimation method was used to estimate the mean and standard deviation (SD). The between-study heterogeneity was assessed with Higgins and Thompson's I^2 statistic. Statistical tests for funnel plot asymmetry were not performed given the small number of studies per outcome. All statistical computations were performed with R Version 4.0.5.[25]

Results

We identified 27,084 articles after deduplication published between 1988 and 2023 (Fig. 1); 15 studies (including 9802 patients) met inclusion criteria. Among these, 10 were RCTs,[26–35] four pre-post studies,[36–39] and one a prospective observational study.[40] Ten RCTs were considered eligible for effect size calculation; eight RCTs had an intervention and a control group, one study described two intervention arms and a control group (Steiner and colleagues[34]), and one study reported the outcomes for two subgroups only (Foran and colleagues[30]). The two intervention arms in Steiner and colleagues[34] were analysed as separate and independent group comparisons. Similarly, the two subgroups in Foran and colleagues[30] were analysed as two independent intervention arms compared with the control group. The limitation of this approach is outlined in the Limitations section. The meta-analysis of RCTs involved 1070 children, 803 from the operating theatre and 267 from the neonatal intensive care unit. Study characteristics are outlined in Table 1.

Risk of bias assessment

Figure 2 summarises the risk of bias assessment (RoB2, ROBINS-I, pre-post-studies). The overall risk of bias from RCTs was considered to be low in four trials[26,31,33,35] and to have some concerns in six trials.[27–30,32,34] Across the trials, the risk of deviations from intended interventions and missing outcome data was deemed low. Some concerns were noted for two trials[27,28] mainly because of inadequate reporting of the randomisation procedure (allocation concealment), concerns over the validity of outcome measurements were noted in three trials[30,32,34] as the assessors were aware of the interventions received by study participants, while in three trials[27,29,30] we were unable to assess adherence to a prespecified study protocol because of unavailability of the latter (outcome-reporting bias). Despite our efforts to contact the authors, we failed to obtain additional clarifying information. The quality rating for the before-after studies assessment was good in one study[36] and fair in three studies.[37–39]

Meta-analyses

The forest plots of the meta-analyses appear in Figures 3 and 4.

First-pass success rate of tracheal intubation

Three RCTs[28,30,33] with a total of 374 patients reported the success rate of first attempt at tracheal intubation, which was achieved in 66.8% (N=102/155) of the patients with apnoeic oxygenation and 51.5% (N=87/169) in the control group. The overall pooled analysis (Fig. 3a) showed a higher likelihood of first-pass successful tracheal intubation in the apnoeic oxygenation group compared with the control group (RR 1.27, 95% CI 1.03–1.57, P=0.04; I^2=0). However, a single study[33] largely dominates the pooled estimate, contributing 84.8% to the pooled effect size. The certainty of evidence was graded low given the small sample size, and as the optimal information size was not met.

Number of tracheal intubation attempts

Three RCTs[28,30,33] with a total of 311 patients met inclusion criteria for assessment of number of tracheal intubation

Table 1 Summary of the findings for the included studies and for the observational and pre-post trials. aOR, adjusted odds ratio; ETT, ; int., intervention group; NHF, nasal high flow; PICU, paediatric intensive care unit; RR, risk ratio; Risk of bias methodological quality tools used:* RoB 2: A revised Cochrane risk-of-bias tool for randomised trials. † ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. ‡ checklist from the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies.

Author year (country)	Study design	Total *n*	Setting	Age	Intervention	Control	Primary outcome	Secondary outcomes	Conclusions in the study	Comment	Risk of bias
Randomised controlled trials											
Ledbetter and colleagues 1988 (USA)[27]	RCT Two arms	20	Operating room (single centre)	1–24 Months	*n*=10 Flow: 4 L min^{-1} Device: Miller #1 Oxyscope	*n*=10 Flow: 0 L min^{-1} Device: Miller #1 Oxyscope	Maintenance of transcutaneous oxygen tension during tracheal intubation in children mean (SD) int. 24.2 (7.7) 95% CI (18.7–29.6) *vs* control 15.6 (6.3) CI (11.2 –20.1); *P*-value 0.014	None	Oxygen insufflation during laryngoscopy and intubation of spontaneously breathing anaesthetised infants effectively minimises the decrease in transcutaneous oxygen tension ($TcPo_2$) from pre-laryngoscopy levels	This study is not directly comparable with the other RCTs since $TcPo_2$ was used and this measure specifically reflects the oxygen tension in the tissues and not in blood	Some concerns*
Windpassinger and colleagues 2016 (Austria)[26]	RCT Two arms	48	Operating room (single centre)	0–2 Yr	*n*=24 Flow: 4 L min^{-1} Device: Air Traq laryngoscope size 0 –1	*n*=24 Flow: 0 L min^{-1} Device: Air Traq laryngoscope size 0–1	Time to SpO_2 95% after intubation with or without posterior pharynx oxygen insufflation mean (SD) int. 166 (47) s *vs* control 131 (39) s	Time to intubation	Oxygen insufflation prolongs the period of adequate oxygen saturation in infants and small children by an amount that is potentially clinically important	The duration of safe apnoea after intubation was longer with apnoeic oxygenation in small children than without oxygen	Low risk*
Humphreys and colleagues 2017 (Australia)[35]	RCT Two arms	48	Operating room (single centre)	0–10 Yr	*n*=24 Flow: flow rates 0–15 kg, 2 L kg^{-1} min^{-1} 15–30 kg, 35 L min^{-1} 30–50 kg, 40 L min^{-1} >50 kg, 50 L min^{-1} Device: Optiflow	*n*=24 Flow: 0 L min^{-1} Device: none	Time to SpO_2 92% in seconds intervention *vs* control 0–6 months: 192 *vs* 109 (95% CI 28.8), 7–24 months: 237 *vs* 147 (95% CI 18.9) 2 –5 yr: 320 *vs* 191 (95% CI 15.3) 6 –10 yr: 430 *vs* 261 (95% CI 37.5)	Changes in transcutaneous oxygen saturation Changes in transcutaneous CO_2 tension	Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) prolongs the safe apnoea time in healthy children but has no effect to improve CO_2 clearance	Safe apnoea time was with different oxygen flow rates (weight and age dependent) significantly longer than without supplementary oxygen	Low risk*
Dias and colleagues 2017 (India)[29]	RCT Two arms	95	Operating room (single centre)	<6 Months	*n*=47 Flow: 4 L min^{-1} Device: Oxiport	*n*=48 Flow: 0 L min^{-1} Device: Miller Blade	Lowest SpO_2 Mean (SD) int. 97.55% (2.93%) *vs* control 95.9% (5.75%) *P*-value 0.049	Incidence of SpO_2 <90% SpO_2 85–89% SpO_2 <85% Correlation between time to intubation and SpO_2	Apnoeic laryngeal oxygen insufflation with Oxiport laryngoscope blade decreases the incidence of severe desaturation during neonatal and infant intubations	The use of apnoeic oxygenation mostly in neonates requiring general anaesthesia shows a reduction in the incidence of desaturation	Some concerns*
Bruckner and colleagues 2021 (Austria)[28]	RCT Two arms	16	Neonatology (single centre)	<1 Month	*n*=7 Flow: flow rates 6 L min^{-1} <1 kg 7 L min^{-1} 1–2 kg 8 L min^{-1} >2 kg Device: oxygen connected direct to the tracheal tube	n=9 Flow: 0 L min^{-1} Device: Miller Blade	Number of intubation attempts median (IQR) int. 1 (1–2) *vs* control 4 (2–5) *P*-value 0.056	First-pass success rate Duration until successful intubation	Continuous gas flow through the endotracheal tube during intubation might result in fewer intubation attempts and a higher rate of successful intubation on the first attempt	With different oxygen flow rates during intubation occurred less aborted intubations, because of desaturation, bradycardia, or both. Multiple intubation attempts were required without supplementary oxygen and the cumulative time to successful intubation was clearly prolonged	Some concerns*
Foran and colleagues	RCT Two arms	50	Neonatology (single centre)	<1 Month	*n*=22 (<34 weeks 15/ ≥34 weeks 7)	*n*=28 (<34 weeks 18/ ≥34 weeks 10)	Duration of SpO_2 <75% <34 weeks' gestation Median int. 29 s (0–126	Duration of SpO_2 >85% and 65% Lowest oxygen	No significant differences were noted in duration of oxygen saturation of	The duration and not the incidence of hypoxia was defined as primary	Some concerns*

Continued

Table 1 Continued

Author year (country)	Study design	Total *n*	Setting	Age	Intervention	Control	Primary outcome	Secondary outcomes	Conclusions in the study	Comment	Risk of bias
2023 (Ireland)[30]	Stratified by gestational age				Flow: 6 L min^{-1} Device: Optiflow	Flow: 0 L min^{-1} Device: none	s) *vs* control 43 s (0 −132 s) (*P*=0.78) ≥34 weeks' gestation Median int. 0 (0−32 s) *vs* control 0 (0−20 s) (*P*-value 0.9)	saturation Bradycardia Number of intubation attempts Time to successful intubation Mortality rate	<75% between groups. The rate of desaturation appeared to decrease with use of NHF therapy in the preterm infant and postulated that greater success may be related to the increased time allowed for intubation	outcome. NHF therapy increases the rate of intubation without desaturation or bradycardia in newborns	
Gandhi and colleagues 2021 (India)[31]	RCT Two arms	80	Operating room (single centre)	<1 Yr	*n*=40 Flow: 2 L min^{-1} Device: Oxiport	*n*=40 Flow: 0 L min^{-1} Device: Miller Blade	Lowest SpO_2 Mean (SD) int. 97.77 (2.81) *vs* control 92.42 (3.71) with a *P*-value <0.001	Time for 1% desaturation from baseline Desaturation rate Time for intubation Heart rate	Apnoeic laryngeal oxygen insufflation with Oxiport Blade decreases the incidence and severity of desaturation during intubation in neonates and infants	Significantly higher saturation was maintained with oxygen insufflation in neonates and infants compared with without oxygen	Low risk*
Olayan and colleagues 2018 (Saudi Arabia)[32]	RCT Two arms	30	Operating room (single centre)	1−8 Yr	*n*=15 Flow: 3 L min^{-1} Device: nasal cannula	*n*=15 Flow: 0 L min^{-1} Device: nasal cannula	Apnoea time until SpO_2 92% or time to successful intubation Median (IQR) int. 39 (19 −64) *vs* control 34 (21 −55) *P*=0.870). Lowest SpO_2 (median (IQR) 99 (98 −100) *vs* 100 (100 −100) *P*-value 0.870	SpO_2 <95% SpO_2 <92%	There was no difference in the duration of safe apnoea between the apnoeic oxygenation group and the standard care group. The lowest SpO_2 in the apnoeic oxygenation group was significantly higher than that in the standard care group.	This study defined safe apnoea duration as time to first event. The measure represents the time to successful secure the airway in both groups	Some concerns*
Steiner and colleagues 2016 (USA)[34]	RCT Three arms	457	Operating room (single centre)	1−17 Yr	Intervention 1 *n*=153 Flow: flow rates 2 L min^{-1} blade sizes 0 −1 3 L min^{-1} blade sizes 2 −3 Device: Truview Intervention 2 *n*=145 Flow: flow rates 2 L min^{-1} blade sizes 1 −2 3 L min^{-1} blade size ≥3 Device: oxygen cannula attached to the side of standard laryngoscope	*n*=159 Flow: 0 L min^{-1} Device: standard laryngoscope	Time for 1% desaturation from baseline 25th percentile (95% CI) 75 s (37−122 s) *vs* int. 2 67 s (35−149) *vs* control 30 s (24−39 s)	SpO_2 <90%	Laryngeal oxygen insufflation increases the time to 1% desaturation and reduces the overall rate of desaturation during laryngoscopy in children	Regardless the delivery method, supplementary oxygen reduces the rate of desaturation in apnoeic children	Some concerns*
Hodgson and colleagues 2022 (Australia)[33]	RCT Two arms	251	Delivery room or neonatal intensive care (multicentre)	<1 Month	*n*=124 Flow: 8 L min^{-1} Device: Optiflow	*n*=127 Flow: 0 L min^{-1} Device: Optiflow	First-pass success rate without physiological instability Int. 50% (62/124) control 31.5% (69/127) Adjusted risk difference 17.6 (95% CI 6.0−29.2)	Median SpO_2 Time to and duration of desaturation Duration and number of intubation attempts	The likelihood of successful intubation on the first attempt without physiological instability in the infant was higher with high-flow therapy than with standard care	NHF therapy maintained the physiological stability and prolonged the time available to intubation	Low risk*
Prospective observational study											
Soneru and colleagues 2019 (USA)[40]	Prospective cohort Study	356	Operating room (single centre)	<8 Yr	*n*=160 Flow: 5 L min^{-1} Device: nasal cannula	*n*=196 Flow: 0 L min^{-1} Device: nasal cannula	SpO_2 <95% RR before intubation 0.05 (95% CI 0.03−0.09); *P*-value 0.0001	SpO_2 <95% SpO_2 <90% Lowest SpO_2 Intervention by	Apnoeic nasal oxygenation during intubation of paediatric surgical patients prolongs	Especially in trainees, extended safe apnoea time is relevant for the	Serious†

Continued

Table 1 Continued

Author year (country)	Study design	Total *n*	Setting	Age	Intervention	Control	Primary outcome	Secondary outcomes	Conclusions in the study	Comment	Risk of bias
								senior operator required	time before desaturation, thus extending the safe interval for airway management by learners	airway management in children	
Pre-Post Studies											
Overmann and colleagues 2019 (USA)[38]	Obser vational cohort study (before and after intervention)	305	Emergency department (single centre)	<18 Yr	Postimplementation *n*=227 Flow: flow rates <3 yr 2 L min^{-1} 3–8 yr 4 L min^{-1} >8 years 6 L min^{-1} Device: nasal cannula	Preimplementation *n*=78 Flow: 0 L min^{-1} Device: none	SpO_2 <90% post 14% (95% CI 7–24%) *vs* pre 22% (95% CI 17–28%); *P*-value 0.05	Time to desaturation Duration of desaturation Lowest SpO_2	Apnoeic oxygenation was not associated with a lower risk of oxyhaemoglobin desaturation during RSI[¶]	As a part of an intervention bundle in an emergency department, apnoeic oxygenation with low flow rates was not associated with lower desaturation during rapid sequence intubation in children	Fair[‡]
Napolitano and colleagues 2019 (USA)[36]	Observational cohort study (before and after intervention)	1373	Paediatric intensive care unit (single centre)	<18 Yr	Postimplementation *n*=712 Flow: flow rates <12 months 5 L min^{-1} 1–7 Yr 10 L min^{-1} >8 Yr 15 L min^{-1} Device: nasal cannula	Preimplementation *n*=661 Flow: 0 L min^{-1} Device: none	SpO_2 <80% post 11.8% *vs* pre 15.4% *P*-value 0.049	SpO_2 <70% Adverse events	Apnoeic oxygenation in PICU was associated with significant reduction in moderate and severe oxygen desaturation	The implementation of apnoeic oxygenation in a PICU was feasible und associated with less desaturation	Good[‡]
Napolitano and colleagues 2023 (USA)[37]	Observational cohort study (before and after intervention)	6549	Paediatric intensive care unit (multicentre)	<18 Yr	Postimplementation *n*=3318 Flow: flow rates <12 months 5 L min^{-1} 1–7 yr 10 L min^{-1} >8 yr 15 L min^{-1} Device: nasal cannula	Preimplementation *n*=3231 Flow: 0 L min^{-1} Device: none	Tracheal intubation associated events (TIAEs) aOR 0.75 (95% CI 0.58–0.98); *P*-value 0.03	SpO_2 <80%	Apnoeic oxygenation utilisation was associated with a lower incidence of adverse TIAEs in children who required tracheal intubation in the PICU	The implementation of apnoeic oxygenation in 14 PICUs was associated with a lower occurrence of adverse events	Fair[‡]
Vukovic and colleagues 2019 (USA)[39]	Observational cohort study (before and after intervention)	149	Emergency department (single centre)	<18 Yr	Postimplementation *n*=90 Flow: flow rates <2 yr 4 L min^{-1} 2–12 yr 6 L min^{-1} >12 yr 8 L min^{-1}s Device: nasal cannula	Preimplementation *n*=59 Flow: 0 L min^{-1} Device: none	Lowest SpO_2 Median [IQR] post 100 [95–100] *vs* pre 93 [69–99]; *P*-value 0.001	Number of attempts	Apnoeic oxygenation is associated with decreases in hypoxaemia during paediatric endotracheal intubation	The use of apnoeic oxygenation and video laryngoscope in a paediatric emergency department showed a reduction in the incidence of hypoxaemia	Fair[‡]

Table 2 Grading of Recommendations Assessment, Development, and Evaluation (GRADE) table of certainty of evidence for the main outcomes. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; RR, risk ratio. *Optimal information size is not met - when the dominant study (in terms of sample size) is removed as sensitivity analysis. †Wide variance of point estimates across studies, minimal overlap of confidence intervals, high I-squared statistic (>50%) ‡Optimal information size not met - in particular when the dominant study (in terms of sample size) is removed as sensitivity analysis. ¶Wide variance of point estimates across studies, minimal overlap of confidence intervals, high I-squared statistic (60%) §Very high I-squared statistic (96%), however, this heterogeneity is largely dominated by a single study.

Patient or population: tracheal intubation in children aged 0–16 yr requiring elective or emergency tracheal intubation.
Setting: in-hospital patients.
Intervention: apnoeic oxygenation with either low- or high-flow oxygen.
Comparison: no oxygen.

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no oxygen	Risk difference with apnoeic oxygenation with either low- or high-flow oxygen
First-pass success rate (%)	322 Bruckner and colleagues (2021)[28] Foran and colleagues (2023; pre-term group)[30] Foran and colleagues (2023; term group)[30] Hodgson and colleagues (2022)[33]	⨁⨁◯◯ Low*	RR 1.27 (1.03–1.57)	51 Per 100	14 More per 100 (2 more to 29 more)
Incidence of hypoxaemia (SpO2 <90%)	769 Windpassinger and colleagues (2016)[26] Dias and colleagues (2017)[29] Steiner and colleagues (2016; VL-O_2 group)[34] Steiner and colleagues (2016; DL-O_2 group)[34]	⨁⨁◯◯ Low†,‡	RR 0.24 (0.17–0.33)	40 Per 100	31 Fewer per 100 (33 fewer to 27 fewer)
Lowest SpO2 (%)	500 Dias and colleagues (2017)[29] Foran and colleagues (2022; Pre-term group) Foran and colleagues (2023; term group)[30] Gandhi and colleagues (2021)[31] Olayan and colleagues (2018)[32] Hodgson and colleagues (2022)[33]	⨁⨁⨁⨁ High	—	The mean lowest SpO2 (%) ranged from 44.3 to 99.0%	Mean difference 3.6% higher (0.8 higher to 6.5 higher)
Incidence of bradycardia (<80 beats min−1 or <100 beats min−1)	306 Foran and colleagues (2023; pre-term group)[30] Foran and colleagues (2023; term group)[30]	⨁⨁◯◯ Low	RR 0.76 (0.37–1.53)	10 Per 100	2 Fewer per 100 (6 fewer to 5 more)

Continued

Table 2 Continued

	Hodgson and colleagues (2022)[33]				
Number of attempts (-)	311 Bruckner and colleagues (2021)[28] Foran and colleagues (2023; pre-term group)[30] Foran and colleagues (2023; term group)[30] Hodgson and colleagues (2022)[33]	⨁⨁⨁◯ Moderate[¶]	—	The mean number of attempts ranged from 1.5 to 3.7	Mean difference 0.6 lower (2.4 lower to 1.6 higher)
First intubation success time (s)	1117 Ledbetter and colleagues (1988)[27] Windpassinger and colleagues (2016)[26] Dias and colleagues (2017)[29] Gandhi and colleagues (2021)[31] Steiner and colleagues (2016; VL-O_2 group)[34] Steiner and colleagues (2016; DL-O_2 group)[34] Hodgson and colleagues (2022)[33]	⨁⨁⨁◯ Moderate[§]	—	The mean first intubation success time ranged from 19.1 to 74.0 s	Mean difference 10.5 s higher (4.4 lower to 25.4 higher)

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

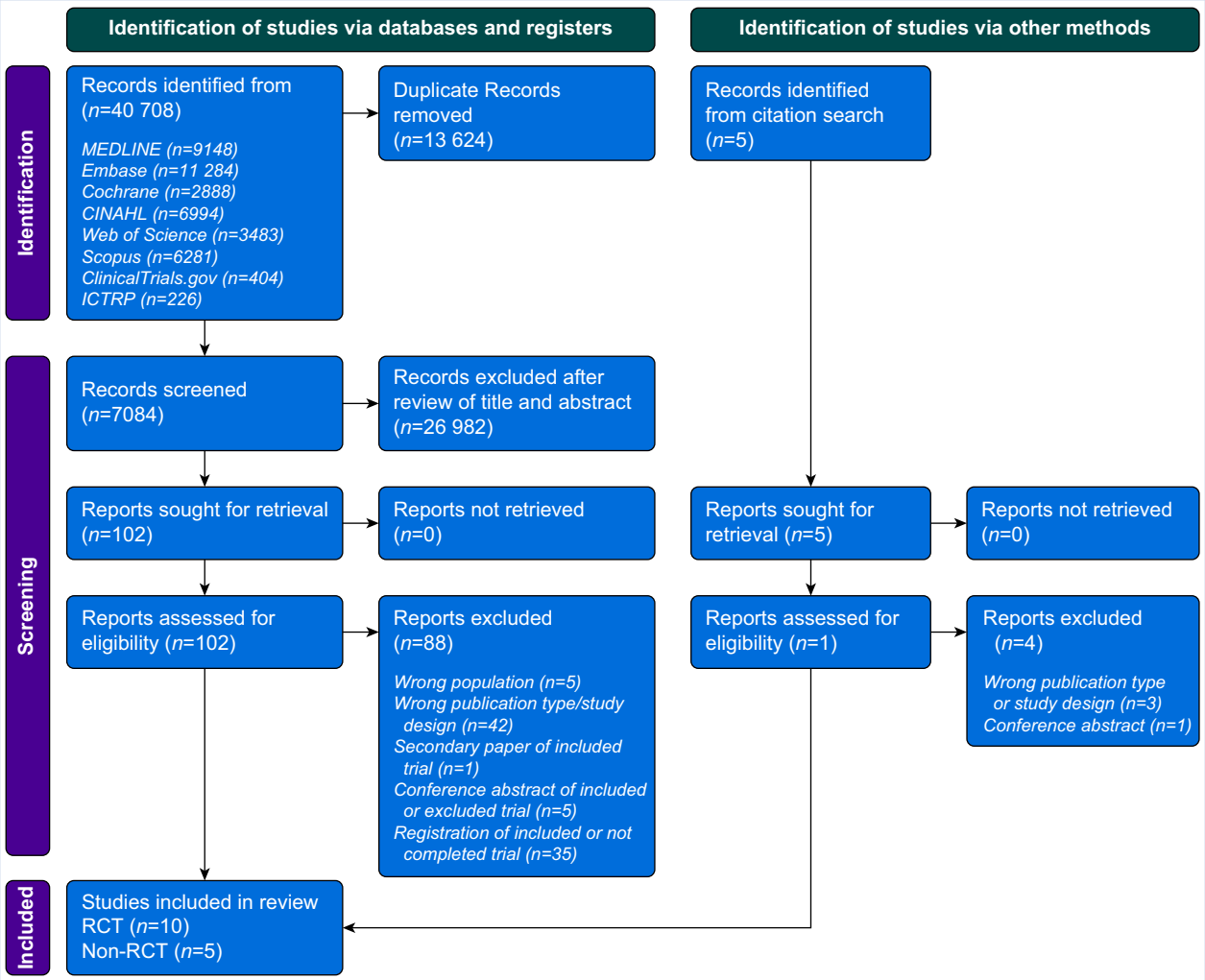


Fig 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram of study selection. ICTRP, International Clinical Trials Registry Platform.

attempts (153 neonates with apnoeic oxygenation and 158 in the control group; Fig. 4c). No statistical difference in the number of intubation attempts was detected (mean difference −0.6, 95% CI −2.4 to 1.2, P=0.35). Between-study heterogeneity was substantial (I^2=60%), and the certainty of the evidence was graded moderate because of a wide variance of point estimates across studies and minimal overlap of confidence intervals.

Lowest oxygen saturation

Five RCTs[29–33] with six comparisons reported the lowest haemoglobin oxygen saturation during tracheal intubation for 500 children, 248 children in the apnoeic oxygenation group and 252 in the control group (Fig. 3b). Patients in the apnoeic oxygenation group had a higher oxygen saturation than those in the control group (mean difference 3.6%, 95% CI 0.8–6.5%, P=0.02). Substantial between-study heterogeneity (I^2=63%) was detected. The certainty of evidence was graded high.

Incidence of hypoxaemia

Three RCTs[26,29,34] with 769 children reported the incidence of hypoxaemia during tracheal intubation (379 children in the apnoeic oxygenation group and 390 children in the control group; Fig. 4a). Overall pooled estimate showed a significant reduction in hypoxaemia incidence (RR 0.24, 95% CI 0.17–0.33, P<0.01). Between-study heterogeneity was substantial (I^2=51%). The certainty of evidence was graded very low because of a wide variance of point estimates across studies, a minimal overlap of confidence intervals, a high I^2 statistic, and as optimal information sizes were not met. More importantly, 99.4% of the pooled effect size is derived from the two group comparisons of a single study.[34]

Incidence of bradycardia

Two RCTs[30,33] reported the incidence of bradycardia with 306 children (146 in the apnoeic oxygenation group and 160 in the control group; Fig. 4b). No reduction was detected in the

a

Domains of risk of bias version 2 (RoB2) of the cochrane risk-of-bias tool for randomised trials

	D1	D2	D3	D4	D5	Overall
Ledbetter and colleagues (1988)[27]	!	+	+	+	!	!
Windpassinger and colleagues (2016)[26]	+	+	+	+	+	+
Steiner and colleagues (2016)[34]	+	+	+	!	+	!
Humphreys and colleagues (2017)[35]	+	+	+	+	+	+
Dias and colleagues (2017)[29]	+	+	+	+	!	!
Olayan and colleagues (2018)[32]	+	+	+	!	+	!
Bruckner and colleagues (2021)[28]	!	+	+	+	+	!
Gandhi and colleagues (2021)[31]	+	+	+	+	+	+
Hodgson and colleagues (2022)[33]	+	+	+	+	+	+
Foran and colleagues (2023)[30]	+	+	+	!	!	!

Criteria
D1: Bias arising from the randomisation process.
D2: Bias because of deviations from the intended interventions.
D3: Bias because of missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in the selection of the reported result.

Judgement
+ Low risk
! Some concerns

b

ROBINS-I: risk of bias in non-randomised studies of interventions

	D1	D2	D3	D4	D5	D6	D7	Overall
Sonaru and colleagues (2019)[40]	×	–	–	–	–	–	–	×

Criteria
D1: Bias because of confounding
D2: Bias in selection of participants into the study
D3: Bias in classification of interventions
D4: Bias because of deviations from intended interventions
D5: Bias because of missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported result

Judgement
– Moderate
× Serious

c

NIH quality assessment tool for before-after studies: The checklist from the National Institutes of Health.

	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	Quality rating
Overmann and colleagues (2019)[38]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Fair
Napolitano and colleagues (2019)[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	No	Good
Napolitano and colleagues (2023)[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	NR	Yes	No	No	Fair
Vukovic and colleagues (2019)[39]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	NR	Yes	Yes	No	Fair

NR=not reported

Criteria
D1: Was the study question or objective clearly stated?
D2: Were eligibility/selection criteria for the study population prespecified and clearly described?
D3: Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?
D4: Were all eligible participants who met the prespecified entry criteria enrolled?
D5: Was the sample size sufficiently large to provide confidence in the findings?
D6: Was the test/service/intervention clearly described and delivered consistently across the study population?
D7: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?

Fig 2. Risk of bias assessment. NIH, National Institutes of Health.

incidence bradycardia when applying apnoeic oxygenation (RR 0.76, 95% CI 0.37–1.53, P=0.44; I^2=0). The study by Hodgson and colleagues[33] contributed the entire weight (100%) to the pooled estimates. The certainty of evidence was graded low.

Time to successful intubation

Six RCTs[26,27,29,31,33,34] with seven group comparisons reported the time to successful intubation with a total of 1117 children

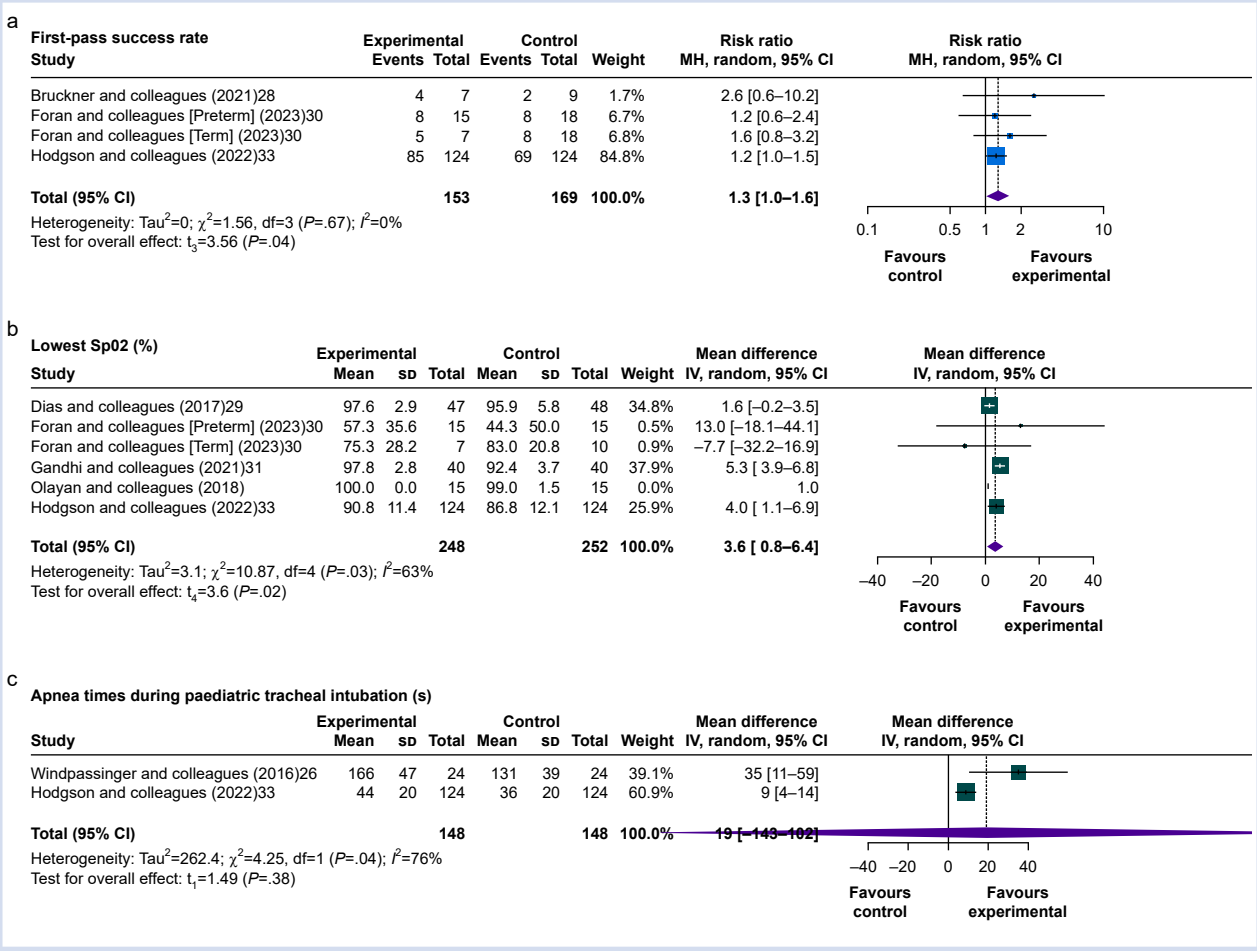


Fig 3. Forest plots for the outcomes (a) first-pass success rate, (b) lowest SpO_2, and (c) apnoea times during paediatric tracheal intubation. CI, confidence interval; df, degrees of freedom; MH, Mantel-Haenszel; SD, standard deviation.

(553 children with apnoeic oxygenation and 564 in the control group; Fig. 4d). The pooled estimate showed no difference in the intubation success time (mean difference 10.5 s, 95% CI −4.4 to 25.4 s, P=0.14). Between-study heterogeneity was very high (I^2=96%), and the certainty of evidence was graded moderate as the heterogeneity was largely dominated by a single study.[33]

Apnoea time

Two RCTs[26,33] reported apnoea times during paediatric tracheal intubation with a total of 296 patients (148 children with apnoeic oxygenation and 148 in the control group; Fig. 3c). No difference was detected in apnoea times (mean difference 19 s, 95% CI −143 to 182 s, P=0.38). Between-study heterogeneity was substantial (I^2=60%), and the random effects models demonstrated large uncertainties in the pooled estimates as the two studies differed in their mean estimates and SD by a factor of almost 4. The evidence was not graded as the two studies used different apnoea time definitions. The first study[33] reported on duration of apnoea for intubation, whereas in the other study[26] children were first intubated and then left apnoeic until the onset of desaturation with or without oxygenation.

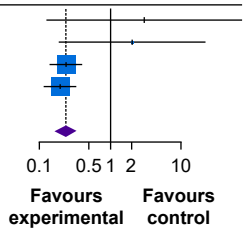
Adverse events

Two RCTs[28,33] reported adverse events during the tracheal intubation. Hodgson and colleagues[33] reported serious adverse events such as chest compressions or epinephrine administration within 1 h after tracheal intubation in 0 of the 124 patients with apnoeic oxygenation *vs* 1.6% (N=2/127) in the control group. Pneumothorax was reported in 1.6% (N=2/124) patients in the apnoeic oxygenation group and 4.7% (N=6/127) in the control group. Death within 72 h after tracheal intubation in 0.8% (N=1/124) of patients with apnoeic oxygenation and 2.4% (N=3/127) in the control group. Bruckner and colleagues[28] reported aborted tracheal intubation because of desaturation, bradycardia, or both in 33% (N=3/10) of intubation attempts with apnoeic oxygenation and in 69% (N=20/29) when intubation was attempted without oxygen. Because of variability in methods and reporting across these studies, no meta-analysis was conducted.

a **Incidence of hypoxaemia (SpO2<90%)**

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, fixed, 95% CI
Windpassinger and colleagues (2016)26	1	24	0	24	0.0%	3.0 [0.1–70.1]
Dias and colleagues (2017)29	2	47	1	48	0.6%	2.0 [0.2–21.8]
Steiner and colleagues [VL-O2] (2016)34	18	153	78	159	49.5%	0.2 [0.2–0.4]
Steiner and colleagues [DL-02] (2016)34	15	155	78	159	49.8%	0.2 [0.1–0.3]
Total (95% CI)		**379**		**390**	**100.0%**	**0.2 [0.2–0.3]**

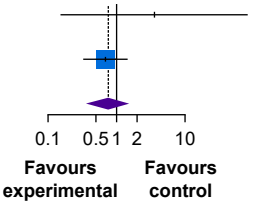
Heterogeneity: Tau^2=1.0; χ^2=6.18, df=3 (*P*=.10); I^2=51%
Test for overall effect: Z=–8.56 (*P*<.01)



b **Bradycardia**

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio MH, fixed, 95% CI
Foran and colleagues [Preterm] (2023)30	1	15	0	18	0.0%	3.6 [0.2–81.8]
Foran and colleagues [Term] (2023)30	0	7	0	18	0.0%	
Hodgson and colleagues (2022)33	11	124	16	124	100.0%	0.7 [0.3–1.4]
Total (95% CI)		**146**		**160**	**100.0%**	**0.8 [0.4–1.5]**

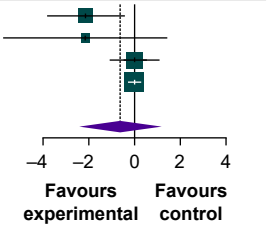
Heterogeneity: Tau^2<0.1; χ^2=1.01, df=1 (*P*=.31); I^2=1%
Test for overall effect: Z=–0.78 (*P*=.44)



c **Number of attempts**

Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, random, 95% CI
Bruckner and colleagues (2021)28	1.5	1.1	7	3.7	2.2	9	21.4%	–2.1 [–3.8– –0.5]
Foran and colleagues [Preterm] (2023)30	1.5	1.1	15	3.7	7.0	15	7.7%	–2.2 [–5.7–1.4]
Foran and colleagues [Term] (2023)30	1.5	1.1	7	1.5	1.1	10	30.2%	–0.0 [–1.1–1.1]
Hodgson and colleagues (2022)33	1.5	1.1	124	1.5	1.1	124	40.6%	0.0 [–0.3–0.3]
Total (95% CI)			**153**			**158**	**100.0%**	**–0.6 [–2.4–1.2]**

Heterogeneity: Tau^2=0.8; χ^2=7.52, df=3 (*P*=.06); I^2=60%
Test for overall effect: t_3=–1.1 (*P*=.35)



d **First intubation success time (s)**

Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, random, 95% CI
Ledbetter and colleagues (1988)27	29.0	9.0	10	28.0	11.0	10	14.6%	1.0 [–7.8–9.8]
Windpassinger and colleagues (2016)26	70.2	53.5	24	60.0	29.7	24	9.7%	10.2 [–14.3–34.7]
Dias and colleagues (2017)29	42.9	24.4	47	40.6	21.3	48	14.5%	2.3 [–6.9–11.6]
Gandhi and colleagues (2021)31	19.3	5.9	40	19.1	5.7	40	15.7%	0.1 [–2.4–2.7]
Steiner and colleagues [VL-O2] (2016)34	117.0	41.0	153	74.0	20.8	159	15.0%	43.0 [35.7–50.2]
Steiner and colleagues [DL-02] (2016)34	91.3	31.9	155	74.0	20.8	159	15.2%	17.3 [11.4–23.3]
Hodgson and colleagues (2022)33	52.7	19.6	124	53.1	29.5	124	15.2%	–0.4 [–6.7–5.8]
Total (95% CI)			**553**			**564**	**100.0%**	**10.5 [–4.4–25.4]**

Heterogeneity: Tau^2=247.8; χ^2=139.79, df=6 (*P*<.01); I^2=96%
Test for overall effect: t_6=1.7 (*P*=.14)

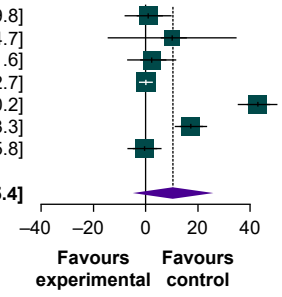


Fig 4. Forest plots for the outcomes (a) incidence of hypoxaemia, (b) bradycardia, (c) number of intubation attempts, and (d) first pass intubation success time. CI, confidence interval; df, degrees of freedom; MH, Mantel-Haenszel; SD, standard deviation.

Discussion

This systematic review and meta-analysis investigated the effectiveness of apnoeic oxygenation during tracheal intubation in children under 16 yr of age. Despite the low certainty of evidence according to GRADE, apnoeic oxygenation was associated with a higher probability of first-pass tracheal intubation success and a reduced number of intubation attempts for each patient. Regardless of the method of administration, apnoeic oxygenation reduced the incidence of hypoxaemia when compared with no oxygen administration. Apnoeic oxygen administered during tracheal intubation

improved and stabilised respiratory and haemodynamic variables and facilitated overall airway management.

First-attempt success is critical in paediatric airway management, as adverse events are directly associated with the overall number of intubation attempts.[2,41,42] Our findings indicate that administration of oxygen reduces the overall number of attempts by improving first attempt success rate. This is highly important for neonates, small infants, and children with limited cardiopulmonary reserve, as they are more prone to rapid oxygen desaturation. These patients often have higher oxygen consumption, lower closing capacity, low functional residual capacity, and increased risk of airway collapse compared with older children.[43]

The main obstacle of tracheal intubation in children is often the short apnoea time before severe arterial oxygen desaturation, which is more severe in neonates, infants, and those with severe comorbidities.[12] Thus, methods to extend the safe apnoea time are highly desirable. Across the studies included in this systematic review, oxygen delivery techniques, flow rates, and significant hypoxaemia levels were heterogeneous. Nevertheless, in eight RCTs[26–29,31,33–35] apnoeic oxygenation during intubation prolonged the safe apnoea time, decreased the incidence of hypoxaemia, and reduced the number of intubation attempts or increased first-pass success without physiological instability. These findings are supported by five observational or pre-post studies[36–40] that were not included in our meta-analyses but showed a benefit of apnoeic oxygenation during tracheal intubation with fewer adverse events, better intubation conditions, and reduction of hypoxaemia. Maintaining adequate oxygenation during tracheal intubation is crucial in neonates and infants to prevent hypoxaemia and the associated complications.[10,12,44,45]

On the one hand, using oxygen at high concentrations in premature babies and infants can lead to complications triggered by oxidative stress, including bronchopulmonary dysplasia[46] or severe retinopathy of prematurity.[47] Administering supplemental oxygen to children with a cyanotic congenital heart disease might lead to perfusion mismatch, resulting in haemodynamic instability.[48] However, hypoxaemia is also harmful, and haemoglobin oxygen saturation values of 85–89% in premature babies increase the risk of death before hospital discharge.[49] In addition to potential harm with oxygen, there is also the risk of barotrauma. Hodgson and colleagues[33] diagnosed pneumothorax more often in patients without apnoeic oxygenation and Napolitano and colleagues[37] showed fewer adverse events, including pneumothorax, in an observational study. Causality remains unclear, but rescue facemask ventilation during intubation attempts might pose a risk of barotrauma rather than apnoeic oxygenation. High-flow nasal oxygen administration was reported to reduce the risk of pneumothorax compared with continuous positive airway pressure for respiratory support in preterm infants.[50] In summary, the relatively short period of potential hyperoxia during intubation with apnoeic oxygenation appears to outweigh the benefits of avoiding hypoxaemia

Limitations

The significant heterogeneity in study designs of the included trials constitutes a major limitation together with the limited number of included patients and studies. A further limitation is our assumption of the independence of different treatment arms[34] or subgroups.[30] It is likely that the true uncertainty of the pooled effect sizes (i.e. the confidence intervals), might be wider than reported in this study.

Avoiding hypoxaemia and keeping a normal oxygen saturation is the first step of a cascade of events that might lead to serious adverse events such as bradycardia or cardiac arrest. The aggregated evidence from this systematic review confirms that apnoeic oxygenation during airway management reduces the incidence of hypoxaemia, but the strength of evidence remains low. This is partly as a result of the exclusion of several studies investigating apnoeic oxygenation because of the lack of a control group with no intervention.[15,51,52] Moreover, only two RCTs[28,33] reported data on adverse events, both of which reported a higher incidence of adverse events in children with no apnoeic oxygen administration. However, data were insufficient and not consistently reported to perform a meta-analysis. This is also supported by the findings of the observational studies by Napolitano and colleagues.[36,37] They found an association between oxygen administration and a lower incidence of severe adverse events during tracheal intubation but not a reduction in tracheal intubation attempts or severe peri-intubation hypoxaemia.

Unanswered questions and future research

This systematic review illustrates a high variability in the choice of outcome measures across the included studies. Future study designs on paediatric airway management should standardise the choice of outcomes with actual clinical relevance, allowing better comparison and meta-analysis of studies. First-pass success rate of tracheal intubation and adverse events should be included in any future research as they represent the clinical outcomes of highest relevance. The optimal technique for oxygen delivery during intubation, oxygen flow rate, and concentration of oxygen to be administered during oxygenation have yet to be determined. As financial resources in healthcare and environmental consciousness are increasingly important, cost-effectiveness and environmental impact analysis should be included in future studies.

Severe hypoxaemia, severe bradycardia, cannot intubate and cannot ventilate, emergency front of neck access, cardiac arrest, and death were rarely reported in the included studies, given the relatively small sample sizes of the included individual studies.

Conclusions

This systematic review provides evidence for improved first-attempt intubation success rate during tracheal paediatric intubation with apnoeic oxygenation. Apnoeic oxygenation during tracheal intubation in children decreases the risk of oxygen desaturation. However, as the included data were heterogeneous, more high-quality randomised controlled trials are warranted with a well-defined core set of outcome variables.

Authors' contributions

Wrote the protocol and manuscript: all authors
Study statistician: MH
Medical librarian: MvG
Articles were extracted by: GK, JA, RB, ND, ACL, MvG, TR, AF
Methodologists: AA, CSR
Were involved in the data analysis and interpretation and read and approved the final manuscript: all authors

Declaration of interests

The authors declare that they have no conflicts of interest.

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Data sharing

The data presented in this manuscript are available.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.10.039.

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