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Protective ventilation reduces postoperative pulmonary complications in patients undergoing general anesthesia: a meta-analysis of randomized controlled trials

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ABSTRACT

Objective

To determine whether anesthetized patients undergoing surgery could benefit from intraoperative protective ventilation remains unclear and controversial.

Methods

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to February 2014. Eligible studies evaluated lower versus higher tidal volumes in anesthetized patients at the onset of mechanical ventilation without ARDS. The primary outcome was the incidence of postoperative pulmonary complications. Included studies must report at least one of the following endpoints: the incidence of atelectasis or acute lung injury or pulmonary infections.

Results

Eight studies (804 patients) were included. Meta-analysis using a random effect model showed a decrease in the incidence of atelectasis (OR=0.45; 95% CI=0.27-0.76; *P*=0.003; I^2 =9%), lung injury (OR=0.37; 95% CI=0.14-0.97; *P*=0.04; I^2 =0%) and pulmonary infections (OR=0.32; 95% CI=0.18-0.57; *P*=0.0001; I^2 =0%) in patients receiving protective ventilation. Ventilation with lower tidal volumes did not reduce the all-cause mortality (OR=0.86; 95% CI=0.40-1.86; *P*=0.71; I^2 =0%), the length of hospital stay (WMD=-0.55, 95% CI=-2.67-1.56; *P*=0.61; I^2

=66%) or the length of ICU stays (WMD=-0.81, 95% CI=-1.77-0.15; P=0.10; I^2 =46%).

Conclusions

Intraoperative use of protective ventilation strategy has the potential to reduce the incidence of postoperative pulmonary complications in patients undergoing general anesthesia. Prospective, well-designed clinical trials are warranted to confirm the beneficial effect of protective ventilation strategy in surgical patients.

Strengths and limitations of this study

Strengths: Accumulating evidence suggested that mechanical ventilation using a high tidal volume in particular may cause alveolar overstretching or even induce lung injury. Whether anesthetized patients undergoing surgery could benefit from intraoperative protective ventilation remains unclear and controversial. We reported in this meta-analysis based on the data available that intraoperative use of protective ventilation strategy in patients undergoing general anesthesia could reduce the incidence of postoperative complications including atelectasis, pulmonary infections and lung injury. Our study involved only eligible RCTs in the combined analysis to minimize the potential biases. Hence, our study may provide the latest evidence of protective ventilation in the operating room.

Limitations: Firstly, most trials enrolled this meta-analysis did not allow to differentiate between the effects of low tidal volumes and higher PEEP or application of recruitment maneuvers. Pooled analysis of the effects of PEEP or recruitment maneuvers was also part of meta-analysis of lower tidal volumes. Secondly, although no significant heterogeneity was observed in our analysis, the primary studies varied in the design, study population and follow-up periods, and so pooled results need to be viewed cautiously. Finally, despite a comprehensive search strategy, we could not assess the publication bias due to the small number of studies involved.

INTRODUCTION

Postoperative pulmonary complications are the main cause of overall perioperative morbidity and mortality in patients following general anesthesia [1, 2]. Induction of anesthesia is consistently accompanied by a significant reduction in lung volume and rapid formation of atelectasis[3]. Prevention of these complications would improve the quality of medical care and decrease the hospital costs[4]. However, few interventions have been identified to clearly or possibly reduce the postoperative lung function impairment[5].

Mechanical ventilation is an essential supportive strategy in patients undergoing general anesthesia. Knowing that a high tidal volume (10 to 15ml per kilogram of predicted body weight) can maintain better gas exchange and intraoperative mechanics, it has conventionally been recommended for intraoperative ventilation[6]. However, accumulating evidence from both experimental and clinical studies indicated that mechanical ventilation using a high tidal volume in particular may cause alveolar overstretching or even induce organ injury[7, 8].

Protective ventilation strategy refers to the use of low tidal volume (in the range of 4–8 ml/kg of predicted body weight) with or without positive end expiratory pressure (PEEP) and recruitment maneuvers, which appears to protect lung from ventilator-induced lung injury. Protective ventilation has been considered the optimal practice in patients suffering from the acute respiratory distress syndrome (ARDS)[9, 10]. However, few human studies have assessed how to ventilate healthy lungs in patients undergoing general anesthesia. In a large retrospective cohort study, Gajic *et al*[11] found that the development of acute lung injury (ALI) was independently associated with a high tidal volume and high peak airway pressure. Subsequently, several studies attempted to uncover the cause of ventilator associated lung injury and find ways to minimize the side effects of high volume-high pressure ventilation in surgical patients. A prior meta-analysis of clinical trials performed by Hemmes *et al*[12] reported that intraoperative lung protective ventilator settings had the potential to protect against pulmonary complications. Their study included six randomized controlled trials (349 patients) and two observational studies (1320 patients). Owing to the relatively small sample size in the RCTs, the evidence derived from the meta-analysis by Hemmes *et al* might lack reliability. Recently, two well-designed RCTs [13, 14] with a much larger sample size, conducted in patients receiving abdominal surgery, have been published in leading medical journals. Therefore, we conducted the present meta-analysis of all RCTs available in an attempt to determine the overall effectiveness of protective ventilation in surgical patients at the onset of mechanical ventilation.

METHODS

Search strategy

This analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the QUOROM (quality of reporting of meta-analyses) statement. We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), update to February 2014. Our search was restricted to RCTs published in full-text versions, without a language restriction. Additional relevant articles were identified by manually searching bibliographies and conferences. Our search strategy was based on three search themes all combined with the Boolean OR operator. The protective ventilation filter contained the following MeSH terms: "protection ventilation", "low tidal volume ventilation" and "conventional ventilation". The surgical patients filter included: "surgical", "surgery", "general anesthesia" and "operating room". The clinical trials filter included the MeSH terms "clinical trials [publication type]," "clinical trials as topic" with text words "trial*," or "random*".

Selection criteria

Study inclusion criteria were based on the following attributes: 1) population: adult (>18 yr) surgical patients receiving mechanical ventilation in the operating room; 2) intervention: the use of a protective

ventilation strategy (lower tidal volume, with or without PEEP and recruitment maneuvers) versus the conventional ventilation method (high tidal volume, with or without PEEP and recruitment maneuvers) regardless of surgical types or duration; 3) predefined outcomes: the incidence of atelectasis, acute lung injury, pulmonary infections, short-term postoperative mortality(<60d), the length of hospital stay and ICU stay, $PaCO_2$ and/or plateau pressure; 4) design: randomized controlled parallel trials. Eligible studies must report at least one of the following endpoints: the incidence of atelectasis or acute lung injury or pulmonary infections.

Data extraction and validity assessment

Three authors screened the titles and abstracts of initial search results, extracted the data and assessed the risk of bias independently. Any disagreements between the reviewers were resolved by discussion. Additional information was obtained by directly questioning the correspondence authors in relevant articles whenever needed.

Methodologic quality was assessed using the Cochrane Collaboration risk of bias tool that considered seven different domains: adequacy of sequence generation, allocation concealment, blinding of participants, blinding for outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias.

Statistical analysis

We extracted data regarding the study design, patient population, interventions and parallel controls, intraoperative ventilation mechanics and clinical outcomes. The primary endpoints concerned were the incidence of atelectasis, acute lung injury and pulmonary infections. The secondary outcomes included the all-cause mortality, length of ICU stay and length of hospital stay. Some trials reported median as a treatment effect, with accompanying interquartile(IQR) or range. For the purpose of analysis, the median was assumed as equivalent to the mean, and SD was estimated with IQR/1.35 or Range/4 according to the sample size and distribution (Cochrane Handbook). For dichotomous data, odds ratio (OR) was used to describe the size of treatment effect, and for continuous variables, weighted mean difference (WMD) was employed.

Homogeneity assumption was measured by the I^2. It is calculated as: I^2= 100% * (Q-df)/Q, where Q is the Cochran's heterogeneity. A value of 0% indicates no observed heterogeneity, and larger values correlated with increasing heterogeneity.

Synthesis of the data was performed using the random-effects model. Funnel plots of the incidence of atelectasis was used to visually assess the publication bias. Sensitivity analyses were carried out for different subgroups according to relevant clinical features. In addition, we performed subgroup analyses to determine whether the treatment effects were similar in one-lung ventilation (OLV) or two-lung ventilation (TLV).

All analyses were performed using Review Manager (RevMan) [Computer program] Version 5.1. Significant differences are set at $P<0.05$.

RESULTS

Literature identification and study characteristics

Our initial search yielded 1447 publications (547 from MEDLINE, 480 from EMBASE, and 420 from CENTRAL). After removing 307 duplicates, abstracts of 1140 articles were screened by three independent authors. Of them, 58 records were retrieved for detailed evaluation. Subsequently, 50 articles were excluded for the following reasons: no data on outcomes of interest; observational cohort study, not for treatment of surgical patients. The remaining eight randomized controlled trials enrolling 804 patients were included in the final analysis (Figure 1).

Table 1 describes the characteristics of the eight studies including patient enrollment, surgical type, duration of ventilation, intervention and control treatment, primary outcome. Two-lung ventilation was conducted in five studies and one-lung ventilation was performed in the remaining three studies. Tidal volume was set to 5-7 ml/kg of the body weight in the protective group and 9-12ml/kg in the control group. Tidal volume was calculated using predicted body weight in six studies and the other two studies [15, 16] did not reported what weight was used. Six studies used PEEP (3-12cm H_2O) only in the treatment group and one study [17] used PEEP (5 cm H_2O) in both groups. Recruitment maneuver was employed in the protective group in four studies [13, 14, 17, 18]. Atelectaisis was diagnosed with chest radiograph (six studies using X-rays and one study using CT scan). Lung injury was diagnosed according to the American-European Consensus Conference definition in four studies [13, 17-19], with no specific statement in one study [20].

An overview of the risk of bias is described in Figure 2. The randomized sequence was adequately generated in seven studies, and in one study[16], where it was judged as unclear due to inadequacy of the report. Six studies [13, 14, 17-20] reported adequate allocation concealment. Double-blinded fashion was performed in two studies [13, 17] while outcome assessment was blinded in five studies [13, 15, 17, 19, 20]. Age, weight, gender and duration of ventilation were parallelly comparable. Plateau pressure was lower in the protective ventilation group compared with that in the control group in the final follow-up (WMD=-2.4 cm H_2O, 95%CI=-4.69--0.11, P=0.04). $PaCO_2$ tended to be higher in the protective ventilation group, but the difference did not reach statistical significance (WMD=-2.15 mmHg, 95%CI=-0.74-5.04, P=0.14).

Primary outcome

Seven studies reported the incidence of atelectasis during follow-up periods. Atelectasis developed in 64 of the 375 patients ventilated with lower tidal volumes and 98 of the 375 patients ventilated with conventional tidal volumes. Our meta-analysis of these trials indicated that there was a significant decrease in the incidence of atelectasis in those using the protective ventilation strategy (OR=0.45; 95% CI=0.27-0.76; *P*=0.003; *P* for heterogeneity=0.36, I^2 =9%; Figure 3). The incidence of acute lung injury and pulmonary infections were lower in the protective ventilation group compared with the conventional ventilation group (OR=0.37; 95% CI=0.14-0.97; *P*=0.04; *P* for heterogeneity=0.65, I^2 =0%; and OR=0.32; 95% CI=0.18-0.57; *P*=0.0001; *P* for heterogeneity=0.42, I^2 =0% respectively; Figure 4, 5). Subgroup analysis indicated that the incidence of atelectasis and pulmonary infections were significantly lower in patients of the protective ventilation group during two-lung ventilation, with a trend toward a decreased (but not significant) incidence of acute lung injury (Figure 3, 4). During one-lung ventilation, low tidal volumes were associated with decreased incidence of atelectasis, acute lung injury and postoperative pulmonary infections, but the difference did not reach statistically significant (OR=0.81, 95% CI=0.17-3.84; OR=0.36, 95% CI=0.10-1.25; OR=0.33, 95% CI=0.10-1.09, respectively)(Figure 3, 4, 5).

Secondary outcomes

Data from five studies were available for assessing mortality during the follow-up periods. For the 693 evaluable patients, no significant reduction in the risk of mortality was observed in patients receiving protective ventilation strategy (OR=0.86; 95% CI=0.40-1.86; *P*=0.71; *P* for heterogeneity=0.94, I^2 =0%). Length of ICU stay or hospital stay was not significantly different in the protective ventilation group compared with control group (WMD=-0.81 day, 95% CI=-1.77, 0.15; *P*=0.10; *P* for heterogeneity=0.13, I^2 =46%; WMD=-0.55 day, 95% CI=-2.67-1.56; *P*=0.61; *P* for heterogeneity=0.03, I^2 =66%).

Sensitivity analysis

Stratified analysis was performed based on a number of key study characteristics and clinical features. The results of stratified analysis are summarized in Table 2. Three studies incorporated recruitment maneuvers in the protective ventilation group versus no recruitment maneuvers in the control group. Pooled analysis indicated that low tidal volumes combined with recruitment maneuvers led to a significant reduction in the incidence of atelectasis and pulmonary infections, with a trend towards a lower incidence in acute lung injury(OR=0.39, 95% CI=0.22-0.70, *P*=0.002; OR=0.19, 95% CI=0.08-0.45, *P*=0.0001; OR=0.40, 95% CI=0.07-2.15, *P*=0.28, respectively). Regarding the incidence of atelectasis, no significant difference was found when excluded the largest study by Futier [13].

DISCUSSION

The main finding of this meta-analysis is that the protective ventilation strategy can reduce postoperative pulmonary complications in surgical patients receiving mechanical ventilation. Protective ventilation strategy did not reduce the all-cause mortality, length of hospital stay or length of ICU stay. Only three studies were involved in the subgroup analysis of one-lung ventilation, and the beneficial effect of protective ventilation in these patients was not convincing with respect to the postoperative complications.

Prescription of mechanical ventilation has changed over the past few decades, with low tidal volumes strong advocated, especially in patients with acute lung injury[9, 21]. Both basic and clinical evidence indicated that an injurious ventilation setting could result in the development of diffuse alveolar damage, pulmonary edema, recruitment of inflammatory cells, and production of cytokines[22, 23]. It is evident that the use of low tidal volumes is associated with reduced morbidity and mortality in ARDS patients, and thus guidelines strongly advise using protective ventilation strategy in these patients[24-26]. However, there is little evidence regarding the benefits of ventilation with low tidal volumes in patients undergoing surgery without obvious lung injury or ARDS preoperatively. In order to prevent atelectasis and hypoxemia in surgical patients, it is still common today for surgical patients undergoing general anesthesia to receive a larger tidal volume [27, 28]. Later animal studies indicated that ventilation with a higher tidal volume could damage the healthy lungs, stimulate the release of inflammatory chemicals and predispose animals to organ damage [29-31]. However, some observational studies in humans argued the usefulness of ventilation with a low tidal volume [32, 33]. Recently, several clinical trials were conducted in the operating room to study the influence of ventilator settings on the surrogate endpoints, including inflammatory responses, postoperative pulmonary complications, postoperative lung function, and oxygenation. Despite heterogeneity of surgical types, most trials found that the protective ventilation strategy could attenuate the inflammatory responses, improve lung function and minimize potential oxygen desaturation [14, 16, 19, 20, 34, 35].

Our aim was to combine data from all well-designed RCTS available that had the scope to show the effects of protective ventilation in surgical patients. The current meta-analysis focused mainly on the clinical outcomes with protective ventilation. The results of our meta-analysis are mainly in line with a previous systematic review suggesting that protective ventilation significantly reduced the incidence of atelectasis, lung injury and pulmonary infections[12]. It is worthwhile to note that their analysis included two large scale observational studies, which accounted for 79.1% of the total sample size in the meta-analysis. It is generally known that assignment of treatments is outside the control of investigators and confounding variables may differ between the two groups in an observational study. The results in the previous meta-analysis may be biased owing to the wide set of selection criteria to some extent. In contrast, our current analysis excluded all the retrospective or cohort studies and involved two further RCTs with larger samples (455 patients), which were well-designed and of high quality. Hence, our study may provide more valid evidence and minimize potential bias.

It seems rational to draw a conclusion that lower tidal volumes can decrease the intrapulmonary pressure and reduce the risk of ventilation-associated lung injury. However, we could not exclude the possibility that it may increase cyclic alveolar collapse of dependent lung regions, thus raising the risk of atelectasis and hypercapnia[36, 37]. Application of PEEP and recruitment maneuvers may counteract these side-effects of low tidal volume ventilation. The use of moderate levels of PEEP was effective to maintain the end-expiratory lung volume, improve oxygenation and dynamic compliance of respiratory system [38]. Therefore, it would be reasonable to assume that PEEP may contribute to the beneficial effect of protective ventilation. Traschan *et al*[17] used a minimum of 5 cmH_2O PEEP in both groups to counter-balance the component of cyclic of airway opening and closing. Interestingly, their study found that ventilation with lower tidal volumes during upper abdominal surgery did not improve the postoperative lung function. However, their results should be interpreted cautiously because significantly higher minute ventilation and a two-fold higher respiration rate were used in the low tidal volume group (7.8±2.1 *vs.* 6.2±1.9 L/min; 17±4 *vs.* 8±4 times/min， respectively).

Three clinical trials in this meta-analysis used recruitment maneuvers in the protective ventilation group versus no recruitment maneuvers in the control group. Sensitivity analysis of trials with or without recruitment maneuvers did not change the results of the incidence of pulmonary infections between groups. However, there is a significantly lower incidence of atelectasis observed in the subgroup with recruitment maneuvers only (Table 2). Thinking PEEP alone cannot effectively reopen the collapsed lung, one may argue that repeated recruitment maneuver is an essential component of protective ventilation for complete reopening of atelectasis. Serita *et al*[39] found that individualized recruitment maneuvers brought improvement in oxygenation and lung compliance in patients undergoing selective cardiac surgery. The beneficial effects of recruitment maneuvers were also demonstrated in obese patients during laparoscopic surgery [40], while these effects in other types of surgery need to be clarified. It should be noted that recruitment maneuvers could cause a decrease in right ventricular preload and reduction in left ventricular stroke volume, which should be used cautiously in hemodynamically unstable patients. Given the uncertain influence of recruitment maneuvers on clinical outcomes, it is prudent to neither recommend nor reject recruitment maneuvers as a routine at present.

Thoracic surgical candidates represent a particular group of non-critically ill patients in whom mechanical ventilation produces a pro-inflammatory state that renders the host more vulnerable to subsequent ischemia reperfusion, hypoxia-reoxygenation and alveolar damage[20]. Studies by Lin *et al* [16]and Michelet *et al* [20]found that the lung protective ventilation strategy decreased the IL-6 and IL-8 release, and inhibited the lung inflammatory response during one lung ventilation and postoperatively. Our subgroup analysis of one lung ventilation indicated that patients in the protective ventilation group tend to have a lower incidence of postoperative complications, but the difference did not reach statistical significance. None of interaction P values for subgroup difference was significant, suggesting that the effect of protective ventilation was not different between the two subgroups. Owing to the limited data in one lung ventilation studies, the special role of protective ventilation on clinical outcomes remains to be elucidated.

There are several limitations in the current study. First, most trials enrolled this meta-analysis did not allow to differentiate between the effects of low tidal volumes and higher PEEP or application of recruitment maneuvers. Pooled analysis of the effects of PEEP or recruitment maneuvers was also part of meta-analysis of lower tidal volumes. Second, the incidence of atelectasis and acute lung injury could be higher than that reported in the enrolled trials. It is reported that X-rays may underestimate the presence of atelectasis compared with CT scan[41]. Atelectasis was diagnosed by X-rays in most trials except that by Cai *et al*[15], where CT scan showed a significantly higher incidence of atelectasis. Clinical manifestations of ARDS were often similar to pulmonary infection characterized by pulmonary infiltrate, high fever and leucocytosis. It would be possible that some patients with ventilator-associated injuries were incorrectly diagnosed as pneumonia arising from other reasons[42]. Third, although no significant heterogeneity was observed in our analysis, the primary studies varied in the design, study population and follow-up periods, and so pooled results need to be viewed cautiously. Finally, despite a comprehensive search strategy, we could not assess the publication bias due to the small number of studies involved.

CONCLUSION

Based on the data available, intraoperative use of protective ventilation strategy in patients undergoing general anesthesia could reduce the incidence of postoperative atelectasis, pulmonary infections and lung injury. Prospective, well-designed clinical trials are warranted to confirm the beneficial effect of protective ventilation strategy in surgical patients, especially in those with high risk of lung morbidity.

Table 1 Characteristics of the clinical trials included in the meta-analysis

Source	No. of patients	Protective $V_{T(ml/kg)}$	Protective No	Conventional $V_{T(ml/kg)}$	Conventional No	Setting	Design	Duration of ventilation PV(h)	Duration of ventilation CV(h)	PEEP(PV/CV) (cmH_2O)	RM	Primary outcome
Severgnini 2013	55	7	28	9	27	Abdominal	P,R,NB,S	3.2±1.1	3.7±1.3	10/0	Yes	Pulmonary infection
Futier 2013	400	6-8	200	10-12	200	Abdominal	P,R,DB,M	5.3±2.3	5.7±2.1	6-8/0	Yes	Pneumonia
Treschan 2012	101	6	50	12	51	Abdominal	P,R,DB,S	8.7±5.2	8.7±5.9	5/5	Yes	Spirometry
Yang 2011	100	6	50	10	50	Thoracic	P,R,OB,S	2.0±0.7	2.1±0.9	5/0	No	Lung injury
Weingarten 2009	40	6	20	10	20	Abdominal	P,R,NB,S	5.1±1.9	5.7±1.7	12/0	Yes	Oxygenation
Lin 2008	40	5-6	20	10	20	Thoracic	P,R,OB,S	3.8±0.5	4.0±0.5	3-5/0	No	Cytokines
Michelet 2006	52	5	26	9	26	Thoracic	P,R,OB,S	1.4±0.5	1.5±0.5	5/0	No	Cytokines
Cai 2004	16	6	8	10	8	Neurosurgery	P,R,OB,S	6.9±2.2	7.3±3.1	0/0	No	Atelectasis
Total	804	-	402	-	402	-	-	4.9±3.2	5.2±3.4	-	-	-

P, prospective; R, randomized; DB, double blinded; OB, outcome assessors only blinded; NB, non-blinded; M, multicenter; S, single center; RM, recruitment maneuver

Table 2 Summary of stratified analysis

Stratified analysis	No. of trials	No. of patients	Odds Ratio(95%CI)	P value	P for heterogeneity
Atelectasis					
Recruited maneuvers*					
Yes	3	493	0.39(0.22, 0.70)	0.002	0.63
No	3	156	1.24(0.32, 4.88)	0.76	0.32
Blinded					
Yes	5	657	0.47(0.22, 1.01)	0.05	0.20
No	2	93	0.60(0.19, 1.90)	0.39	0.65
Sample size>200					
Yes	1	400	0.34(0.17, 0.66)	0.002	-
No	6	350	0.57(0.28, 1.17)	0.13	0.34
Diagnosis					
X-rays	6	734	0.40(0.25, 0.64)	0.0002	0.64
CT	1	16	4.20(0.33, 53.12)	0.27	-
Pulmonary infections					
Recruited maneuvers					
Yes	3	493	0.19(0.08, 0.45)	0.0001	0.95
No	2	152	0.33(0.10, 1.09)	0.07	0.28
Blinded					
Yes	4	653	0.35(0.16, 0.81)	0.01	0.24
No	2	93	0.21(0.07, 0.66)	0.008	0.78
Sample size>200					
Yes	1	400	0.18(0.05, 0.61)	0.006	-
no	5	346	0.37(0.19, 0.72)	0.004	0.43

* One study (Treschan 2012) used recruited maneuvers in both protective group and control group, and it was excluded in stratified analysis.

Abbreviation

RCTS: randomized controlled trial; ICU: intensive care unit; PEEP: positive end expiratory pressure; ARDS: acute respiratory distress syndrome; ALI: acute lung injury; WMD: weighted mean difference; RM: recruitment maneuvers; TLV: two lung ventilation; OLV: one lung ventilation

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Authors' contributions

TT, LB contributed equally to this article. They all participated to the study design, data collection and also draft the manuscript. FC, QX, YZ, BH helped in the design of the study and analysed the data. Both XD and JL designed this study, supervised the data collection and revised this article. All authors read and approved the final manuscript.

Competing interests

The author(s) declare that they have no competing interests.

Data Sharing Statement

No additional data

Reference

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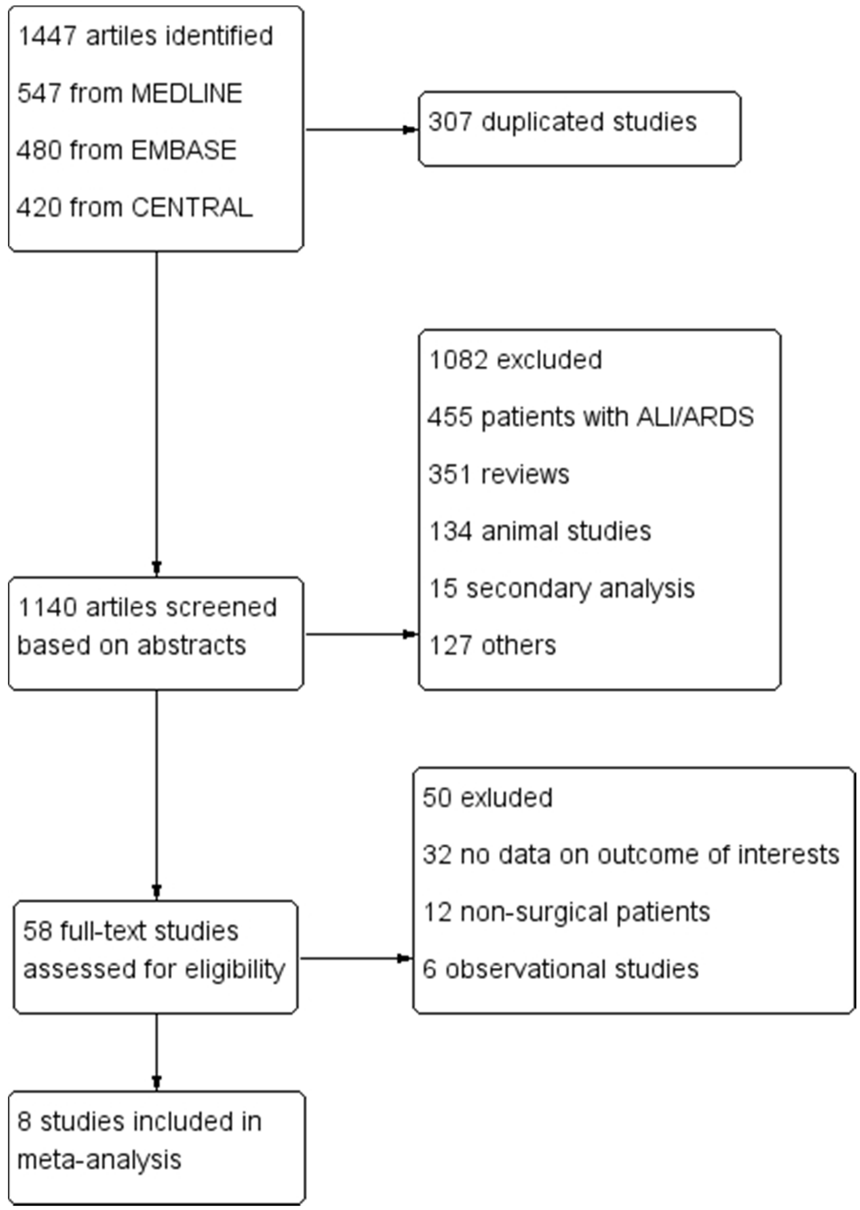

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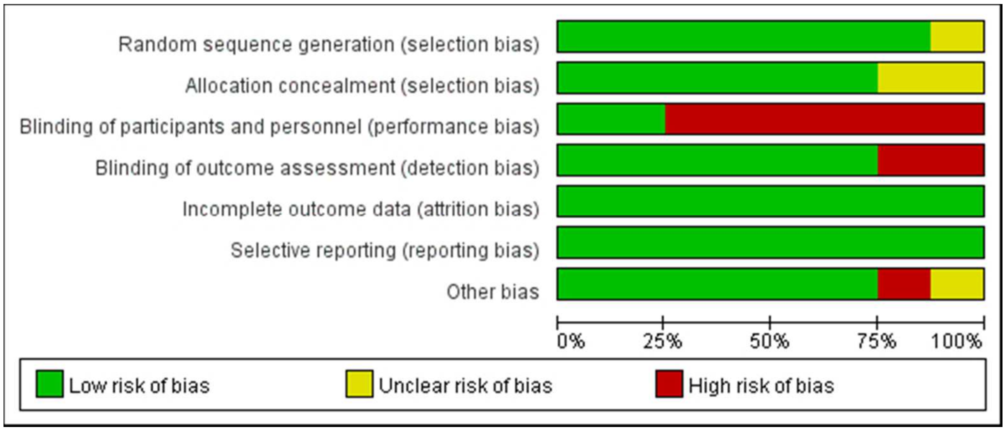

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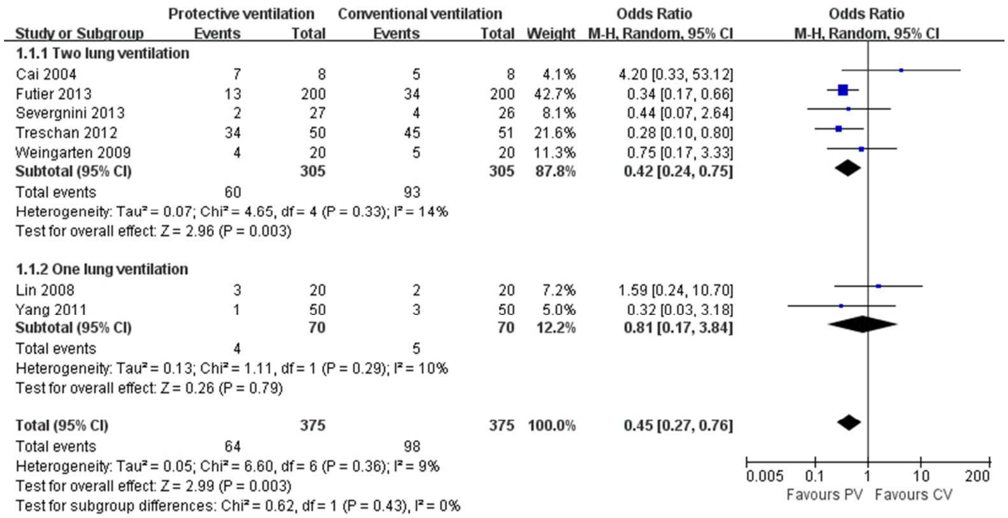

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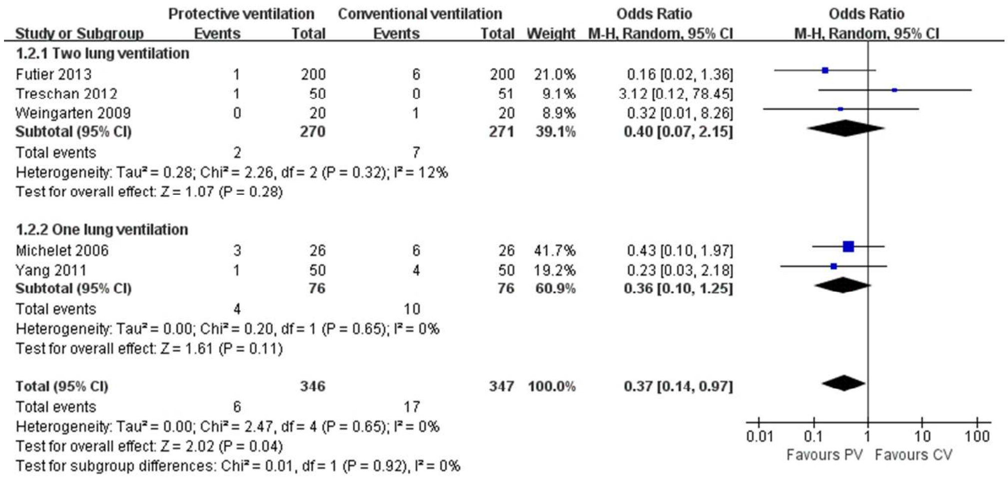

Study or Subgroup	Protective ventilation Events	Protective ventilation Total	Conventional ventilation Events	Conventional ventilation Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Two lung ventilation						
Futier 2013	1	200	6	200	21.0%	0.16 [0.02, 1.36]
Treschan 2012	1	50	0	51	9.1%	3.12 [0.12, 78.45]
Weingarten 2009	0	20	1	20	8.9%	0.32 [0.01, 8.26]
Subtotal (95% CI)		**270**		**271**	**39.1%**	**0.40 [0.07, 2.15]**
Total events	2		7			
Heterogeneity: Tau² = 0.28; Chi² = 2.26, df = 2 (P = 0.32); I² = 12%						
Test for overall effect: Z = 1.07 (P = 0.28)						
1.2.2 One lung ventilation						
Michelet 2006	3	26	6	26	41.7%	0.43 [0.10, 1.97]
Yang 2011	1	50	4	50	19.2%	0.23 [0.03, 2.18]
Subtotal (95% CI)		**76**		**76**	**60.9%**	**0.36 [0.10, 1.25]**
Total events	4		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.61 (P = 0.11)						
Total (95% CI)		**346**		**347**	**100.0%**	**0.37 [0.14, 0.97]**
Total events	6		17			
Heterogeneity: Tau² = 0.00; Chi² = 2.47, df = 4 (P = 0.65); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

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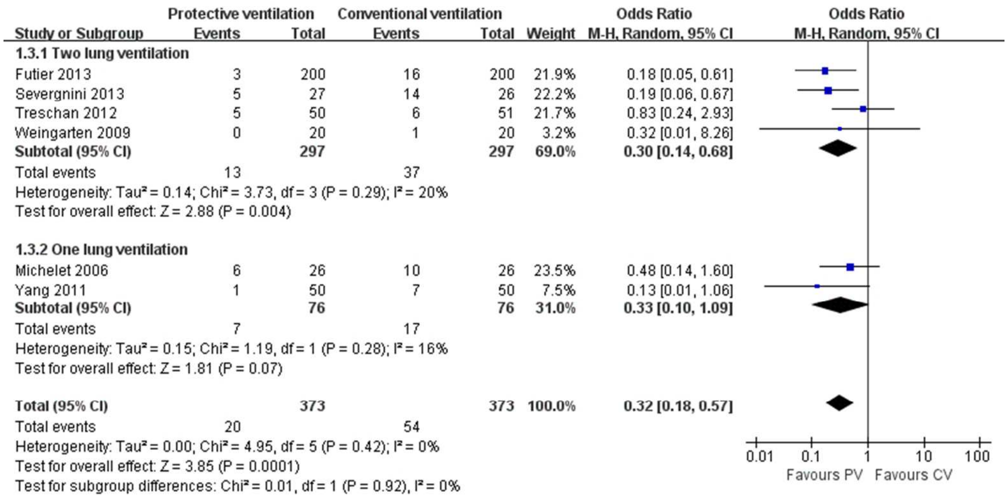

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NO
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P22
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P12-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P27

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Effect of protective ventilation on postoperative pulmonary complications in patients undergoing general anesthesia: a meta-analysis of randomized controlled trials

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Key words: Protective ventilation; low tidal volume; PEEP; surgical patients;

Word counts: 2606

ABSTRACT

Objective

To determine whether anesthetized patients undergoing surgery could benefit from intraoperative protective ventilation strategy.

Methods

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to February 2014. Eligible studies evaluated protective ventilation versus conventional ventilation in anesthetized patients without lung injury at the onset of mechanical ventilation. The primary outcome was the incidence of postoperative pulmonary complications. Included studies must report at least one of the following endpoints: the incidence of atelectasis or acute lung injury or pulmonary infections.

Results

Four studies (594 patients) were included. Meta-analysis using a random effect model showed a significant decrease in the incidence of atelectasis (OR=0.36; 95% CI=0.22-0.60; P<0.0001; I^2 =0%) and pulmonary infections (OR=0.30; 95% CI=0.14-0.68; P=0.004; I^2 =20%) in patients receiving protective ventilation. Ventilation with protective strategies did not reduce the incidence of acute lung injury (OR=0.40; 95% CI=0.07-2.15; P=0.28; I^2 =12%), all-cause mortality (OR=0.77; 95% CI=0.33-1.79; P=0.54; I^2 =0%), the length of hospital stay (WMD=-0.52

day, 95% CI=-4.53-3.48 day; *P*=0.80; I^2 =63%) or the length of ICU stays (WMD=-0.55 day, 95% CI=-2.19-1.09 day; *P*=0.51; I^2 =39%).

Conclusions

Intraoperative use of protective ventilation strategy has the potential to reduce the incidence of postoperative pulmonary complications in patients undergoing general anesthesia. Prospective, well-designed clinical trials are warranted to confirm the beneficial effect of protective ventilation strategy in surgical patients.

Strengths and limitations of this study

Strengths: Accumulating evidence suggested that mechanical ventilation using a high tidal volume in particular may cause alveolar overstretching or even induce lung injury. Whether anesthetized patients undergoing surgery could benefit from intraoperative protective ventilation remains unclear and controversial. We reported in this meta-analysis based on the data available that intraoperative use of protective ventilation strategy in patients undergoing general anesthesia could reduce the incidence of postoperative complications including atelectasis and pulmonary infections. Our study involved only eligible RCTs in the combined analysis to minimize the potential biases. Hence, our study may provide the latest evidence of protective ventilation in the operating room.

Limitations: Firstly, most trials enrolled this meta-analysis did not allow to differentiate between the effects of low tidal volumes and higher PEEP or application of recruitment maneuvers. Secondly, although no significant heterogeneity was observed in our analysis, the primary studies varied in the design, study population and follow-up periods, and so pooled results need to be viewed cautiously. Finally, despite a comprehensive search strategy, we could not assess the publication bias due to the small number of studies involved.

INTRODUCTION

Postoperative pulmonary complications are the main cause of overall perioperative morbidity and mortality in patients following general anesthesia [1, 2]. Induction of anesthesia is consistently accompanied by a significant reduction in lung volume and rapid formation of atelectasis[3]. Prevention of these complications would improve the quality of medical care and decrease the hospital costs[4]. However, few interventions have been identified to clearly or possibly reduce the postoperative lung function impairment[5].

Mechanical ventilation is an essential supportive strategy in patients undergoing general anesthesia. Knowing that a high tidal volume (10 to 15ml per kilogram of predicted body weight) can maintain better gas exchange and intraoperative mechanics, it has conventionally been recommended for intraoperative ventilation[6]. However, accumulating evidence from both experimental and clinical studies indicated that mechanical ventilation using a high tidal volume in particular may cause alveolar overstretching or even induce organ injury[7, 8].

Protective ventilation strategy refers to the use of low tidal volume (in the range of 4–8 ml/kg of predicted body weight) with positive end expiratory pressure (PEEP), with or without recruitment maneuvers. Protective ventilation has been considered the optimal practice in patients suffering from the acute respiratory distress syndrome (ARDS)[9, 10]. However, few human studies have assessed how to ventilate healthy lungs in patients undergoing general anesthesia. In a large retrospective cohort study, Gajic *et al*[11] found that the development of acute lung injury (ALI) was independently associated with a high tidal volume and high peak airway pressure. Subsequently, several studies attempted to uncover the cause of ventilator associated lung injury and find ways to minimize the side effects of high volume-high pressure ventilation in surgical patients. A prior meta-analysis of clinical trials performed by Hemmes *et al*[12] reported that intraoperative lung protective ventilator settings had the potential to protect against pulmonary complications. Their study included eight articles with 1669 patients. Of these, two large scale studies (1320 patients) were observational and three studies were on one-lung ventilation settings. Therefore, the results of this study cannot be considered as definitive. Recently, two additional well-designed RCTs were published. To better specify the effect of protective ventilation in surgical patients, excluding cardiac and thoracic surgery, we conducted the present meta-analysis of RCTs focusing on the effects of protective ventilation on the incidence of postoperative pulmonary complications.

METHODS

Search strategy

This analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the QUOROM (quality of reporting of meta-analyses) statement. We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), update to February 2014. Our search was restricted to RCTs published in full-text versions, without a language restriction. Additional relevant articles were identified by manually searching bibliographies and conferences. Our search strategy was based on three search themes all combined with the Boolean OR operator. The protective ventilation filter contained the following MeSH terms: “protection ventilation”, “low tidal volume ventilation” and “conventional ventilation”. The surgical patients filter included: “surgical”, “surgery”, “general anesthesia” and “operating room”. The clinical trials filter included the MeSH terms “clinical trials [publication type],” “clinical trials as topic” with text words “trial*,” or “random*”.

Selection criteria

Study inclusion criteria were based on the following attributes: 1) population: adult (>18 yr) surgical patients receiving mechanical ventilation in the operating room; 2) intervention: the use of a protective

ventilation strategy (lower tidal volume with PEEP, with or without recruitment maneuvers) versus the conventional ventilation method (high tidal volume, with or without PEEP and recruitment maneuvers), cardiac surgery and one-lung ventilation studies were excluded; 3) predefined outcomes: the incidence of atelectasis, acute lung injury, pulmonary infections, short-term postoperative mortality(<60d), the length of hospital stay and ICU stay, $PaCO_2$ and/or plateau pressure; 4) design: randomized controlled parallel trials. Eligible studies must report at least one of the following endpoints: the incidence of atelectasis or acute lung injury or pulmonary infections.

Data extraction and validity assessment

Three authors screened the titles and abstracts of initial search results, extracted the data and assessed the risk of bias independently. Any disagreements between the reviewers were resolved by discussion. Additional information was obtained by directly questioning the correspondence authors in relevant articles whenever needed.

Methodologic quality was assessed using the Cochrane Collaboration risk of bias tool that considered seven different domains: adequacy of sequence generation, allocation concealment, blinding of participants, blinding for outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias.

Statistical analysis

We extracted data regarding the study design, patient population, interventions and parallel controls, intraoperative ventilation mechanics and clinical outcomes. The primary endpoints concerned were the incidence of atelectasis, acute lung injury and pulmonary infections. The secondary outcomes included the all-cause mortality, length of ICU stay and length of hospital stay. Some trials reported median as a treatment effect, with accompanying interquartile(IQR) or range. For the purpose of analysis, the median was assumed as equivalent to the mean, and SD was estimated with IQR/1.35 or Range/4 according to the sample size and distribution (Cochrane Handbook). For dichotomous data, odds ratio (OR) was used to describe the size of treatment effect, and for continuous variables, weighted mean difference (WMD) was employed. Homogeneity assumption was measured by the I^2. It is calculated as: I^2= 100% * (Q-df)/Q, where Q is the Cochran's heterogeneity[13]. A value of 0% indicates no observed heterogeneity, and larger values correlated with increasing heterogeneity.

Synthesis of the data was performed using the random-effects model. Funnel plots of the incidence of atelectasis was used to visually assess the publication bias. Sensitivity analyses were carried out for different subgroups according to relevant clinical features.

All analyses were performed using Review Manager (RevMan) [Computer program] Version 5.1. Significant differences are set at $P<0.05$.

RESULTS

Literature identification and study characteristics

Our initial search yielded 1447 publications (547 from MEDLINE, 480 from EMBASE, and 420 from CENTRAL). After removing 307 duplicates, abstracts of 1140 articles were screened by three independent authors. Of these, 58 records were retrieved for detailed evaluation. Subsequently, 50 articles were excluded for the following reasons: no data on outcomes of interest, observational cohort study, not for treatment of surgical patients, cardiac or one-lung ventilation, etc. The remaining four randomized controlled trials enrolling 594 patients were included in the final analysis (Figure 1).

Table 1 describes the characteristics of the four studies including patient enrollment, surgical type, duration of ventilation, ventilation settings and primary outcomes. All these studies were conducted on abdominal surgical patients with one study focusing on elderly population (40 patients, age>65). Tidal volume was set to 6-8 ml/kg of the predicted body weight in the protective group and 9-12ml/kg in the control. Three studies used PEEP (4-12cm H_2O) only in the treatment group and one study [14] used PEEP (5 cm H_2O) in both groups. Recruitment maneuver was employed in the protective group in all included studies [14-17]. Chest radiograph (X rays) was used in all studies to detect atelectasis. Lung injury was diagnosed according to the American-European Consensus Conference definition in three studies [14, 15, 17], with no specific report in one study [16].

An overview of the risk of bias is described in Figure 2. All these studies reported adequate methods of sequence generation and allocation concealment. Double-blinded fashion was performed in two studies [14, 17] while the other two studies were open labeled. Age, weight, gender and duration of ventilation were parallelly comparable. Plateau pressure tended to be lower in the protective ventilation group compared with that in the control group in the final follow-up, but the difference did not reach statistically significant. (WMD=-0.63 cm H_2O, 95%CI=-1.85--0.58, *P*=0.31).

Primary outcome

All studies reported the incidence of atelectasis during follow-up periods. Atelectasis developed in 53 of the 297 patients ventilated with protective strategies and 88 of the 297 patients ventilated with conventional tidal volumes. Our meta-analysis of these trials indicated that there was a significant decrease in the incidence of atelectasis in those using the protective ventilation strategy (OR=0.36; 95% CI=0.22-0.60; P<0.0001; P for heterogeneity=0.75, I^2 =0%; Figure 3). The incidence pulmonary infections were lower in the protective ventilation group compared with the conventional ventilation group (OR=0.30; 95%CI=0.14-0.68;

P=0.004; *P* for heterogeneity=0.29, I^2 =20%; Figure 4). Protective ventilation was associated with decreased incidence of acute lung injury, but the difference did not reach statistically significant (OR=0.40; 95% CI=0.07-2.15; *P*=0.28; *P* for heterogeneity=0.32, I^2 =12%; Figure 5).

Secondary outcomes

Data from three studies were available for assessing mortality during the follow-up periods. For the 541 evaluable patients, no significant reduction in the risk of mortality was observed in patients receiving protective ventilation strategy (OR=0.77; 95% CI=0.33-1.79; *P*=0.54; *P* for heterogeneity=0.91, I^2 =0%). Length of hospital stay or ICU stay was not significantly different in the protective ventilation group compared with control group (WMD=-0.52 day, 95% CI=-4.53-3.48 day, *P*=0.80, *P* for heterogeneity=0.07, I^2 =63%; WMD=-0.55 day, 95% CI=-2.19-1.09 day, *P*=0.51, *P* for heterogeneity=0.20, I^2 =39%; respectively).

Sensitivity analysis

Stratified analysis was performed based on a number of key study characteristics. Three studies incorporated PEEP and recruitment maneuvers in the protective ventilation group versus no PEEP or recruitment maneuvers in the control group. In one study[6], both groups received the same PEEP and recruitment maneuvers. Excluding this study did not change the results of any primary outcomes. Weingarten *et* *al.* [15]investigated 40 elderly patients undergoing abdominal surgery. Exclusion of this trial did not change the results. Regarding the incidence of atelectasis, no significant difference was found when excluded the largest study by Futier [17].

DISCUSSION

The main finding of this meta-analysis is that the protective ventilation strategy can reduce the incidence of atelectasis and pulmonary infections in surgical patients at the onset of ventilation. Protective ventilation strategy did not reduce the incidence of acute lung injury, all-cause mortality, length of hospital stay or length of ICU stay.

Prescription of mechanical ventilation has changed over the past few decades, with low tidal volumes strong advocated, especially in patients with acute lung injury[9, 18]. Both basic and clinical evidence indicated that an injurious ventilation setting could result in the development of diffuse alveolar damage, pulmonary edema, recruitment of inflammatory cells, and production of cytokines[19, 20]. It is evident that the use of low tidal volumes is associated with reduced morbidity and mortality in ARDS patients, and thus guidelines strongly advise using protective ventilation strategy in these patients[21-23]. However, there is little evidence regarding the benefits of ventilation with low tidal volumes in patients undergoing surgery without ARDS preoperatively. In order to prevent atelectasis and hypoxemia in surgical patients, it is still common today for surgical patients undergoing general anesthesia to receive a larger tidal volume [24, 25]. Later animal studies indicated that ventilation with a higher tidal volume could damage the healthy lungs, stimulate the release of inflammatory chemicals and predispose animals to organ damage [26-28]. However, some observational studies in humans argued the usefulness of ventilation with a low tidal volume [29, 30]. Recently, several clinical trials were conducted in the operating room to study the influence of ventilator settings on the surrogate endpoints, including inflammatory responses, postoperative pulmonary complications, postoperative lung function, and oxygenation. Despite heterogeneity of surgical types, most trials found that the protective ventilation strategy could attenuate the inflammatory responses, improve lung function and minimize potential oxygen desaturation [16, 31-35].

Our aim was to combine data from all well-designed RCTS available that had the scope to show the effects of protective ventilation in surgical patients. The current meta-analysis focused mainly on the clinical outcomes with protective ventilation. Cardiac or thoracic surgery studies were excluded to minimize the heterogeneity. The results of our meta-analysis are mainly in line with a previous systematic review suggesting that protective ventilation significantly reduced the incidence of postoperative pulmonary complications [12]. But we did not find significantly decreased incidence of acute lung injury in the protective ventilation group. The difference can be explained by the fact that we excluded the observational studies in this meta-analysis and involved two further RCTs, which were not analyzed in the prior study. Furthermore, we excluded one-lung ventilation studies to provide a more definitive analysis. Hence, our study may provide more valid evidence and minimize potential bias.

It seems rational to draw a conclusion that lower tidal volumes can decrease the intrapulmonary pressure and reduce the risk of ventilation-associated lung injury. However, we could not exclude the possibility that it may increase cyclic alveolar collapse of dependent lung regions, thus raising the risk of atelectasis and hypercapnia[36, 37]. Application of PEEP and recruitment maneuvers may counteract these side-effects of low tidal volume ventilation. The use of moderate levels of PEEP was effective to maintain the end-expiratory lung volume, improve oxygenation and dynamic compliance of respiratory system [38]. Although the optimal level of PEEP is undetermined, it has been repeatedly shown that the application of zero PEEP was associated with increased hypoxaemia and infections [39, 40]. We speculate that PEEP may contribute to the beneficial effect of protective ventilation and could be an indispensable component. Therefore, we defined protective ventilation as low tidal volume with PEEP and excluded the study [41] which applied low tidal volume without PEEP in the experimental group. Traschan *et al*[14] used a minimum of 5 cmH_2O PEEP in both groups to counter-balance the component of cyclic of airway opening and closing. Interestingly, their study found that ventilation with lower tidal volumes during upper abdominal surgery did not improve the postoperative lung function. However, their results should be interpreted cautiously because significantly higher minute ventilation and a two-fold higher respiration rate were used in the low tidal volume group (7.8 ± 2.1 *vs.* 6.2 ± 1.9 L/min; 17 ± 4 *vs.* 8 ± 4 times/min, respectively).

Three clinical trials in this meta-analysis used recruitment maneuvers in the protective ventilation group versus no recruitment maneuvers in the control group. Pooled analysis of these trials indicate that protective ventilation with recruitment maneuvers led to lower incidence of atelectasis and pulmonary infections versus conventional ventilation without recruitment maneuvers. Thinking PEEP alone cannot effectively reopen the collapsed lungs, one may argue that repeated recruitment maneuver is an essential component of protective ventilation for complete reopening of atelectasis. Serita *et al*[42] found that individualized recruitment maneuvers brought improvement in oxygenation and lung compliance in patients undergoing selective cardiac surgery. The beneficial effects of recruitment maneuvers were also demonstrated in obese patients during laparoscopic surgery [43], while these effects in other types of surgery need to be clarified. It should be noted that recruitment maneuvers could cause a decrease in right ventricular preload and reduction in left ventricular stroke volume, which should be used cautiously in hemodynamically unstable patients.

Given the uncertain influence of recruitment maneuvers on clinical outcomes, it is prudent to neither recommend nor reject recruitment maneuvers as a routine at present.

There are several limitations in the current study. First, the present study included only four clinical trials due to more restricted section criteria. Publication bias could not be assessed owing to the small number of studies. Second, all the trials enrolled in this meta-analysis applied lower tidal volumes, higher PEEP and recruitment maneuvers in the protective ventilation group, it seems impossible to simply attribute the beneficial effects to certain one of these components. In fact, PEEP and recruitment maneuvers could be helpful to overcome the potential effects of low VT ventilation on oxygenation. It would be reasonable to use these methods in combination. To address the issue which one is more closely related to lower incidence of postoperative complications, further studies are still warranted. Finally, although no significant heterogeneity was observed in our analysis, the primary studies varied in the design, study population and follow-up periods, and pooled results need to be viewed cautiously.

CONCLUSION

Intraoperative use of protective ventilation strategy in patients undergoing general anesthesia could reduce the incidence of postoperative atelectasis and pulmonary infections. Prospective, well-designed clinical trials are warranted to confirm the beneficial effect of protective ventilation strategy in surgical patients, especially in those with high risk of lung morbidity.

Table 1 Characteristics of the clinical trials included in the meta-analysis

Source	No. of patients	Protective		Conventional		Setting	Design	Duration of ventilation		PEEP(PV/CV) (cmH_2O)	RM	Primary outcome
		$V_{T(ml/kg)}$	No	$V_{T(ml/kg)}$	No			PV(h)	CV(h)			
Severgnini 2013	53	7	27	9	26	Abdominal	P,R,NB,S	3.2±1.1	3.7±1.3	10/0	Yes	Pulmonary infection
Futier 2013	400	6-8	200	10-12	200	Abdominal	P,R,DB,M	5.3±2.3	5.7±2.1	6-8/0	Yes	Pneumonia
Treschan 2012	101	6	50	12	51	Abdominal	P,R,DB,S	8.7±5.2	8.7±5.9	5/5	Yes	Spirometry
Weingarten 2009	40	6	20	10	20	Abdominal	P,R,NB,S	5.1±1.9	5.7±1.7	12/0	Yes	Oxygenation
Total	594	-	297	-	297	-	-	5.7±3.3	6.0±3.3	-	-	-

P, prospective; R, randomized; DB, double blinded; NB, non-blinded; M, multi-center; S, single center; RM, recruitment maneuver

Abbreviation

RCTS: randomized controlled trial; ICU: intensive care unit; PEEP: positive end expiratory pressure; ARDS: acute respiratory distress syndrome; ALI: acute lung injury; WMD: weighted mean difference; RM: recruitment maneuvers;

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

TT, LB contributed equally to this article. They all participated to the study design, data collection and also draft the manuscript. FC, QX, YZ, BH helped in the design of the study and analysed the data. Both XD and JL designed this study, supervised the data collection and revised this article. All authors read and approved the final manuscript.

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Data sharing

Statistical code and dataset available from the corresponding author (Tianzhu Tao), who will provide a permanent, citable and open access home for the dataset.

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Figure legends

Figure 1 Literature search strategy

CENTRAL, Cochrane Central Register of Controlled Trials; ARDS, acute respiratory distress syndrome

Figure 2 Overall risk of bias using the Cochrane risk of bias tool

Figure 3 Forrest plot for the incidence of atelectasis

A pooled OR (odds ratio) was calculated using Random-effect model according to the Mantel-Haenszel (M-H) method. CV, conventional ventilation; PV, protective ventilation; The incidence of atelectasis was significant lower in the PV group.

Figure 4 Forrest plot for the incidence of pulmonary infections

A pooled OR (odds ratio) was calculated using Random-effect model according to the Mantel-Haenszel (M-H) method. CV, conventional ventilation; PV, protective ventilation; The incidence of pulmonary infections was significant lower in the PV group.

Figure 5 Forrest plot for the incidence of ALI

A pooled OR (odds ratio) was calculated using Random-effect model according to the Mantel-Haenszel (M-H) method. CV, conventional ventilation; PV, protective ventilation; Protective ventilation was associated with decreased incidence of acute lung injury, but the difference did not reach statistically significant.

Protective ventilation reduces postoperative pulmonary complications in patients undergoing general anesthesia: a meta-analysis of randomized controlled trials

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Key words: Protective ventilation; low tidal volume; PEEP; surgical patients;

Word counts: 2606

ABSTRACT

Objective

To determine whether anesthetized patients undergoing surgery could benefit from intraoperative protective ventilation strategy.

Methods

MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to February 2014. Eligible studies evaluated protective ventilation versus conventional ventilation in anesthetized patients without lung injury at the onset of mechanical ventilation. The primary outcome was the incidence of postoperative pulmonary complications. Included studies must report at least one of the following endpoints: the incidence of atelectasis or acute lung injury or pulmonary infections.

Results

Four studies (594 patients) were included. Meta-analysis using a random effect model showed a significant decrease in the incidence of atelectasis (OR=0.36; 95% CI=0.22-0.60; P<0.0001; I^2 =0%) and pulmonary infections (OR=0.30; 95% CI=0.14-0.68; P=0.004; I^2 =20%) in patients receiving protective ventilation. Ventilation with protective strategies did not reduce the incidence of acute lung injury (OR=0.40; 95% CI=0.07-2.15; P=0.28; I^2 =12%), all-cause mortality (OR=0.77; 95% CI=0.33-1.79; P=0.54; I^2 =0%), the length of hospital stay (WMD=-0.52

day, 95% CI=-4.53-3.48 day; *P*=0.80; I^2 =63%) or the length of ICU stays (WMD=-0.55 day, 95% CI=-2.19-1.09 day; *P*=0.51; I^2 =39%).

Conclusions

Intraoperative use of protective ventilation strategy has the potential to reduce the incidence of postoperative pulmonary complications in patients undergoing general anesthesia. Prospective, well-designed clinical trials are warranted to confirm the beneficial effect of protective ventilation strategy in surgical patients.

Strengths and limitations of this study

Strengths: Accumulating evidence suggested that mechanical ventilation using a high tidal volume in particular may cause alveolar overstretching or even induce lung injury. Whether anesthetized patients undergoing surgery could benefit from intraoperative protective ventilation remains unclear and controversial. We reported in this meta-analysis based on the data available that intraoperative use of protective ventilation strategy in patients undergoing general anesthesia could reduce the incidence of postoperative complications including atelectasis and pulmonary infections. Our study involved only eligible RCTs in the combined analysis to minimize the potential biases. Hence, our study may provide the latest evidence of protective ventilation in the operating room.

Limitations: Firstly, most trials enrolled this meta-analysis did not allow to differentiate between the effects of low tidal volumes and higher PEEP or application of recruitment maneuvers. Secondly, although no significant heterogeneity was observed in our analysis, the primary studies varied in the design, study population and follow-up periods, and so pooled results need to be viewed cautiously. Finally, despite a comprehensive search strategy, we could not assess the publication bias due to the small number of studies involved.

INTRODUCTION

Postoperative pulmonary complications are the main cause of overall perioperative morbidity and mortality in patients following general anesthesia [1, 2]. Induction of anesthesia is consistently accompanied by a significant reduction in lung volume and rapid formation of atelectasis[3]. Prevention of these complications would improve the quality of medical care and decrease the hospital costs[4]. However, few interventions have been identified to clearly or possibly reduce the postoperative lung function impairment[5].

Mechanical ventilation is an essential supportive strategy in patients undergoing general anesthesia. Knowing that a high tidal volume (10 to 15ml per kilogram of predicted body weight) can maintain better gas exchange and intraoperative mechanics, it has conventionally been recommended for intraoperative ventilation[6]. However, accumulating evidence from both experimental and clinical studies indicated that mechanical ventilation using a high tidal volume in particular may cause alveolar overstretching or even induce organ injury[7, 8].

Protective ventilation strategy refers to the use of low tidal volume (in the range of 4–8 ml/kg of predicted body weight) with positive end expiratory pressure (PEEP), with or without recruitment maneuvers.

Protective ventilation has been considered the optimal practice in patients suffering from the acute respiratory distress syndrome (ARDS)[9, 10]. However, few human studies have assessed how to ventilate healthy lungs in patients undergoing general anesthesia. In a large retrospective cohort study, Gajic *et al*[11] found that the development of acute lung injury (ALI) was independently associated with a high tidal volume and high peak airway pressure. Subsequently, several studies attempted to uncover the cause of ventilator associated lung injury and find ways to minimize the side effects of high volume-high pressure ventilation in surgical patients. A prior meta-analysis of clinical trials performed by Hemmes *et al*[12] reported that intraoperative lung protective ventilator settings had the potential to protect against pulmonary complications. Their study included eight articles with 1669 patients. Of these, two large scale studies (1320 patients) were observational and three studies were on one-lung ventilation settings. Therefore, the results of this study cannot be considered as definitive. Recently, two additional well-designed RCTs were published. To better specify the effect of protective ventilation in surgical patients, excluding cardiac and thoracic surgery, we conducted the present meta-analysis of RCTs focusing on the effects of protective ventilation on the incidence of postoperative pulmonary complications.

METHODS

Search strategy

This analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the QUOROM (quality of reporting of meta-analyses) statement. We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), update to February 2014. Our search was restricted to RCTs published in full-text versions, without a language restriction. Additional relevant articles were identified by manually searching bibliographies and conferences. Our search strategy was based on three search themes all combined with the Boolean OR operator. The protective ventilation filter contained the following MeSH terms: “protection ventilation”, “low tidal volume ventilation” and “conventional ventilation”. The surgical patients filter included: “surgical”, “surgery”, “general anesthesia” and “operating room”. The clinical trials filter included the MeSH terms “clinical trials [publication type],” “clinical trials as topic” with text words “trial*,” or “random*”.

Selection criteria

Study inclusion criteria were based on the following attributes: 1) population: adult (>18 yr) surgical patients receiving mechanical ventilation in the operating room; 2) intervention: the use of a protective

ventilation strategy (lower tidal volume with PEEP, with or without recruitment maneuvers) versus the conventional ventilation method (high tidal volume, with or without PEEP and recruitment maneuvers), cardiac surgery and one-lung ventilation studies were excluded; 3) predefined outcomes: the incidence of atelectasis, acute lung injury, pulmonary infections, short-term postoperative mortality(<60d), the length of hospital stay and ICU stay, $PaCO_2$ and/or plateau pressure; 4) design: randomized controlled parallel trials. Eligible studies must report at least one of the following endpoints: the incidence of atelectasis or acute lung injury or pulmonary infections.

Data extraction and validity assessment

Three authors screened the titles and abstracts of initial search results, extracted the data and assessed the risk of bias independently. Any disagreements between the reviewers were resolved by discussion. Additional information was obtained by directly questioning the correspondence authors in relevant articles whenever needed.

Methodologic quality was assessed using the Cochrane Collaboration risk of bias tool that considered seven different domains: adequacy of sequence generation, allocation concealment, blinding of participants, blinding for outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias.

Statistical analysis

We extracted data regarding the study design, patient population, interventions and parallel controls, intraoperative ventilation mechanics and clinical outcomes. The primary endpoints concerned were the incidence of atelectasis, acute lung injury and pulmonary infections. The secondary outcomes included the all-cause mortality, length of ICU stay and length of hospital stay. Some trials reported median as a treatment effect, with accompanying interquartile(IQR) or range. For the purpose of analysis, the median was assumed as equivalent to the mean, and SD was estimated with IQR/1.35 or Range/4 according to the sample size and distribution (Cochrane Handbook). For dichotomous data, odds ratio (OR) was used to describe the size of treatment effect, and for continuous variables, weighted mean difference (WMD) was employed. Homogeneity assumption was measured by the I^2. It is calculated as: I^2= 100% * (Q-df)/Q, where Q is the Cochran's heterogeneity[13]. A value of 0% indicates no observed heterogeneity, and larger values correlated with increasing heterogeneity.

Synthesis of the data was performed using the random-effects model. Funnel plots of the incidence of atelectasis was used to visually assess the publication bias. Sensitivity analyses were carried out for different subgroups according to relevant clinical features.

All analyses were performed using Review Manager (RevMan) [Computer program] Version 5.1. Significant differences are set at $P<0.05$.

RESULTS

Literature identification and study characteristics

Our initial search yielded 1447 publications (547 from MEDLINE, 480 from EMBASE, and 420 from CENTRAL). After removing 307 duplicates, abstracts of 1140 articles were screened by three independent authors. Of these, 58 records were retrieved for detailed evaluation. Subsequently, 50 articles were excluded for the following reasons: no data on outcomes of interest, observational cohort study, not for treatment of surgical patients, cardiac or one-lung ventilation, etc. The remaining four randomized controlled trials enrolling 594 patients were included in the final analysis (Figure 1).

Table 1 describes the characteristics of the four studies including patient enrollment, surgical type, duration of ventilation, ventilation settings and primary outcomes. All these studies were conducted on abdominal surgical patients with one study focusing on elderly population (40 patients, age>65). Tidal volume was set to 6-8 ml/kg of the predicted body weight in the protective group and 9-12ml/kg in the control. Three studies used PEEP (4-12cm H_2O) only in the treatment group and one study [14] used PEEP (5 cm H_2O) in both groups. Recruitment maneuver was employed in the protective group in all included studies [14-17]. Chest radiograph (X rays) was used in all studies to detect atelectasis. Lung injury was diagnosed according to the American-European Consensus Conference definition in three studies [14, 15, 17], with no specific report in one study [16].

An overview of the risk of bias is described in Figure 2. All these studies reported adequate methods of sequence generation and allocation concealment. Double-blinded fashion was performed in two studies [14, 17] while the other two studies were open labeled. Age, weight, gender and duration of ventilation were parallelly comparable. Plateau pressure tended to be lower in the protective ventilation group compared with that in the control group in the final follow-up, but the difference did not reach statistically significant. (WMD=-0.63 cm H_2O, 95%CI=-1.85--0.58, *P*=0.31).

Primary outcome

All studies reported the incidence of atelectasis during follow-up periods. Atelectasis developed in 53 of the 297 patients ventilated with protective strategies and 88 of the 297 patients ventilated with conventional tidal volumes. Our meta-analysis of these trials indicated that there was a significant decrease in the incidence of atelectasis in those using the protective ventilation strategy (OR=0.36; 95% CI=0.22-0.60; $P<0.0001$; P for heterogeneity=0.75, I^2 =0%; Figure 3). The incidence pulmonary infections were lower in the protective ventilation group compared with the conventional ventilation group (OR=0.30; 95%CI=0.14-0.68;

P=0.004; P for heterogeneity=0.29, I^2 =20%; Figure 4). Protective ventilation was associated with decreased incidence of acute lung injury, but the difference did not reach statistically significant (OR=0.40; 95% CI=0.07-2.15; P=0.28; P for heterogeneity=0.32, I^2 =12%; Figure 5).

Secondary outcomes

Data from three studies were available for assessing mortality during the follow-up periods. For the 541 evaluable patients, no significant reduction in the risk of mortality was observed in patients receiving protective ventilation strategy (OR=0.77; 95% CI=0.33-1.79; P=0.54; P for heterogeneity=0.91, I^2 =0%). Length of hospital stay or ICU stay was not significantly different in the protective ventilation group compared with control group (WMD=-0.52 day, 95% CI=-4.53-3.48 day, P=0.80, P for heterogeneity=0.07, I^2 =63%; WMD=-0.55 day, 95% CI=-2.19-1.09 day, P=0.51, P for heterogeneity=0.20, I^2 =39%; respectively).

Sensitivity analysis

Stratified analysis was performed based on a number of key study characteristics. Three studies incorporated PEEP and recruitment maneuvers in the protective ventilation group versus no PEEP or recruitment maneuvers in the control group. In one study[6], both groups received the same PEEP and recruitment maneuvers. Excluding this study did not change the results of any primary outcomes. Weingarten *et* *al.* [15]investigated 40 elderly patients undergoing abdominal surgery. Exclusion of this trial did not change the results. Regarding the incidence of atelectasis, no significant difference was found when excluded the largest study by Futier [17].

DISCUSSION

The main finding of this meta-analysis is that the protective ventilation strategy can reduce the incidence of atelectasis and pulmonary infections in surgical patients at the onset of ventilation. Protective ventilation strategy did not reduce the incidence of acute lung injury, all-cause mortality, length of hospital stay or length of ICU stay.

Prescription of mechanical ventilation has changed over the past few decades, with low tidal volumes strong advocated, especially in patients with acute lung injury[9, 18]. Both basic and clinical evidence indicated that an injurious ventilation setting could result in the development of diffuse alveolar damage, pulmonary edema, recruitment of inflammatory cells, and production of cytokines[19, 20]. It is evident that the use of low tidal volumes is associated with reduced morbidity and mortality in ARDS patients, and thus guidelines strongly advise using protective ventilation strategy in these patients[21-23]. However, there is little evidence regarding the benefits of ventilation with low tidal volumes in patients undergoing surgery without ARDS preoperatively. In order to prevent atelectasis and hypoxemia in surgical patients, it is still common today for surgical patients undergoing general anesthesia to receive a larger tidal volume [24, 25]. Later animal studies indicated that ventilation with a higher tidal volume could damage the healthy lungs, stimulate the release of inflammatory chemicals and predispose animals to organ damage [26-28]. However, some observational studies in humans argued the usefulness of ventilation with a low tidal volume [29, 30]. Recently, several clinical trials were conducted in the operating room to study the influence of ventilator settings on the surrogate endpoints, including inflammatory responses, postoperative pulmonary complications, postoperative lung function, and oxygenation. Despite heterogeneity of surgical types, most trials found that the protective ventilation strategy could attenuate the inflammatory responses, improve lung function and minimize potential oxygen desaturation [16, 31-35].

Our aim was to combine data from all well-designed RCTS available that had the scope to show the effects of protective ventilation in surgical patients. The current meta-analysis focused mainly on the clinical outcomes with protective ventilation. Cardiac or thoracic surgery studies were excluded to minimize the heterogeneity. The results of our meta-analysis are mainly in line with a previous systematic review suggesting that protective ventilation significantly reduced the incidence of postoperative pulmonary complications [12]. But we did not find significantly decreased incidence of acute lung injury in the protective ventilation group. The difference can be explained by the fact that we excluded the observational studies in this meta-analysis and involved two further RCTs, which were not analyzed in the prior study. Furthermore, we excluded one-lung ventilation studies to provide a more definitive analysis. Hence, our study may provide more valid evidence and minimize potential bias.

It seems rational to draw a conclusion that lower tidal volumes can decrease the intrapulmonary pressure and reduce the risk of ventilation-associated lung injury. However, we could not exclude the possibility that it may increase cyclic alveolar collapse of dependent lung regions, thus raising the risk of atelectasis and hypercapnia[36, 37]. Application of PEEP and recruitment maneuvers may counteract these side-effects of low tidal volume ventilation. The use of moderate levels of PEEP was effective to maintain the end-expiratory lung volume, improve oxygenation and dynamic compliance of respiratory system [38]. Although the optimal level of PEEP is undetermined, it has been repeatedly shown that the application of zero PEEP was associated with increased hypoxaemia and infections [39, 40]. We speculate that PEEP may contribute to the beneficial effect of protective ventilation and could be an indispensable component. Therefore, we defined protective ventilation as low tidal volume with PEEP and excluded the study [41] which applied low tidal volume without PEEP in the experimental group. Traschan *et al*[14] used a minimum of 5 cmH_2O PEEP in both groups to counter-balance the component of cyclic of airway opening and closing. Interestingly, their study found that ventilation with lower tidal volumes during upper abdominal surgery did not improve the postoperative lung function. However, their results should be interpreted cautiously because significantly higher minute ventilation and a two-fold higher respiration rate were used in the low tidal volume group (7.8±2.1 *vs.* 6.2±1.9 L/min; 17±4 *vs.* 8±4 times/min, respectively).

Three clinical trials in this meta-analysis used recruitment maneuvers in the protective ventilation group versus no recruitment maneuvers in the control group. Pooled analysis of these trials indicate that protective ventilation with recruitment maneuvers led to lower incidence of atelectasis and pulmonary infections versus conventional ventilation without recruitment maneuvers. Thinking PEEP alone cannot effectively reopen the collapsed lungs, one may argue that repeated recruitment maneuver is an essential component of protective ventilation for complete reopening of atelectasis. Serita *et al*[42] found that individualized recruitment maneuvers brought improvement in oxygenation and lung compliance in patients undergoing selective cardiac surgery. The beneficial effects of recruitment maneuvers were also demonstrated in obese patients during laparoscopic surgery [43], while these effects in other types of surgery need to be clarified. It should be noted that recruitment maneuvers could cause a decrease in right ventricular preload and reduction in left ventricular stroke volume, which should be used cautiously in hemodynamically unstable patients.

Given the uncertain influence of recruitment maneuvers on clinical outcomes, it is prudent to neither recommend nor reject recruitment maneuvers as a routine at present.

There are several limitations in the current study. First, the present study included only four clinical trials due to more restricted section criteria. Publication bias could not be assessed owing to the small number of studies. Second, all the trials enrolled in this meta-analysis applied lower tidal volumes, higher PEEP and recruitment maneuvers in the protective ventilation group, it remains unknown whether the improved pulmonary complications are associated with lower tidal volume or presence or absence of PEEP and recruitment maneuvers. Finally, although no significant heterogeneity was observed in our analysis, the primary studies varied in the design, study population and follow-up periods, and pooled results need to be viewed cautiously.

CONCLUSION

Intraoperative use of protective ventilation strategy in patients undergoing general anesthesia could reduce the incidence of postoperative atelectasis and pulmonary infections. Prospective, well-designed clinical trials are warranted to confirm the beneficial effect of protective ventilation strategy in surgical patients, especially in those with high risk of lung morbidity.

Table 1 Characteristics of the clinical trials included in the meta-analysis

Source	No. of patients	Protective		Conventional		Setting	Design	Duration of ventilation		PEEP(PV/CV) (cmH$_2$O)	RM	Primary outcome
		$V_{T(ml/kg)}$	No	$V_{T(ml/kg)}$	No			PV(h)	CV(h)			
Severgnini 2013	53	7	27	9	26	Abdominal	P,R,NB,S	3.2±1.1	3.7±1.3	10/0	Yes	Pulmonary infection
Futier 2013	400	6-8	200	10-12	200	Abdominal	P,R,DB,M	5.3±2.3	5.7±2.1	6-8/0	Yes	Pneumonia
Treschan 2012	101	6	50	12	51	Abdominal	P,R,DB,S	8.7±5.2	8.7±5.9	5/5	Yes	Spirometry
Weingarten 2009	40	6	20	10	20	Abdominal	P,R,NB,S	5.1±1.9	5.7±1.7	12/0	Yes	Oxygenation
Total	594	-	297	-	297	-	-	5.7±3.3	6.0±3.3	-	-	-

P, prospective; R, randomized; DB, double blinded; NB, non-blinded; M, multi-center; S, single center; RM, recruitment maneuver

Abbreviation

RCTS: randomized controlled trial; ICU: intensive care unit; PEEP: positive end expiratory pressure; ARDS: acute respiratory distress syndrome; ALI: acute lung injury; WMD: weighted mean difference; RM: recruitment maneuvers;

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

TT, LB contributed equally to this article. They all participated to the study design, data collection and also draft the manuscript. FC, QX, YZ, BH helped in the design of the study and analysed the data. Both XD and JL designed this study, supervised the data collection and revised this article. All authors read and approved the final manuscript.

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Data sharing

Statistical code and dataset available from the corresponding author (Tianzhu Tao), who will provide a permanent, citable and open access home for the dataset.

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Figure legends

Figure 1 Literature search strategy

CENTRAL, Cochrane Central Register of Controlled Trials; ARDS, acute respiratory distress syndrome

Figure 2 Overall risk of bias using the Cochrane risk of bias tool

Figure 3 Forrest plot for the incidence of atelectasis

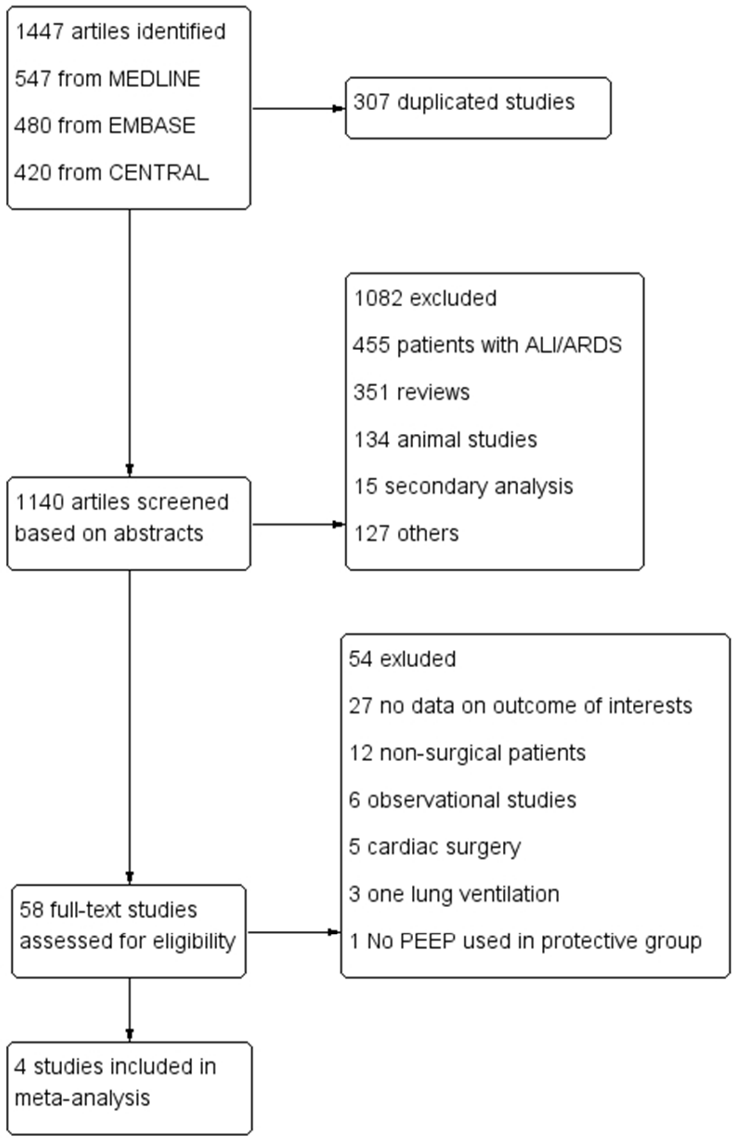
A pooled OR (odds ratio) was calculated using Random-effect model according to the Mantel-Haenszel (M-H) method. CV, conventional ventilation; PV, protective ventilation; The incidence of atelectasis was significant lower in the PV group.

Figure 4 Forrest plot for the incidence of pulmonary infections

A pooled OR (odds ratio) was calculated using Random-effect model according to the Mantel-Haenszel (M-H) method. CV, conventional ventilation; PV, protective ventilation; The incidence of pulmonary infections was significant lower in the PV group.

Figure 5 Forrest plot for the incidence of ALI

A pooled OR (odds ratio) was calculated using Random-effect model according to the Mantel-Haenszel (M-H) method. CV, conventional ventilation; PV, protective ventilation; Protective ventilation was associated with decreased incidence of acute lung injury, but the difference did not reach statistically significant.



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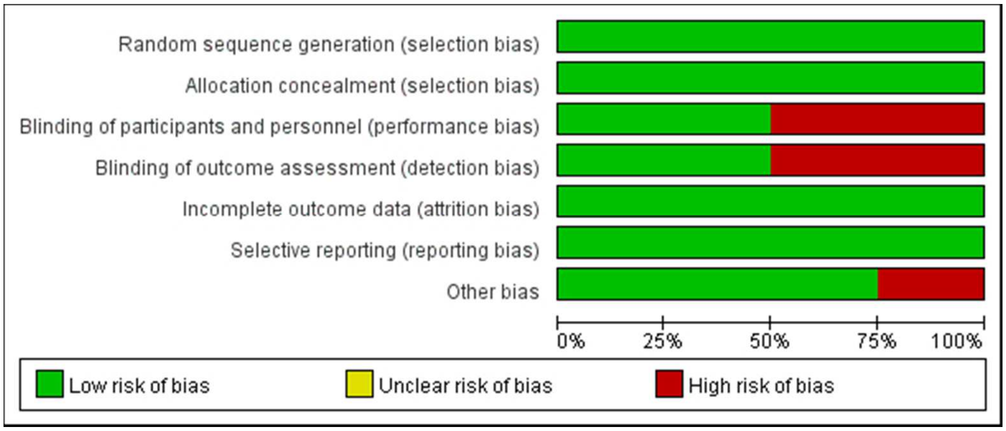

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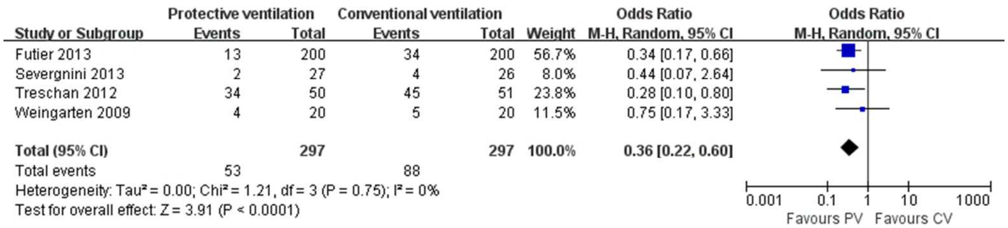

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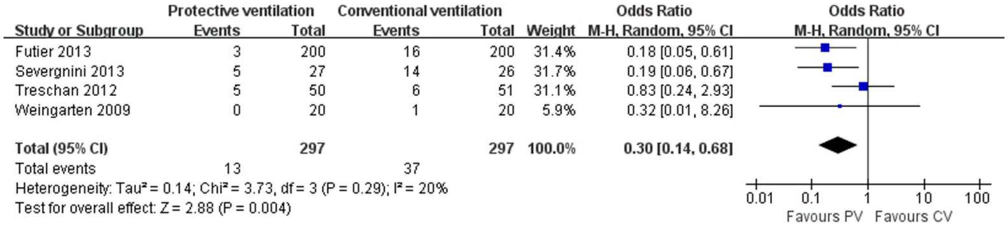

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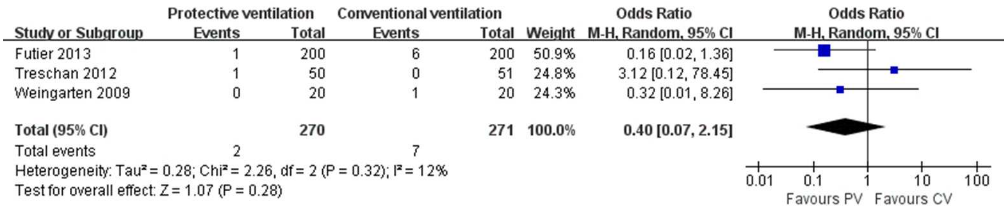

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	P6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NO
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P21
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	P21
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P12-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P13-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P24

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