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Review Article

Intra-operative ventilation strategies and their impact on clinical outcomes: a systematic review and network meta-analysis of randomised trials

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Summary

Introduction Postoperative pulmonary complications are common and associated with significant morbidity and mortality; however, the optimal intra-operative ventilation strategy to prevent postoperative pulmonary complications remains unclear. The aim of this study was to evaluate the effect of intra-operative ventilation strategy, including tidal volumes, positive end-expiratory pressure (PEEP) and use of recruitment manoeuvres on the incidence of postoperative pulmonary complications in adults having non-cardiothoracic surgery.

Methods Relevant databases were searched to identify randomised controlled trials that directly compared intra-operative ventilation strategies among surgical patients who were followed up for > 24 hours postoperatively and reported at least one outcome of interest.

Results A total of 51 randomised controlled trials were included. Compared with a high tidal volume/zero PEEP strategy, low tidal volume strategies likely reduced the risk of postoperative pulmonary complications when combined with: high PEEP (risk ratio (RR) 0.44, 95%CI 0.22–0.87); high PEEP with recruitment manoeuvres (RR 0.60, 95%CI 0.49–0.75); personalised PEEP with recruitment manoeuvres (RR 0.53, 95%CI 0.42–0.69); low PEEP (RR 0.63, 95%CI 0.50–0.78); and low PEEP with recruitment manoeuvres (RR 0.65, 95%CI 0.46–0.93) (all moderate certainty evidence). Compared with a low tidal volume/low PEEP strategy, a low tidal volume strategy with personalised PEEP likely reduces the risk of postoperative pulmonary complications (RR 0.85, 95%CI 0.73–0.99, moderate certainty).

Discussion Among patients undergoing non-cardiothoracic surgery, the use of intra-operative low tidal volume ventilation with a range of acceptable PEEP levels likely reduced the risk of postoperative pulmonary complications compared with high tidal volumes and zero PEEP. This study highlights the need for implementation research at both the provider and system levels to improve intra-operative adherence to lung protective ventilation strategies.

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Introduction

Over 240 million people require surgery each year and, of these, up to 23% experience a postoperative pulmonary complication (PPC) [1–4]. As a composite outcome, PPCs include a range of respiratory complications including atelectasis; hypoxaemia; pneumonia; pleural effusion; pneumothorax; aspiration pneumonitis; and respiratory failure [5]. After wound infection, PPCs represent the second most common complication after surgery [6, 7]. Postoperative pulmonary complications may lead to prolonged hospitalisation, increased rates of unplanned tracheal reintubation and increased short- and long-term mortality [1]. These complications also impose substantial financial burdens on global healthcare systems, with marked increases in hospitalisation costs and resource utilisation, highlighting the importance of targeted preventative strategies to mitigate their impact [1, 6, 8, 9].

Intra-operative lung-protective ventilation is recommended by international consensus as a key intervention to prevent PPCs [10, 11]. Core components of lung-protective ventilation strategies include the use of low tidal volumes; optimisation of positive end-expiratory pressure (PEEP); and the inclusion of brief recruitment manoeuvres [12, 13]. More recent evidence of variable quality has also drawn attention to limiting driving pressure and mechanical power [14, 15].

Previous meta-analyses that compared the effectiveness of intra-operative ventilation strategies on PPC prevention have yielded inconsistent findings [16–18]. A recent Bayesian network meta-analysis suggested that low tidal volume ventilation combined with moderate PEEP and recruitment manoeuvres likely reduces the risk of PPCs. However, this analysis focused primarily on pre-determined PEEP levels with recruitment manoeuvres relative to conventional mechanical ventilation but did not explore personalised PEEP approaches [17]. Recent studies suggest that PEEP tailored to patient-specific respiratory static and/or dynamic compliance may enhance lung protection [19]. A separate conventional meta-analysis that compared driving pressure-guided PEEP with fixed PEEP strategies showed reductions in PPCs, improved intra-operative oxygenation and decreased pulmonary atelectasis [18]. Existing reviews, however, do not include more contemporary studies; include limited evaluation of personalised PEEP strategies; and are bound by the inherent constraints of conventional meta-analyses, which only include strategies directly compared in clinical trials [17, 18].

Network meta-analysis may extend what is currently known about intra-operative lung-protective ventilation by pooling direct and indirect evidence from trials that compare alternative ventilatory support approaches. To address identified gaps in the literature, we conducted a systematic review and network meta-analysis of randomised controlled trials, to compare ventilation strategies that include low tidal volume strategies; varied PEEP levels; and recruitment manoeuvres. Our primary aim was to evaluate the effects of intra-operative ventilation strategies on PPCs in adults undergoing non-cardiothoracic surgery.

Methods

The protocol for this network meta-analysis was developed following PRISMA guidelines [20] and reported using the PRISMA-NMA tool [21].

The population of interest was adults undergoing surgery with invasive mechanical ventilation. We included cluster or parallel-group randomised controlled trials that enrolled adult patients (aged ≥ 18 y) who underwent invasive ventilation with general anaesthesia for non-cardiothoracic surgery. We did not include trials that evaluated unconventional ventilation strategies (e.g. single lung, jet or airway pressure release ventilation). In addition, we did not include trials that involved cardiothoracic surgery, which represent unique populations and have been reviewed elsewhere [22, 23]. Conference abstracts, case reports, case series and observational studies were excluded. We applied no restrictions on language or publication date.

We included trials that compared two intra-operative ventilation strategies and allocated patients at random to receive varying tidal volume, PEEP levels, with or without protocolised recruitment manoeuvres. Tidal volume was dichotomised as either low (4–8 $ml.kg^{-1}$) or high (> 8 $ml.kg^{-1}$). Similarly, we categorised PEEP as zero end-expiratory pressure (ZEEP, 0 cmH_2O), low (1–5 cmH_2O), high (> 5 cmH_2O) or personalised (providing the highest dynamic or static lung compliance or the best aeration pattern using lung ultrasound).

The primary outcome of interest was the development of PPCs at any point following surgery. The European Perioperative Clinical Outcome guidelines suggest the PPC composite outcome includes respiratory failure; respiratory infection; atelectasis; bronchospasm; pleural effusion; pneumothorax; and aspiration pneumonitis (described further in online Supporting Information Table S1) [5]. However, significant variability remains in the definitions used in the published literature [1, 24]. Postoperative pulmonary complications were assessed as an outcome irrespective of how individual studies operationalised the definition.

Secondary outcomes defined a priori included use of and/or escalation to non-invasive respiratory support, high flow nasal cannulae or invasive ventilation; all-cause mortality (most protracted measure reported); ICU admission; tracheal reintubation (within hospitalisation); duration of ICU and hospital stay; hypoxaemia (as defined by study authors); and arterial partial pressure of carbon dioxide ($PaCO_2$, last $PaCO_2$ measured). Included trials reported at least one outcome of interest and followed patients for at least 24 h postoperatively.

In collaboration with an experienced health sciences librarian, we searched MEDLINE, PubMed, Embase, Scopus, Web of Science and the Cochrane Database of Systematic Reviews from inception to 30 June 2024. Additionally, we identified potentially relevant trials for inclusion by searching the `related articles´ feature, references of included trials, reviews and guidelines (online Supporting Information Appendix S1).

Pairs of reviewers (NJ, IL, SE and KB) screened retrieved titles and abstracts independently. Subsequently, six pairs of reviewers (IL, MM, SS, JP, AJ, VP, VT, DC, BG, CL, SL, SE) assessed the full texts of potentially relevant articles independently. Disagreements were resolved with a third author (KB or NJ) if needed. A data extraction form developed and pilot-tested by NJ and KB is provided in online Supporting Information Appendix S2. Pairs of reviewers extracted relevant data independently and resolved disagreements through discussion.

Each pair of reviewers assessed the risk of bias among the included trials independently using a modified version of the Cochrane Collaboration risk of bias 2.0 tool [25]. This included assessing the risk of bias arising from the randomisation process; due to deviations from the intended interventions; due to missing outcome data; in the measurement of the outcome; and in the selection of the reported result. One reviewer (NJ) resolved disagreements through correspondence with the trial primary authors as needed.

We calculated relative risks and their corresponding 95%CI for binary outcomes and mean differences and corresponding 95%CIs for duration of ICU and hospital stay, $PaCO_2$ and duration of advanced respiratory support. We used methods described previously to impute mean (SD) when only median (IQR [range]) and sample size are reported [26]. For all direct comparisons informed by two or more randomised controlled trials, we performed conventional pairwise meta-analysis using a DerSimonian and Laird random-effects model and assessed heterogeneity through visual inspection of the forest plots and the I^2 statistic. We assessed small-study effect in direct comparisons informed by ≥ 10 randomised controlled trials using Harbord's test for binary outcomes and Egger's test for continuous outcomes [27, 28].

We assessed the feasibility of performing a network meta-analysis and examined individual complications by checking network connectivity, ensuring the availability of at least 7–10 trials for a network of treatments and having more trials than the number of treatment nodes [29]. We then used Stata 18.0 Network Suite (StataCorp, College Station, TX, USA) to perform a frequentist random-effects model network meta-analysis with a common heterogeneity estimate [30, 31]. We confirmed the coherence assumption in the entire network using `design-by-treatment´ model and used the side-splitting method to assess the presence of incoherence between direct and indirect estimates of the effect [32, 33]. We estimated ranking probabilities using the surface under the cumulative ranking curve (SUCRA), mean ranks and rankograms [34].

We performed random-effects network meta-regression at the study level for the following a priori-defined subgroup analyses: impact of surgery type (open abdomen vs. none, laparoscopic vs. none); procedure duration (< 120 min vs. ≥ 120 min); patient position (prone vs. supine); and population obesity (yes vs. no). We performed further post-hoc subgroup analyses to evaluate the impact of weight calculations used in trials to determine tidal volume (i.e. ideal vs. predicted body weight) and inclusion of trials at high risk of bias. We performed a sensitivity analysis, excluding studies performed before 2010, to evaluate differences compared with more contemporary practice across all outcomes. Recognising the heterogeneity in definitions of PPCs reported across studies, we extracted these definitions systematically and performed network meta-regression for studies that reported a consistent definition (i.e. atelectasis).

We assessed the certainty of evidence for each network estimate using the GRADE framework [35]. Three reviewers (NJ, SB and IL) evaluated the certainty of evidence for direct comparisons, considering risk of bias, consistency, directness and publication bias. We judged the certainty of evidence for indirect comparisons using the lowest certainty of contributing direct comparisons. We used the dominant first-order loop wherever possible and, in its absence, we used a higher-order loop. We considered rating the certainty of evidence further down for intransitivity, namely if important differences were noted in patient characteristics, interventions or comparators between direct comparisons. For network comparisons, the certainty of evidence was judged as the higher of the direct or indirect evidence for a given comparison. Certainty was further rated down if there was evidence of incoherence between indirect and direct estimates or imprecision around the treatment effect estimates.

Results

The search strategy yielded 1047 unique citations after the removal of duplicates. Of these, we selected 81 trials for full text review and included 51 randomised controlled trials involving 8280 patients in our analysis (online Supporting Information Figure S1) [19, 36–85]. We present the characteristics of included trials in Table 1 and online Supporting Information Table S2. The majority of trials evaluated patients undergoing laparoscopic (22/51, 43%) [36, 37, 41, 45, 49, 50, 52, 54, 57, 58, 61, 64, 66, 72, 76–82, 84] or open abdominal surgery (14/51, 31%; Table 1) [38, 42, 43, 46, 47, 51, 59, 60, 63, 68, 69, 71, 73, 83]. Six trials (12%) evaluated patients with obesity (BMI > 30 kg.m^2) exclusively [39, 57, 64, 66, 76, 80]. The majority of included trials used either predicted body weight (30 trials) or ideal body weight (14 trials) to determine tidal volume; six trials did not specify the method; and one trial used lean or actual body weight (online Supporting Information Table S2). Studies employed varied approaches to neuromuscular blockade, monitoring and antagonism (online Supporting Information Table S3). Similarly, studies assessing recruitment manoeuvres varied in both technique and the intervals at which they were performed during surgery (see online Supporting Information Table S4). Online Supporting Information Figure S2 depicts the risk of bias assessment of the included trials. Eight trials were judged to be at low risk of bias in all domains.

Among included trials, 24 (total patients = 6634) assessed PPCs [19, 36, 39–41, 44, 48, 50, 51, 54–56, 60, 64, 65, 67–69, 71, 72, 74, 76, 77, 85]. Online Supporting Information Table S5 provides definitions of PPCs among the included trials and online Supporting Information Figure S3a provides the network of trials for this outcome. We did not observe any evidence of incoherence in the network or across available closed loops of evidence (online Supporting Information Tables S6–S13).

Compared with a high tidal volume/ZEEP strategy, moderate certainty evidence suggests that low tidal volume/high PEEP (risk ratio (RR) 0.44, 95%CI 0.22–0.87); low tidal volume/high PEEP with recruitment manoeuvres (RR 0.60, 95%CI 0.49–0.75); low tidal volume/personalised PEEP with recruitment manoeuvres (RR 0.53, 95%CI 0.42–0.69); low tidal volume/low PEEP (RR 0.63, 95% CI 0.50–0.78); and low tidal volume/low PEEP with recruitment manoeuvres (RR 0.65 95%CI 0.46–0.93) likely reduce the risk of PPCs (Fig. 1). Low certainty evidence suggests high tidal volume/low PEEP (RR 0.65, 95%CI 0.50–0.84) may result in a reduction of PPCs compared with the high tidal volume/ZEEP strategy. No other treatment strategy showed a statistically significant difference with the high tidal volume/ZEEP strategy (Fig. 1). Online Supporting Information Table S14 provides SUCRA values and ranking probabilities. Finally, when each ventilation strategy was compared with others, a low tidal volume strategy with

Table 1 Characteristics of included trials. Values are number (proportion).

Characteristics	Trials n = 51	Patients n = 8280
Age; y		
< 50	17 (33%)	2967 (36%)
> 65	11 (22%)	2474 (30%)
50–65	21 (41%)	2735 (33%)
Not reported	2 (4%)	104 (1%)
Female		
100%	8 (16%)	467 (6%)
50–99%	21 (41%)	4354 (53%)
1–49%	16 (31%)	3126 (38%)
0%	3 (6%)	179 (2%)
Not reported	3 (6%)	154 (2%)
Surgery type		
Laparoscopic abdominal	22 (43%)	1279 (15%)
Neurosurgery	2 (4%)	139 (2%)
Open abdominal	14 (27%)	1758 (22%)
Open and laparoscopic abdominal	3 (5%)	477 (6%)
Spine	4 (8%)	262 (3%)
Multiple surgical procedures	6 (12%)	4365 (53%)
Duration of surgery; h		
< 2	4 (7%)	244 (3%)
≥ 2	35 (69%)	6947 (84%)
Not reported	12 (24%)	1089 (13%)
Prone procedure		
All patients	4 (8%)	262 (3%)
Some patients[a]	2 (4%)	1266 (15%)
BMI > 30 kg.m^2		
All	6 (12%)	2277 (28%)
Some[b]	2 (4%)	2173 (26%)
None	8 (16%)	537 (6%)
Not reported	35 (68%)	3293 (39%)

[a]Proportion of patients in the prone position ranges from 22% to 27%.
[b]Proportion of patients defined as BMI > 30 kg.m^2 range from 14% to 37%.

Low V_T / ZEEP									
3.77 (0.16-89.77)	**Low V_T / High PEEP**								
2.66 (0.12-59.40)	0.71 (0.37-1.35)	**Low V_T / Low PEEP**							
2.77 (0.12-61.66)	0.74 (0.38-1.42)	1.04 (0.93-1.16)	**Low V_T / High PEEP + RM**						
2.56 (0.11-58.51)	0.68 (0.32-1.45)	0.96 (0.65-1.42)	0.93 (0.63-1.37)	**Low V_T / Low PEEP + RM**					
3.12 (0.14-69.93)	0.83 (0.43-1.61)	**1.17 (1.01-1.36)**	1.13 (0.94-1.36)	1.22 (0.81-1.84)	**Low V_T / Personal PEEP + RM**				
2.77 (0.12-61.66)	0.74 (0.01-36.08)	1.04 (0.02-48.35)	1.00 (0.02-46.41)	1.08 (0.02-51.14)	0.89 (0.02-41.33)	**Low V_T / ZEEP + RM**			
2.56 (0.11-57.34)	0.68 (0.36-1.28)	0.96 (0.84-1.11)	0.93 (0.78-1.10)	1.00 (0.66-1.51)	0.82 (0.67-1.01)	0.93 (0.02-43.12)	**High V_T / Low PEEP**		
0.80 (0.03-22.01)	**0.21 (0.06-0.80)**	**0.30 (0.10-0.95)**	**0.29 (0.09-0.92)**	0.31 (0.09-1.06)	**0.26 (0.08-0.82)**	0.29 (0.01-15.95)	0.31 (0.10-1.00)	**High V_T / ZEEP + RM**	
1.67 (0.07-37.43)	**0.44 (0.22-0.87)**	**0.63 (0.50-0.78)**	**0.60 (0.49-0.75)**	**0.65 (0.46-0.93)**	**0.53 (0.42-0.69)**	0.60 (0.01-28.13)	**0.65 (0.50-0.84)**	2.08 (0.64-6.70)	**High V_T / ZEEP**

Figure 1 Network estimates and their corresponding certainty of evidence (using GRADE rating) for intra-operative ventilation strategy on postoperative pulmonary complications (24 randomised controlled trials). Values are risk ratio (RR) and 95%CIs. For column compared with row, RR < 1 means the top-left treatment is better (RR < 1 favours the treatment in the column). Dark blue, high certainty; light blue, moderate certainty; light red, low certainty; red, very low certainty. V_T, tidal volume; RM, recruitment manoeuvre; ZEEP, zero peak end expiratory pressure.

personalised PEEP likely reduced the risk of PPCs when compared with a low tidal volume/low PEEP strategy (RR 0.85, 95%CI 0.73–0.99, moderate certainty; Fig. 1).

There were sufficient trials to perform network meta-analysis for selected complications, including pneumonia, atelectasis and hypoxaemia.

Among 19 trials that reported postoperative pneumonia [39, 42, 44, 51, 54, 56, 57, 60, 61, 63, 65, 67–69, 72, 79, 80, 82, 83], definitions of pneumonia varied widely (online Supporting Information Table S15). Moderate certainty evidence suggests that low tidal volume/high PEEP with recruitment manoeuvres (RR 0.58, 95%CI 0.39–0.87); low tidal volume/low PEEP (RR 0.62, 95%CI 0.44–0.88); or low tidal volume/low PEEP with recruitment manoeuvres (RR 0.60; 95%CI: 0.41–0.88), likely reduced the risk of postoperative pneumonia when compared with a high tidal volume/ZEEP strategy (Fig. 2).

Among 12 trials that evaluated hypoxaemia postoperatively [19, 44, 51, 57, 63, 66, 68, 72, 78–80, 83], there was significant heterogeneity in the definition of hypoxaemia (online Supporting Information Table S16). High certainty evidence suggests that a low tidal volume/low PEEP strategy alone (RR 0.34, 95%CI 0.13–0.87) or with recruitment manoeuvres (RR 0.32, 95%CI 0.14–0.74) reduces hypoxaemia compared with a high tidal volume/ZEEP strategy. A low tidal volume/personalised PEEP strategy likely results in a reduction in the incidence of postoperative hypoxaemia compared with most ventilation strategies (Fig. 3).

Similarly, among the 17 trials that reported postoperative atelectasis [36, 43, 44, 51, 54–57, 61, 65, 67,

Low V_T / ZEEP												
5.60 (0.13-248.31)	**Low V_T / High PEEP**											
2.44 (0.23-26.24)	0.44 (0.02-8.41)	**Low V_T / Low PEEP**										
2.62 (0.24-28.53)	0.47 (0.02-8.99)	1.07 (0.82-1.40)	**Low V_T / High PEEP + RM**									
2.55 (0.23-28.71)	0.46 (0.02-8.95)	1.04 (0.64-1.69)	0.97 (0.57-1.65)	**Low V_T / Low PEEP + RM**								
3.85 (0.27-54.37)	0.69 (0.03-16.34)	1.58 (0.49-5.09)	1.47 (0.45-4.86)	1.51 (0.45-5.07)	**Low V_T / Personal PEEP + RM**							
2.22 (0.01-343.89)	0.40 (0.00-82.96)	0.91 (0.01-77.71)	0.85 (0.01-73.17)	0.87 (0.01-76.53)	0.58 (0.01-57.41)	**High V_T / High PEEP + RM**						
0.74 (0.01-67.04)	0.13 (0.00-16.72)	0.30 (0.01-13.95)	0.28 (0.01-13.15)	0.29 (0.01-13.80)	0.19 (0.00-10.55)	0.33 (0.01-7.76)	**High V_T / Low PEEP + RM**					
2.48 (0.21-29.54)	0.44 (0.02-9.16)	1.01 (0.50-2.06)	0.95 (0.45-2.00)	0.97 (0.45-2.12)	0.64 (0.17-2.44)	1.12 (0.01-100.94)	3.35 (0.07-164.57)	**High V_T / Low PEEP**				
1.07 (0.16-7.36)	0.19 (0.00-8.52)	0.44 (0.04-4.72)	0.41 (0.04-4.48)	0.42 (0.04-4.76)	0.28 (0.02-3.94)	0.48 (0.00-74.83)	1.45 (0.02-131.29)	0.43 (0.04-5.16)	**High V_T / High PEEP**			
5.05 (0.30-84.43)	0.90 (0.03-24.57)	2.07 (0.45-9.41)	1.93 (0.42-8.91)	1.98 (0.43-9.11)	1.31 (0.20-8.53)	2.27 (0.02-249.86)	6.82 (0.11-419.32)	2.04 (0.40-10.37)	4.71 (0.28-78.68)	**High V_T / Personal PEEP**		
0.74 (0.01-38.02)	0.13 (0.00-9.91)	0.30 (0.01-7.02)	0.28 (0.01-6.63)	0.29 (0.01-6.99)	0.19 (0.01-5.51)	0.33 (0.01-7.76)	1.00 (0.11-8.92)	0.30 (0.01-7.49)	0.69 (0.01-35.42)	0.15 (0.00-4.80)	**High V_T / ZEEP + RM**	
1.52 (0.14-16.78)	0.27 (0.01-5.23)	**0.62 (0.44-0.88)**	**0.58 (0.39-0.87)**	**0.60 (0.41-0.88)**	0.40 (0.13-1.25)	0.69 (0.01-59.42)	2.06 (0.04-96.23)	0.61 (0.31-1.22)	1.42 (0.13-15.63)	0.30 (0.07-1.32)	2.06 (0.09-48.59)	**High V_T / ZEEP**

Figure 2 Network estimates and their corresponding certainty of evidence (using GRADE rating) for intra-operative ventilation strategy on pneumonia (19 randomised controlled trials). Values are risk ratio (RR) and 95%CIs. For the column compared with the row, RR < 1 means the top-left treatment is better (RR < 1 favours the treatment in the column). Dark blue, high certainty; light blue, moderate certainty; light red, low certainty; red, very low certainty. V_T, tidal volume; RM, recruitment manoeuvre; ZEEP, zero peak end expiratory pressure.

Low V_T / Low PEEP										
8.15 (1.58-42.05)	**Low V_T / Personal PEEP**									
0.89 (0.70-1.14)	**0.11 (0.02-0.58)**	**Low V_T / High PEEP + RM**								
1.06 (0.35-3.24)	**0.13 (0.02-0.95)**	1.19 (0.38-3.72)	**Low V_T / Low PEEP + RM**							
1.30 (1.04-1.63)	**0.16 (0.03-0.84)**	**1.46 (1.05-2.03)**	1.23 (0.39-3.83)	**Low V_T / Personal PEEP + RM**						
0.65 (0.02-23.42)	0.08 (0.00-4.11)	0.72 (0.02-26.46)	0.61 (0.01-26.16)	0.50 (0.01-18.14)	**High V_T / High PEEP + RM**					
0.13 (0.01-1.73)	**0.02 (0.00-0.34)**	0.14 (0.01-1.97)	0.12 (0.01-2.06)	0.10 (0.01-1.35)	0.20 (0.01-3.94)	**High V_T / Low PEEP + RM**				
1.07 (0.66-1.76)	**0.13 (0.02-0.73)**	1.20 (0.69-2.08)	1.01 (0.30-3.43)	0.83 (0.48-1.42)	1.66 (0.04-62.27)	8.31 (0.59-116.78)	**High V_T / Low PEEP**			
0.67 (0.18-2.47)	**0.08 (0.01-0.67)**	0.75 (0.20-2.83)	0.63 (0.19-2.17)	0.52 (0.14-1.94)	1.04 (0.02-47.43)	5.21 (0.29-95.04)	0.63 (0.16-2.52)	**High V_T / Personal PEEP**		
0.13 (0.02-0.96)	**0.02 (0.00-0.21)**	0.14 (0.02-1.09)	0.12 (0.01-1.20)	**0.10 (0.01-0.74)**	0.20 (0.01-3.94)	1.00 (0.19-5.23)	**0.12 (0.02-0.95)**	0.19 (0.02-2.09)	**High V_T / ZEEP + RM**	
0.34 (0.13-0.87)	**0.04 (0.01-0.27)**	0.38 (0.14-1.00)	**0.32 (0.14-0.74)**	**0.26 (0.10-0.69)**	0.52 (0.01-21.35)	2.60 (0.16-41.34)	**0.31 (0.11-0.91)**	0.50 (0.21-1.22)	2.60 (0.28-23.85)	**High V_T / ZEEP**

Figure 3 Network estimates and their corresponding certainty of evidence (using GRADE rating) for intra-operative ventilation strategy on hypoxaemia (12 randomised controlled trials). Values are risk ratio (RR) and 95%CIs. For column compared with row, RR < 1 means the top-left treatment is better (RR < 1 favours the treatment in the column). Dark blue, high certainty; light blue, moderate certainty; light red, low certainty; red, very low certainty. V_T, tidal volume; RM, recruitment manoeuvre; ZEEP, zero peak end expiratory pressure.

Low V_T/ ZEEP											
6.75 (0.77-58.93)	**Low V_T/ High PEEP**										
6.11 (0.76-49.21)	0.91 (0.50-1.63)	**Low V_T / Low PEEP**									
6.80 (0.83-55.63)	1.01 (0.59-1.72)	1.11 (0.86-1.44)	**Low V_T / High PEEP + RM**								
4.90 (0.49-48.66)	0.73 (0.24-2.19)	0.80 (0.31-2.09)	0.72 (0.27-1.90)	**Low V_T / Low PEEP + RM**							
15.97 (0.90-284.60)	2.37 (0.30-18.58)	2.61 (0.36-19.05)	2.35 (0.32-17.18)	3.26 (0.37-28.71)	**Low V_T/ Personal PEEP + RM**						
2.19 (0.20-24.29)	0.32 (0.09-1.24)	0.36 (0.11-1.19)	0.32 (0.09-1.10)	0.45 (0.10-2.08)	0.14 (0.01-1.40)	**High V_T / High PEEP + RM**					
2.07 (0.19-22.96)	0.31 (0.08-1.17)	0.34 (0.10-1.12)	0.30 (0.09-1.04)	0.42 (0.09-1.96)	0.13 (0.01-1.32)	0.95 (0.73-1.23)	**High V_T / Low PEEP + RM**				
4.50 (0.28-72.79)	0.67 (0.12-3.83)	0.74 (0.12-4.65)	0.66 (0.11-4.11)	0.92 (0.12-7.26)	0.28 (0.02-4.20)	2.05 (0.23-18.55)	2.17 (0.24-19.53)	**High V_T / Low PEEP**			
5.37 (0.67-43.08)	0.80 (0.05-12.96)	0.88 (0.06-13.43)	0.79 (0.05-12.21)	1.10 (0.06-19.75)	0.34 (0.01-9.81)	2.45 (0.12-48.27)	2.59 (0.13-50.86)	1.19 (0.04-32.11)	**High V_T / Personal PEEP**		
2.07 (0.19-22.70)	0.31 (0.08-1.14)	0.34 (0.11-1.10)	0.30 (0.09-1.01)	0.42 (0.09-1.93)	0.13 (0.01-1.30)	0.95 (0.73-1.23)	1.00 (0.79-1.26)	0.46 (0.05-4.10)	0.39 (0.02-7.51)	**High V_T / ZEEP + RM**	
2.59 (0.30-22.52)	**0.38 (0.18-0.82)**	**0.42 (0.24-0.75)**	**0.38 (0.22-0.65)**	0.53 (0.20-1.40)	0.16 (0.02-1.19)	1.19 (0.31-4.47)	1.25 (0.33-4.70)	0.58 (0.09-3.86)	0.48 (0.03-7.82)	1.25 (0.34-4.60)	**High V_T / ZEEP**

Figure 4 Network estimates and their corresponding certainty of evidence (using GRADE rating) for intra-operative ventilation strategy on atelectasis (17 randomised controlled trials). Values are risk ratio (RR) and 95%CIs. For column compared with row, RR < 1 means the top-left treatment is better (RR < 1 favours the treatment in the column). Dark blue, high certainty; light blue, moderate certainty; light red, low certainty; red, very low certainty. V_T, tidal volume; RM, recruitment manoeuvre; ZEEP, zero peak end expiratory pressure.

72, 78, 79, 81–83], eight trials used the same radiographic definition for atelectasis, while the remaining studies utilised varying definitions (online Supporting Information Table S17). Moderate certainty evidence suggests that low tidal volume/high PEEP (RR 0.38, 95%CI 0.18–0.82) and low tidal volume/high PEEP with recruitment manoeuvres (RR 0.42; 95%CI: 0.24–0.75) likely reduced the risk of postoperative atelectasis compared with a high tidal volume/ZEEP strategy. Meanwhile, low certainty evidence suggests that low tidal volume/low PEEP (RR 0.42, 95%CI 0.24–0.75) may result in a reduction in the incidence of atelectasis compared with high tidal volume/ZEEP strategy (Fig. 4). The relevant network plots for each complication are shown in online Supporting Information Figure S3 and the associated SUCRA rankings are in online Supporting Information Tables S18–S20.

There were insufficient trials to assess the escalation of respiratory support using network meta-analysis. Among the seven included trials [19, 38–40, 57, 66, 77], only one comparison leveraged two studies [38, 66]; the remaining estimates relied on individual study estimates (online Supporting Information Figure S4). A low tidal volume/personalised PEEP (vs. a low tidal volume/low PEEP) strategy may be associated with less escalation of respiratory support (two trials; RR 0.53, 95%CI 0.28–0.99) [38, 66]. Similarly, low tidal volume/personalised PEEP with recruitment manoeuvres may be associated with less escalation than a low tidal volume/low PEEP with recruitment manoeuvre strategy (one trial; RR 0.77, 95%CI 0.63–0.94) [77].

We did not identify an effect of one ventilation strategy compared with another on the most protracted mortality measure, duration of hospital stay, ICU admission and $PaCO_2$ (online Supporting Information Tables S21, S23, S25 and S27, respectively). The relevant network plots are shown in online Supporting Information Figure S5, with associated SUCRA rankings in online Supporting Information Tables S22, S24, S26 and S28.

We identified subgroup effects for the outcome of PPCs. Compared with a high tidal volume/ZEEP strategy, the benefit of a low tidal volume/low PEEP strategy on PPCs was identified in trials that included patients who underwent open abdominal surgery (RR 0.63, 95%CI 0.50–0.78) compared with trials that did not (RR 0.85, 95%CI 0.58–1.25, p value for interaction = 0.044, online Supporting Information Table S29). Similarly, compared with a high tidal volume/ZEEP strategy, the beneficial effect of a low tidal volume/high PEEP with a recruitment manoeuvre strategy (RR 0.60, 95%CI 0.49–0.75) was identified among trials that included patients in the supine (vs. prone) position (RR 0.53, 95%CI 0.42–0.67, p value for interaction = 0.005, online Supporting Information Table S32) We did not identify credible subgroup effects in any other planned subgroup analysis (online Supporting Information Tables S29–S33). We found no significant evidence of subgroup effects based on the risk of bias and the definitions used for tidal volume and atelectasis. Additionally, our sensitivity analysis based on the year of publication did not support that publication year influenced the effect of different interventions on any of the assessed outcomes (online Supporting Information Tables S34–S47).

Discussion

We found that the use of intra-operative low tidal volume alongside a range of acceptable PEEP levels (low, high and personalised PEEP) likely reduced the risk of PPCs compared with high tidal volume and ZEEP. Among low tidal volume strategies, choosing between a set level of PEEP (low or high, with or with a recruitment manoeuvre) likely does not reduce the risk of PPCs. Similarly, the addition of a recruitment manoeuvre to a fixed PEEP strategy did not confer a meaningful benefit over high or low PEEP alone. However, a low tidal volume and personalised PEEP strategy may result in a slight reduction in the incidence of PPCs compared with a low tidal volume/low PEEP strategy.

Previous meta-analyses that evaluated the association between ventilation strategies and PPCs restricted assessment to a limited number of intra-operative interventions (i.e. high tidal volume/ZEEP vs. low tidal volume/high PEEP) or combined different approaches for setting PEEP into a single category (e.g. grouped high PEEP and driving pressure-guided PEEP) [16–18]. Consequently, previous meta-analyses had lower ability, compared with our network meta-analysis, to discern important differences in treatment effects between and among alternative ventilation strategies. In addition, the use of a network meta-analysis design enabled comparison of the effects of multiple distinct ventilation strategies concurrently on clinical outcomes, including several ventilation strategies that have not been aggregated in previous pairwise meta-analyses or directly compared in randomised trials.

There are several key findings from this network meta-analysis. First, a low tidal volume strategy combined with low, high, or personalised PEEP strategy likely reduced the risk of PPCs compared with a high tidal volume/ZEEP strategy. This is consistent with previous meta-analyses of intra-operative ventilation as well as the ICU literature [18, 86] and aligns with pre-clinical evidence suggesting that high tidal volume ventilation is associated with mechanical stress and strain and may exacerbate lung inflammation and injury [87–89]. In addition, the presence of PEEP may avoid atelectrauma caused by alveolar collapse and consequent shear stress in the lungs during mechanical ventilation [90]. The physiologic consequences of surgical exploration may further enhance the need for PEEP. Increased intra-abdominal pressure, laparoscopic insufflation and postoperative ileus may all worsen atelectasis; therefore, PEEP may be of particular benefit in patients having surgery. To this end, a low tidal volume/ZEEP strategy results in little to no difference in the incidence of PPCs when compared with a high tidal volume/ZEEP strategy.

Second, we identified that a high tidal volume/low PEEP strategy may reduce the incidence of PPCs when compared with high tidal volume/ZEEP and is no more likely to reduce the risk of PPCs than low tidal volume and any level of PEEP, albeit with low certainty evidence. Recent evidence has shown that the positive effect of lowering tidal volume on outcomes varies according to respiratory system elastance and driving pressure [91]. When patients have severely damaged lungs, namely in acute respiratory distress syndrome, with limited lung available for tidal ventilation (high elastance), lowering tidal volume is associated with a mortality benefit. Conversely, with healthy lungs and low respiratory system elastance, the associated mortality benefit from lowering tidal volume is low [91]. As most patients undergoing general anaesthesia typically have relatively healthy lungs, our findings also suggest that modest increases in intra-operative tidal volume may not be associated with PPCs when PEEP is applied. Where concerns exist, clinicians may consider monitoring and documenting driving pressure intra-operatively to guide ventilation management and ensure lung protection.

Third, the findings from our study suggest that among patients receiving low tidal volume ventilation, the addition of a recruitment manoeuvre afforded little to no reduction in the incidence of PPCs relative to a high or low PEEP strategy alone. There was notable heterogeneity in the provision of recruitment manoeuvres across studies. Studies performed recruitment either by delivering a sustained positive airway pressure for a fixed time period or a step-wise incremental increase in tidal volume or positive airway pressure until a pre-determined plateau or peak inspiratory pressure was reached. Similarly, frequencies of repeat recruitment manoeuvres during surgery varied markedly. A recent Bayesian re-analysis of individual patient data from three large randomised clinical trials found a high likelihood that high PEEP combined with recruitment manoeuvres slightly reduced the probability of PPCs relative to a low PEEP strategy, particularly in patients undergoing laparoscopy and those at higher risk of PPCs [92]. While these findings suggest a potential benefit, the effect size was small and the optimal approach to recruitment manoeuvres – including their frequency, duration and interaction with PEEP levels – remains uncertain. Further studies directly comparing different recruitment strategies and their clinical impact are needed to refine their role in intra-operative ventilation strategies.

Finally, among patients who received a low tidal volume strategy, there was little to no difference in the incidence of PPCs between low (1–5 cmH_2O) or high (> 5 cmH_2O) PEEP, while a personalised PEEP strategy likely reduced PPCs compared with a low, but not high, PEEP strategy. Personalising PEEP titration for individual patients' respiratory system compliance may recruit atelectatic lung where possible and minimise overdistension [93]. In this context, a personalised PEEP strategy likely reduced postoperative hypoxaemia when compared with most ventilation strategies in the included studies. Nevertheless, we cannot conclude that there is an optimal PEEP strategy among patients who are receiving low tidal volume for the prevention of PPCs. While both high and personalised PEEP strategies appear favourable for selected outcomes, these findings are supported by moderate certainty evidence and a range of equally acceptable PEEP strategies likely exist for intra-operative patients with relatively healthy lungs.

Uncertainty exists regarding the role of personalising PEEP using either static or dynamic compliance; transpulmonary pressure; varying recruitment manoeuvres; and stepwise decremental PEEP strategies. While a recent large multicentre trial in patients undergoing one-lung ventilation showed that an alveolar recruitment manoeuvre to 40 cmH_2O of end-inspiratory pressure followed by a decremental PEEP trial to optimise dynamic compliance was associated with fewer PPCs than low PEEP [94], it remains unclear whether similar benefits may be realised for patients undergoing non-cardiothoracic surgery. Others have proposed titrating PEEP to transpulmonary pressure; that is, the lung-distending pressure, using oesophageal manometry, which may have physiological benefits, particularly as the chest wall elastance increases (for example, in cases of pneumoperitoneum or obesity) [95]. However, PEEP titrated using oesophageal manometry, essential for calculating transpulmonary pressure, is challenging to implement at the bedside and has not shown a mortality benefit over a high-PEEP strategy in patients with severe acute respiratory distress syndrome [96].

Despite the suggestion that a lung protective ventilation strategy that includes low tidal volume and moderate PEEP may benefit patients in previous clinical trials and meta-analyses [11], implementation in routine practice has been variable. Audits of health administrative data from the USA and the UK have shown that ventilation with high tidal volume and ZEEP remains commonplace [97, 98]. In this context, findings from this network meta-analysis have implications for intra-operative management and future research. Ventilation strategies that incorporate either high or low tidal volume and ZEEP may be associated with harm. Conversely, a low tidal volume strategy is associated with improved pulmonary outcomes for patients undergoing non-cardiothoracic surgery when paired with a range of acceptable PEEP levels, including low, high and personalised PEEP.

Moderate-certainty evidence suggests that a personalised PEEP strategy, which aims to optimise dynamic or static lung compliance, may be associated with a reduction in the incidence of PPCs and postoperative hypoxaemia. However, these findings are largely based on indirect evidence, and many trials used high tidal volume and ZEEP as the comparator. Additional multicentre trials are needed to evaluate the effects of personalised PEEP strategies compared with low tidal volume and standardised PEEP strategies on patient-centred outcomes. These trials should establish pragmatic approaches for setting personalised PEEP for individual patients and identify specific circumstances (e.g. patients with obesity and laparoscopic procedures) where its use may be most beneficial. Similarly, recent evidence indicates that the benefit of lowering tidal volume on patient outcome may vary depending on respiratory system elastance and driving pressure [91]. The finding that high tidal volume may not be associated with PPCs when low PEEP is applied among patients with potentially healthy lungs may support this hypothesis. As in the ICU context, future trials should focus on assessing whether intra-operative ventilation strategies that limit driving pressure can lead to improved patient outcomes (NCT05440851).

Our network meta-analysis has limitations. There was notable heterogeneity in patient populations, surgical procedures, trial protocols and outcome definitions utilised across the included trials. Most trials focused on patients undergoing open or laparoscopic intra-abdominal and gynaecologic surgeries, which may limit the generalisability of our findings. Although subgroup and sensitivity analyses were conducted to address heterogeneity, residual confounding and variability in treatment effects exist. To this end, we were unable to address the variation in trial protocols and other peri-operative management (neuromuscular blockade antagonism, fluid and blood product administration and postoperative pain management) that may confound the relationship between surgery and PPCs. In addition, trial authors used variable outcome definitions and follow-up periods. The diverse definitions utilised for PPCs precluded subgroup and sensitivity analyses, necessitating caution when interpreting our findings. In this context, future multicentre trials evaluating intra-operative ventilation strategies should prioritise being powered adequately for standardised, guideline-recommended and patient-centred outcomes. The International Standardised Endpoints in Perioperative Medicine initiative, for example, has established clear definitions and severity-based criteria for PPCs, highlighting the importance of using robust, well-defined and clinically relevant outcome measures [24]. We did not include paediatric or cardiothoracic trials, and we did not assess the potential adverse cardiovascular effects related to the use of higher tidal volumes, PEEP or recruitment manoeuvres as assessed elsewhere [18].

In summary, among patients undergoing non-cardiothoracic general anaesthesia, the use of intra-operative low tidal volume ventilation with a range of acceptable PEEP levels likely reduced the risk of PPCs compared with high tidal volumes and ZEEP. Moreover, compared with a low tidal volume/low PEEP strategy, a low tidal volume strategy with personalised PEEP likely reduces the risk of PPCs. This study highlights the need for further work to improve intra-operative adherence to lung protective ventilation strategies and evaluate low tidal volume and personalised PEEP in future randomised trials. Importantly, future multicentre trials evaluating intra-operative ventilation strategies should prioritise being powered adequately for patient-centred, guideline recommendation standardised outcomes to provide greater certainty regarding the efficacy of these strategies.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Search strategy.

Appendix S2. Data extraction form.

Figure S1. Identification of trials included in the network meta-analysis.

Figure S2. Risk of bias of the included trials.

Figure S3. Network plots (a) postoperative pulmonary complications (b) pneumonia (c) hypoxaemia and (d) atelectasis.

Figure S4. Meta-analysis comparing the effect of ventilation strategy on the requirement for escalation of respiratory support.

Figure S5. Network plots (a) mortality (b) hospital duration of stay (c) ICU admission and (d) $PaCO_2$.

Table S1. European Perioperative Clinical Outcome definition of PPCs.

Table S2. Interventions and outcomes assessed in included studies.

Table S3. Neuromuscular blockade, monitoring and antagonism in included studies.

Table S4. Recruitment manoeuvre procedures and frequencies in included studies.

Table S5. Definitions of PPCs in the included studies.

Tables S6–S13. Direct and indirect estimates of effect and p value for pairwise incoherence for ventilation strategy on PPCs, pneumonia, hypoxaemia, atelectasis, mortality, ICU admission, duration of hospital stay and $PaCO_2$, respectively.

Table S14. SUCRA and ranking probabilities for ventilation strategy on PPCs.

Tables S15–S17. Definitions of pneumonia, hypoxaemia and atelectasis in the included studies, respectively.

Tables S18–S20. SUCRA and ranking probabilities for ventilation strategy on pneumonia, hypoxaemia and atelectasis, respectively.

Table S21. Network estimates and their corresponding certainty of evidence for ventilation strategy on mortality.

Table S22. SUCRA and ranking probabilities for ventilation strategy on mortality.

Table S23. Network estimates and their corresponding certainty of evidence for ventilation strategy for length of hospital stay.

Table S24. SUCRA and ranking probabilities for ventilation strategy on duration of hospital stay.

Table S25. Network estimates and their corresponding certainty of evidence for ventilation strategy on ICU admission.

Table S26. SUCRA and ranking probabilities for ventilation strategy on ICU admission.

Table S27. Network estimates and their corresponding certainty of evidence for ventilation strategy on $PaCO_2$.

Table S28. SUCRA and ranking probabilities for ventilation strategy on $PaCO_2$.

Tables S29–S33. Test of interaction for open abdominal surgery, laparoscopic surgery, duration of surgery, prone position and obesity subgroups on PPCs, respectively.

Tables S34–S39. Test of interaction for risk of bias and weight used for tidal volume subgroup on PPCs, hypoxaemia, pneumonia, mortality, duration of hospital stay and arterial $PaCO_2$, respectively.

Table S40. Test of interactions for risk of bias definition used for atelectasis and weight used for tidal volume subgroups on atelectasis.

Tables S41–S47. Network estimates for ventilation strategy on PPCs, atelectasis, hypoxaemia, mortality, pneumonia, duration of hospital stay and $PaCO_2$, respectively, excluding studies before 2010.

