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Major Article

Chest physiotherapy for the prevention of ventilator-associated pneumonia: A meta-analysis

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Background: Ventilator-associated pneumonia (VAP) remains a frequent and severe complication in mechanically ventilated patients. We undertook a meta-analysis to evaluate the efficacy of chest physiotherapy (CPT) for the prevention of VAP.

Methods: A systematic literature search of PubMed and Embase databases were searched up until November 25, 2018 for published studies of mechanically ventilated patients comparing CPT with controls and reporting on the occurrence of VAP. Two authors independently selected studies and abstracted data on study quality and outcomes. We pooled data using random-effects models.

Results: A total of 6 randomized (n = 704) controlled trials were identified. CPT did not significantly reduce the incidence of VAP (risk ratio = 1.02; 95% confidence interval, 0.82-1.26; *P* = .87), but reduced hospital mortality (risk ratio = 0.68; 95% confidence interval, 0.48-0.95; *P* = .02). No significant differences were observed regarding intensive care unit mortality, length of intensive care unit stay, and duration of mechanical ventilation.

Conclusions: CPT may not significantly reduce the incidence of VAP and alter other important clinical outcomes in adult patients receiving mechanical ventilation. However, the results should be interpreted cautiously owing to the heterogeneity and the limited trials. Further large-scale, well-designed randomized controlled trials are needed.

Ventilator-associated pneumonia (VAP), defined as pneumonia in patients receiving mechanical ventilation (MV) that arises >48-72 hours after endotracheal intubation,[1] is the most common hospital-acquired infection in the intensive care unit (ICU) and affects 8%-28% of patients receiving MV.[2] Moreover, VAP has been associated with comparatively higher morbidity and mortality rates and higher health care costs.[3-5] Given the clinical consequences attributable to VAP, prevention strategies are urgently needed to tackle the growing burden of VAP.[6] To date, many interventions aimed at preventing VAP have been assessed, for example; oral antiseptics,[7] probiotics,[8] subglottic secretion drainage,[9] oropharyngeal chlorhexidine,[10] and others. However, the role of chest physiotherapy (CPT) in preventing VAP has received limited attention and remains unclear.

CPT was implemented at the beginning of the 20th century, and deep breathing exercise was 1 of the first methods.[11] CPT is one of the most frequently performed interventions in the intensive care areas and has been recognized as an important aspect to achieve successful weaning from the ventilator.[12] A variety of manual treatments—mainly including gravity-assisted drainage, chest wall percussion, chest wall vibrations, and manual lung hyperinflation (bagging)—were developed and were commonly used intensive care procedures.[13,14] Various combinations of CPT aimed at enhancing secretion clearance may assist in the prevention of VAP.[15] Recently, some studies have evaluated the use of CPT in critically ill patients. However, these studies have a modest sample size and convey inconclusive results. We therefore undertook a meta-analysis of published studies to assess the effects of CPT on the incidence of VAP and other important clinical outcomes in mechanically ventilated patients.

METHODS

Data sources and searches

Data reported in our review are in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16] Relevant trials were identified by searching PubMed and

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Embase databases—up until November 25, 2018. The structured search strategies used the following format of search terms: *(chest physiotherapy* OR *CPT* OR *manual hyperinflation* OR *chest vibrations* OR *respiratory physiotherapy)* AND *pneumonia*. The search was limited to human subjects. No language restriction was imposed. We also manually checked the reference lists of randomized controlled trials (RCTs) to include other potentially eligible trials. This process was performed iteratively until no additional articles could be identified.

The following inclusive selection criteria were applied: (1) study design: RCTs reported in a full article; (2) study population: adult critically ill patients receiving MV; (3) intervention: CPT with or without other preventive measures; (4) comparison intervention: other preventive measures; and (5) outcome measure: the incidence of VAP.

Data extraction and outcome measures

Two authors independently extracted the following data from each trial: first author, publication year, number of patients (intervention and control), type of ICU and study population, severity of illness at ICU admission (intervention and control), study design, intervention group, control group, definition of VAP, the incidence of VAP, and other important clinical outcomes data. Extracted data were entered into a standardized Excel file (Microsoft, Redmond, WA) and were checked by a second author (X.J.H.). Any disagreements were resolved by discussion and consensus. The primary outcome was the incidence of VAP, while the secondary outcomes included ICU mortality, hospital mortality, length of ICU stay, and duration of MV.

Quality assessment

The methodological quality of each study was assessed using the *Cochrane Handbook for Systematic Reviews of Interventions*.[17] Two authors subjectively reviewed all studies and assigned a value of 'high', 'low', or 'unclear' to the following: (1) sequence generation; (2) allocation concealment; (3) blinding; (4) incomplete data addressed; (5) selective data reporting; and (6) free of other bias.

Statistical analysis

Differences were expressed as relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, and weighted mean differences (WMDs) with 95% CIs for continuous outcomes. Heterogeneity across studies was tested by using the I^2 statistic, which was a quantitative measure of inconsistency across studies. Studies with an I^2 statistic of 25%-50% were considered to have low heterogeneity, those with an I^2 statistic of 50%-75% were considered to have moderate heterogeneity, and those with an I^2 statistic of >75% were considered to have a high degree of heterogeneity.[18] If I^2 >50%, potential sources of heterogeneity were identified by sensitivity analyses conducted by omitting 1 study in each turn and investigating the influence of a single study on the overall pooled estimate. Publication bias was not assessed because of the limited number (<10) of studies included in each analysis. A P value of <.05 was considered statistically significant. All statistical analyses were performed using STATA version 11.0 (Stata Corporation, College Station, TX).

RESULTS

Eligible studies and baseline characteristics

The initial search yielded 410 articles of which 400 were excluded for duplicate studies and various reasons based on the titles and abstracts (Fig 1). Finally, 6 RCTs were included in the final analysis.[19-24] The main characteristics of studies included in the meta-analysis are presented in Table 1, and the outcome data of each included trial are described in Table 2. These studies were published between 1998 and 2017. The size ranged from 46-173 (total 704) patients. Among the 6 studies included here, all reported VAP events and length of ICU stay, 3 reported ICU mortality events,[19-21] and 5 trials reported duration of MV[19,21-24] and hospital mortality.[19-23] The quality of the included studies are shown in Table 3.

The selected trials examined various populations in ICUs, including trauma patients,[19] medical-surgical,[20,21] and mixed (medical, surgical and trauma, and neuroscience).[22-24] All of these patients were aged >16 years and received MV for >24 hours, with no current pneumonia.

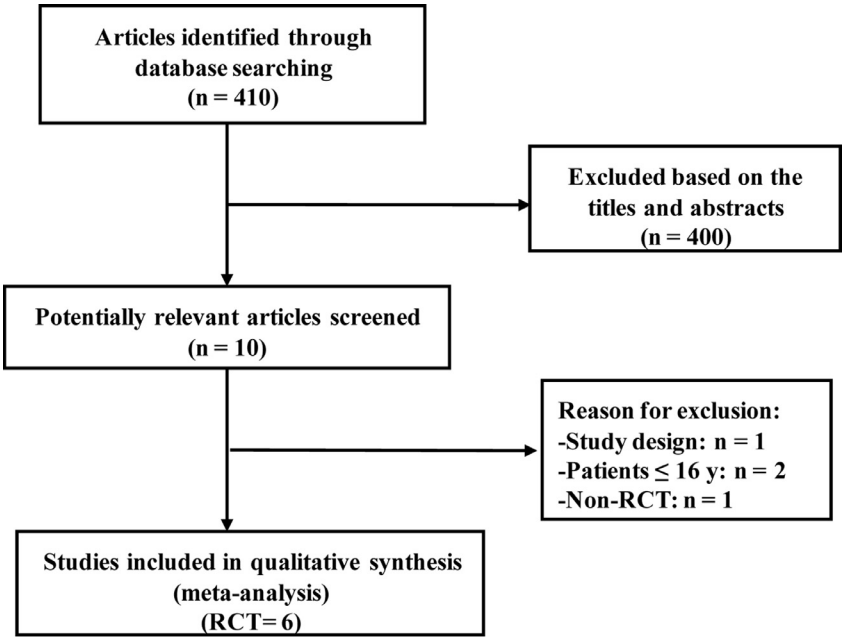

Fig 1. Search strategy and flow chart of screened, excluded, and eventually analyzed articles. *RCT*, randomized controlled trials.

Table 1
Characteristics of included studies

First author/y/ reference	Country	Number of patients (CPT/control)	Setting and patients	Severity of illness (CPT vs control)	Method of CPT	Definition of VAP
Ntoumenopoulos G, 1998[19]	Australia	46 (22/24)	Trauma patients (>18 y) requiring MV >24 h	APACHE II: 12.3 ± 3.8 vs 14.1 ± 7.4	Manual hyperinflation and postural drainage (2 sessions per d)	New pulmonary infiltrate on the chest radiograph, together with at least 3 of the following: temperature >38°C; white cell count >11,000; purulent sputum with bacteria on Gram stain; positive culture
Templeton M, 2007[20]	United Kingdom	172 (87/85)	General ICU patients (>18 y) requiring MV >48 h	APACHE II: 49 (8-96) vs 41 (4-97)	Manual hyperinflation, positioning, rib springing, and general mobilization (twice per d)	New chest radiograph infiltrates, positive microbiology culture from tracheal aspirates, a rise in white cell count and temperature (>38°C)
Patman S, 2009[21]	Australia	144 (72/72)	Acquired brain injury patients (>16 y) requiring MV >24 h	APACHE II: 20.3 ± 5.7 vs 20.5 ± 5.6	Manual hyperinflation, positioning, and airway suctioning (6 sessions per d)	Positive nonbronchoscopic alveolar lavage
Pattanshetty RB, 2010[22]	India	101 (50/51)	ICU patients (>18 y) requiring MV >48 h	NA	Manual hyperinflation, chest vibrations, positioning, and airway suctioning (2 sessions per d)	Clinical pulmonary infection score
Pattanshetty RB, 2011[23]	India	173 (87/86)	ICU patients (>18 y) requiring MV >48 h	NA	Positioning, manual hyperinflation, vibrations and suctioning (2 sessions per d)	Clinical pulmonary infection score
Zeng H, 2017[24]	China	68 (37/31)	Integrated ICU patients (>18 y) with oral indwelling endotracheal tube requiring MV >48 h	APACHE II: 18.49 ± 6.43 vs 18.19 ± 4.82	Positioning, manual hyperinflation, vibrations, and early functional exercise (2 sessions per d)	New pulmonary infiltrate or increased range of original lesions on the chest radiograph, together with at least 2 of the following: temperature >38°C; white cell count >10×10^9/L or <4.0×10^9/L; purulent sputum with bacteria on Gram stain; positive culture

APACHE, acute physiology and chronic health evaluation; *CPT*, chest physiotherapy; *ICU*, intensive care unit; *MICU*, medical intensive care unit; *MV*, mechanical ventilation; *NA*, not available; *SICU*, surgical intensive care unit; *VAP*, ventilator-associated pneumonia.

Of the 6 studies included in the meta-analysis, multimodality CPT (eg, positioning, chest wall vibrations, manual hyperinflation, suctioning, manual lung inflation, vibration expectoration, and early functional exercise) was administered to patients in the experimental group in the 3 studies.[22-24] For the other trials, usual care or same CPT was administered to patients in the control group. The definition of VAP varied across studies, no standard definition was used in reported studies.

Primary outcome: VAP

All 6 trials reported VAP in study patients. The aggregated results of these studies suggest that CPT was not associated with a significant reduction in the incidence of VAP (RR = 1.02; 95% CI, 0.82-1.26; $P = .87$) (Fig 2). The test for heterogeneity was significant (P for heterogeneity = .08; $I^2 = 49\%$). Subsequently, we still performed sensitivity analyses

Table 2
Primary and secondary outcomes of the included trials, CPT versus control

	Primary outcome	Secondary outcomes			
First author/y/reference	Incidence of VAP (n/N)	Hospital mortality (n/N)	ICU mortality (n/N)	Length of ICU stay (d)	Duration of MV (d)
Ntoumenopoulos G, 1998[19]	4/22 vs 8/24	0/22 vs 2/24	0/22 vs 0/24	7.4 ± 5.7 vs 6.8 ± 4.6	6.1 ± 5.4 vs 5.2 ± 3.5
Templeton M, 2007[20]	35/87 vs 25/85	46/87 vs 46/85	40/87 vs 42/85	13 (3-82) vs 12 (4-76)	NA
Patman S, 2009[21]	14/72 vs 19/72	13/72 vs 21/72	7/72 vs 14/72	9.3 ± 5.1 vs 10.7 ± 7.7	7.2 ± 5.0 vs 8.6 ± 6.5
Pattanshetty RB, 2010[22]	48/50 vs 47/51	12/50 vs 25/51	NA	13.9 ± 9.77 vs 11.3 ± 5.73	8.7 ± 5.6 vs 8.5 ± 5.21
Pattanshetty RB, 2011[23]	55/87 vs 48/86	24/87 vs 39/86	NA	11.4 ± 9.75 vs 9.3 ± 5.92	7.6 ± 3.97 vs 6.8 ± 4.46
Zeng H, 2017[24]	2/37 vs 8/31	NA	NA	5.6 ± 3.0 vs 8.6 ± 7.4	3.2 ± 1.7 vs 5.6 ± 4.9

NOTE. Data are mean ± SD, or median (range).
CPT, chest physiotherapy; *ICU*, intensive care unit; *MV*, mechanical ventilation; *n*, number of events; *N*, total number of patients; *NA*, not available; *VAP*, ventilator-associated pneumonia.

Table 3
Assessing risk of bias

First author/y/reference	Sequence generation	Allocation concealment	Blinding	Incomplete data addressed	Selective data reporting	Free of other bias
Ntoumenopoulos G, 1998[19]	Yes	Yes	No	No	No	Unclear
Templeton M, 2007[20]	No	No	Yes	Yes	Yes	Unclear
Patman S, 2009[21]	No	No	Yes	No	No	Unclear
Pattanshetty RB, 2010[22]	Yes	Yes	No	Yes	Yes	Unclear
Pattanshetty RB, 2011[23]	Yes	Yes	No	Yes	Yes	Unclear
Zeng H, 2017[24]	Yes	Yes	No	Yes	Yes	Unclear

NOTE. Yes = low risk of bias; No = high risk of bias.

to explore potential source of heterogeneity. Exclusion of the trial conducted by Zeng et al[24] significantly reduced the heterogeneity but did not change the results (RR = 1.06; 95% CI, 0.93-1.21; $P = .38$; P for heterogeneity = .31; $I^2 = 16\%$). Further exclusion of any single study did not materially alter the overall combined RR, with a range from 0.89 (95% CI, 0.60-1.32; $P = .56$) to 1.06 (95% CI, 0.85-1.32; $P = .63$).

Secondary outcomes

Table 4 outlines secondary outcomes. CPT significantly decreased the hospital mortality (5 trials[19-23]; RR = 0.68; 98% CI, 0.48-0.95; $P = .02$; P for heterogeneity = .09; $I^2 = 50\%$). CPT was not associated with decreases in ICU mortality (3 trials[19-21]; RR = 0.77; 98% CI, 0.43-1.37; $P = .38$; P for heterogeneity = .17; $I^2 = 48\%$), length of ICU stay (5 RCTs[19,21-24]; WMD = 0.12 days; 98% CI, −1.93-2.16; $P = .91$; P for heterogeneity = .02; $I^2 = 66\%$), and duration of MV (5 RCTs[19,21-24]; WMD = −0.41 days; 95% CI, −1.76-0.94; $P = .55$; P for heterogeneity = .03; $I^2 = 62\%$). Subsequently, exclusion of any single study did not materially alter the overall combined effects regarding length of ICU stay and duration of MV.

DISCUSSION

The current findings of our study suggested that CPT could fail to reduce the incidence of VAP in adult critically ill patients with MV. In addition, CPT might not be associated with a markedly reduced ICU mortality, length of ICU stay, and duration of MV except hospital mortality.

The principal findings of our study seem to be contrary with the previous study on the topic. In detail, the present meta-analysis included 6 RCTs involving 704 patients and indicated that CPT might not be associated with reduction in the incidence of VAP and other important clinical endpoints including ICU mortality, length of ICU stay, and duration of MV in critically ill patients receiving MV regardless of sensitivity analyses. The previous study suggested that CPT contributes to the early recovery of the patient in the ICU, reducing length of stay on MV and hospitalization, as well as the incidence of respiratory infection and mortality.[25] However, the main limitation of this study was that the authors designed their study as a cohort so they did not control the recruitment to avoid bias, which was pointed out in the previous study.[25]

In addition, relatively low heterogeneity ($I^2 = 49\%$) for the incidence of VAP was observed among these studies included in the current meta-analysis. Our sensitivity analyses suggested that 1 trial conducted by Zeng et al[24] contributed to the heterogeneity, which was not surprising given the differences in characteristics of CPT protocols and participants. Although the whole results of CPT were very disappointing; however, CPT has a trend of reducing the incidence of VAP. Further well-designed RCTs are needed to investigate the points described earlier.

Next, our results suggested that CPT might not be associated with a markedly reduced ICU mortality, length of ICU stay, and duration of MV except hospital mortality. Subsequently, substantial heterogeneity was observed in analyzing length of ICU stay and duration of MV. However, exclusion of any single study did not materially alter the overall combined effects regarding length of ICU stay and duration of MV. In detail, simple CPT including manual hyperinflation and suctioning

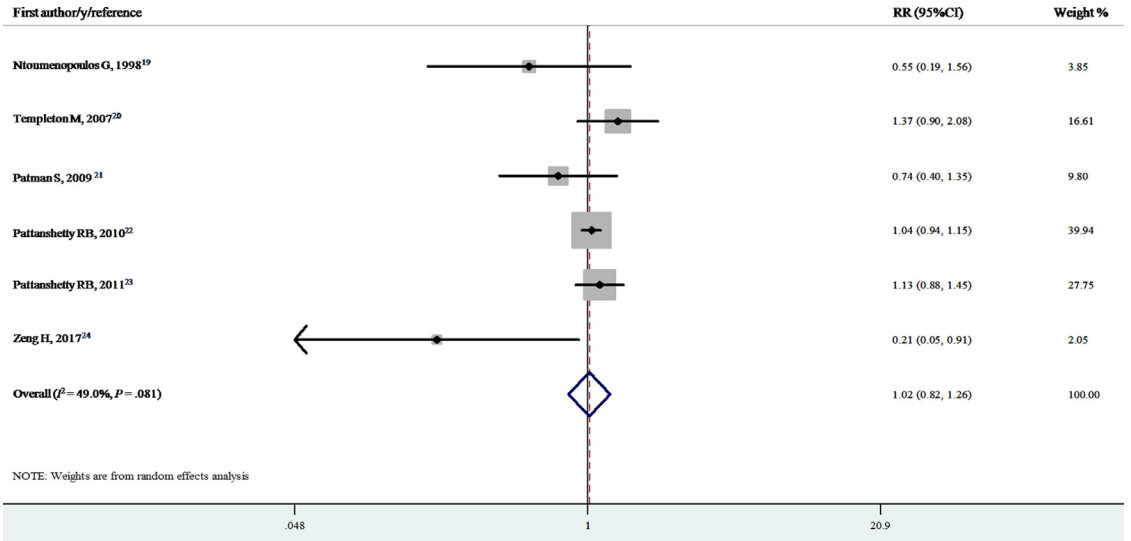

Fig 2. Meta-analysis of 5 trials evaluating the incidence of ventilator-associated pneumonia. Chest physiotherapy did not significantly reduce the incidence of ventilator-associated pneumonia. *CI*, confidence interval; *ID*, identification; *RR*, relative risks.

Table 4
Meta-analyses of secondary outcomes

Outcome	n (N)	Estimate	Effect (95% CI)	*P* value	I^2 (%)	$P_{heterogeneity}$
Hospital mortality[19-23]	636 (5)	RR	0.68 (0.48-0.95)	.02	50	.09
ICU mortality[19-21]	362 (3)	RR	0.77 (0.43-1.37)	.38	48	.17
Length of ICU stay[19,21-24]	532 (5)	WMD	0.12 (−1.93-2.16)	.91	66	.02
Duration of MV[19,21-24]	532 (5)	WMD	−0.41 (−1.76-0.94)	.55	62	.03

CI, confidence interval; *ICU*, intensive care unit; *MV*, mechanical ventilation; *n*, total number of patients; *N*, number of trials; *RR*, risk ratio; *WMD*, weighted mean difference.

were administered in the 3 studies,[19-21] and multimodality CPT was administered in the other 3 studies,[22-24] which may be the potential reason causing the heterogeneity in the present study. However, these results are not conclusive because further adequately powered studies are needed. In fact, these included studies are not adequately powered to examine these secondary outcome measures because they were not the primary outcomes and were the only clinically significant endpoints consistently reported in many of the studies analyzed in the present meta-analysis. Future research should focus on these clinical endpoints rather than just the incidence of VAP.

Our study provides additional interesting clues that may be useful for future research on the topic. Remarkably, the studies conducted by Pattanshetty et al[22,23] and Zeng et al[24] were different trials than what was included in our study, that is multimodality CPT including positioning, chest wall vibrations, manual hyperinflation, suctioning, manual lung inflation, vibration expectoration, and early functional exercise were administered to patients in the experimental group while manual hyperinflation and suctioning were administered to patients in the control group. However, regarding the other trials, usual care or same CPT was administered to patients in the control group. Zeng et al[24] suggested that twice-daily multimodality CPT was associated with a significant decrease in VAP, length of ICU stay, and duration of MV in mechanically ventilated patients. Therefore, whether multimodality CPT is better than simple CPT in ICU patients requires further research to confirm. We believe that the individualized principle of CPT based on the patient's characteristics may be crucial and is needed to be observed in future research. Multimodality CPT may be encouraged to become an available approach as a part of a comprehensive preventive measures program in mechanically ventilated patients.

The included trials did not report complications, side effects, or adverse events of CPT during the study period. However, Templeton and Palazzo[20] believed that CPT, such as coughing increasing intra-abdominal pressure and potentially increasing the risk of regurgitation and microaspiration, is also associated with temporary hemodynamic and metabolic disturbances. Some studies showed that manual hyperinflation reduced cardiac output, dysrhythmias, blood pressure perturbations, increases in oxygen consumption, and carbon dioxide production.[26-28] Primarily, whether these changes adversely affect weaning remain unclear. In addition, Spapen et al[29] conducted a pilot study comparing the effect of a specific and intensive CPT (intrapulmonary percussive ventilation plus assisted autogenic drainage) with conventional CPT (expiratory chest wall percussion and vibration, positioning, rib-springing, aerosol therapy, and airway suctioning) and no CPT in mechanically ventilated patients, and found that adjuvant intrapulmonary percussive ventilation plus assisted autogenic drainage tended to decrease gram-negative infection-related ventilator-associated complications. Future research may need to focus on this endpoint. Although these are not the focus of our study, future study should observe these.

Some limitations of this meta-analysis should be considered. First, our study included only 6 trials and some of them have a modest sample size. Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Second, there were different research purposes and considerable heterogeneity among the included trials. The differences in performed CPT, methodological quality (eg, diagnosis of VAP that considerably differs among studies), and the lack of information on factors that significantly influence VAP incidence (eg, concomitant antibiotic therapy, VAP prevention measures, nutrition policy) varied greatly. Different studies defined survival in widely variant terms. Moreover, the high prevalence of acute cerebral pathology in the included studies renders evaluation of outcome parameters such as duration of MV or ICU length of stay irrelevant. These factors may result in the heterogeneity and have potential impact on our results. Furthermore, because of the limited number of RCTs regarding the secondary outcomes, caution should be taken when interpreting the results. Finally, some missing and unpublished data may lead to bias in effect size.

CONCLUSIONS

Despite its various limitations and poor results, our study is still clinically valuable. CPT may not significantly reduce the incidence of VAP and alter other important clinical outcomes in mechanically ventilated patients. In addition, the individualized principle of CPT based on the patient's characteristics may be crucial but is needed to be observed in future research. Furthermore, heterogeneity among study designs still exists; thus, further well-designed and adequately powered RCTs are urgently needed to confirm our preliminary findings. We believe that research on the field is worthwhile and should be continued.

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