Sequential Non-Invasive Following Short-Term Invasive Mechanical Ventilation in the Treatment of Tuberculosis with Respiratory Failure: A Randomized Controlled Study

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Abstract

Background: Invasive and non-invasive mechanical ventilation (MV) have been combined as sequential MV (SMV) in the treatment of respiratory failure. However, the effectiveness remains unclear. Here, we performed a randomized controlled study to assess the efficacy and safety of SMV in the treatment of tuberculosis with respiratory failure.

Methods. Forty-four tuberculosis patients diagnosed with respiratory failure were randomly divided into SMV group (n=24) and conventional MV (CMV) group (n=20). Initially, the patients in both groups received invasive positive pressure ventilation (IPPV). When the patients' conditions were relieved, the ventilation modality in SMV group was switched to oronasal face continuous positive airway pressure (CPAP) until weaning.

Results. After treatment, the patients in SMV group had similar respiratory rate, heart rate, oxygenation index, alveolo-arterial oxygen partial pressure difference (A-aDO$_2$), blood pH, PaCO$_2$ to those in CMV group (all $P$ value>0.05). There was no significant difference in ventilation time and ICU stay between the two groups ($P$>0.05), but SMV group significantly reduced the time of invasive ventilation (mean difference (MD):-36.2 hrs, 95% confidence interval (CI):-53.6,-18.8 hrs, $P$<0.001). SMV group also reduced the incidence of ventilator-associated pneumonia (VAP; relative risk (RR):0.44, 95% CI:0.24,0.83, $P$=0.006) and atelectasis (RR:0.49,95% CI:0.24,1.00, $P$=0.040).

Conclusions. SMV was effective in treating tuberculosis with respiratory failure. It showed advantages in reducing invasive ventilation time and ventilator-associated adverse events.

Background

Despite the development of effective treatment, pulmonary tuberculosis still accounts for millions of cases with active disease and deaths in both developed and developing countries. In 2011, 8.7 million new cases of active tuberculosis emerged and 1.4 million cases died worldwide [1]. In 2017, tuberculosis caused 1.6 million global deaths, exceeding deaths caused by any other infectious disease [2]. Patients with active pulmonary tuberculosis often suffer from pulmonary dysfunction due to hemoptysis, interstitial infiltration, caseous pneumonia and other severe complications of tuberculosis, which may finally develop to respiratory failure [3]. Although acute respiratory failure occurs in only about 1.5% pulmonary tuberculosis, its mortality often reaches higher than 50% [4].

The most effective way to treat respiratory failure is mechanical ventilation (MV), which supports to relieve symptoms in acute phase and to gain opportunity for the later treatment [5]. The main adverse effects of invasive MV, which usually involves transoral tracheal intubation, include ventilator-associated injury and ventilator-associated infection [6]. Consequently, non-invasive MV has emerged as an optional strategy for patients with respiratory failure due to its fewer complications. It has been broadly applied to patients with severe acute respiratory syndrome (SARS), H1N1, and chronic obstructive pulmonary disease (COPD) [7, 8]. Recently, several clinical trials have also attempted to combine both invasive and...
non-invasive MV as sequential MV in the treatment of COPD [9]. However, the effectiveness of sequential MV for tuberculosis patients with respiratory failure remains unclear. In this study, we performed a randomized controlled study to assess the efficacy and safety of sequential non-invasive MV following short-term invasive MV in the treatment of tuberculosis with respiratory failure.

Methods

Participants

The study was prospectively registered at chictr.org.cn-ChiCTR2000032311, and is reported according to CONSORT guidelines. From April 2020 to December 2020, the active tuberculosis patients diagnosed with respiratory failure and treated in ICU of Beijing Chest Hospital, were enrolled in the study. The research protocol was approved by the Human Ethics Committee of Beijing Chest Hospital (2019-clinic-64) and the study was carried out based on the Declaration of Helsinki 1964. Informed consent was obtained from all participants.

Included criteria: (1) diagnosed with pulmonary tuberculosis according to medical history, tests for Mycobacterium tuberculosis, and chest radiography, (2) respiratory rate > 30 breaths/min, (3) tidal volume < 6 mL/kg, (4) artery pressure of oxygen (PaO₂) < 60 mm Hg, (5) arterial carbon dioxide partial pressure (PaCO₂) > 50 mm Hg, and (6) oxygenation index (PaO₂/FiO₂) < 300 mm Hg.

Exclusion criteria: (1) diagnosed with tuberculosis in central nervous system, (2) with severely damaged lung and probably to be ventilator dependent, (3) with lung cancer or cachexia, (4) acute physiology and chronic health evaluation II (APACHE II) score > 16 [10], (5) with multiple organ dysfunction and risk of ventilator dependent, (6) with stress ulcer-induced gastrointestinal bleeding or gastrointestinal perforation, and (7) with facial deformity and unable to receive non-invasive MV.

Treatment Protocol

All patients were randomly divided into sequential MV (SMV) group and conventional MV (CMV) group. At beginning, patients in both groups received invasive positive pressure ventilation (IPPV) using following ventilation modality: synchronized intermittent mandatory ventilation (SIMV) + pressure support ventilation (PSV) + positive end expiratory pressure (PEEP). Subjects were ventilated with a pressure support level targeting an expired tidal volume of 6–8 mL/kg and a respiratory rate of < 30 breaths/min. FiO₂ was adjusted to maintain peripheral oxygen saturation (SpO₂) at > 92% with PEEP of at least 5 cm H₂O (1 cm H₂O = 0.098 kPa). SIMV was set at 10–12 breaths/min and PSV was adjusted to 10–12 breaths/min.

When the patients' conditions were basically relieved, the ventilation modality in SMV group was switched to oronasal face continuous positive airway pressure (CPAP) until weaning. The indication for non-invasive MV included a stable blood pressure with FiO₂ ≤ 55%, SpO2 ≥ 95%, respiratory rate ≤ 30
breaths/min and tidal volume $\geq 6$ mL/kg. The patients in CMV group received persistent IPPV until weaning.

During the study, all patients received routine treatment of active tuberculosis and mixed infections with fluid therapy and nutritional supports. The vital signs of patients were carefully monitored during the ventilation and any necessary management was placed for symptomatic treatment.

**Data Collection**

The basic characteristics of all patients were collected, including: age, gender, body mass index (BMI), APACHE II score, medical history and chest radiography.

The primary end point of this study was assessed by detecting respiratory parameters (including respiratory rate, heart rate, oxygenation index, alveolo-arterial oxygen partial pressure difference (A-aDO$_2$), PaCO$_2$ and blood pH), and inflammatory parameters (white blood cells (WBC), percentage of neutrophil (NEU) and C-reactive protein (CRP)). The respiratory parameters were recorded before treatment (baseline) and in every 8 hrs during the treatment. And the inflammatory parameters were detected at baseline and in every 24 hrs. The data in baseline and after treatment (defined as the point when FiO$_2$ reduced to 50%) were analyzed and compared between the two groups.

The secondary end-point was evaluated by comparing in-hospital outcomes between the two groups, including ventilation time, invasive mechanical ventilation time, the length of ICU stay, visual analogue scale (VAS) score, total cost (RMB), ventilator-associated pneumonia (VAP) and atelectasis. VAS score was evaluated by doctors and nurses with a scale of 0–10 (0: no pain, 10: utmost pain), and the mean VAS score during the study was calculated and recorded.

**Statistical analysis**

Data analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables such as age, BMI, respiratory and inflammatory parameters were presented as mean ± standard deviation (SD). Categorical variables such as gender were presented as number (percentage). Significance was analyzed using student’s t test for continuous variables and Chi-square test for categorical variables. As for in-hospital outcomes, mean difference (MD) and relative ratio (RR) with 95% confidence interval (CI) were calculated for continuous variables and categorical variables, respectively. Two sided $P < 0.05$ was considered to be statistically significant.

**Results**

After inclusion, forty-four patients with 63.6% of male and an age range of 22–88 were randomly divided into SMV group (n = 24) and CMV group (n = 20). The mean period of tuberculosis in the included participants was $7.1 \pm 89$ yrs, and no one was diagnosed with extra-pulmonary tuberculosis. Thirteen
(29.5%) patients were accompanied with diabetes mellitus, twenty-six (59.1%) subjects were detected with bacterial infection. At baseline, the mean respiratory rate, heart rate, oxygenation index, A-aDO$_2$, PaCO$_2$, blood pH, WBC, percentage of NEU and CRP in all included subjects were $36.3 \pm 4.6$ /min, $136.6 \pm 11.6$ /min, $92.5 \pm 38.0$ mm Hg, $65.3 \pm 26.8$ mm Hg, $68.7 \pm 19.8$ mm Hg, $7.27 \pm 0.09$, $15.8 \pm 5.0 \cdot 10^9/L$, $87.9 \pm 4.2\%$, $157.6 \pm 46.4$ mg/mL, respectively (Table 1).

| Parameters                        | Total (n = 44) | SMV group (n = 24) | CMV group (n = 20) | $P$ value# |
|-----------------------------------|---------------|--------------------|--------------------|------------|
| Age (yrs)                         | $61.3 \pm 14.5$ | $63.9 \pm 13.0$     | $58.3 \pm 15.9$    | 0.209      |
| Male (%)                          | $28 (63.6)$   | 17 (70.8)          | 11 (55.0)          | 0.277      |
| BMI (kg/m$^2$)                    | $22.4 \pm 2.5$ | $22.8 \pm 2.0$     | $22.0 \pm 3.0$     | 0.307      |
| Period of tuberculosis (yrs)      | $7.1 \pm 8.9$ | $8.4 \pm 11.1$     | $5.4 \pm 5.2$      | 0.243      |
| Diabetes mellitus (%)             | $13 (29.5)$   | 7 (29.2)           | 6 (30.0)           | 0.952      |
| Hypertension (%)                  | $8 (18.2)$    | 6 (25.0)           | 2 (10.0)           | 0.199      |
| Bacterial infection (%)           | $26 (59.1)$   | 14 (58.3)          | 12 (60.0)          | 0.911      |
| APACHE II score                   | $11.4 \pm 2.6$ | 12.0 (2.3)         | $10.7 \pm 2.8$     | 0.109      |
| Respiratory rate (/min)           | $36.3 \pm 4.6$ | $35.7 \pm 5.1$     | $37.2 \pm 3.9$     | 0.289      |
| Heart rate (/min)                 | $136.6 \pm 11.6$ | $134.2 \pm 13.8$  | $139.5 \pm 7.7$    | 0.134      |
| Oxygenation index (mm Hg)         | $92.5 \pm 38.0$ | $92.0 \pm 43.8$    | $93.2 \pm 30.8$    | 0.920      |
| A-aDO$_2$ (mm Hg)                 | $65.3 \pm 26.8$ | $63.0 \pm 26.0$    | $68.1 \pm 28.3$    | 0.544      |
| PaCO$_2$ (mm Hg)                  | $68.7 \pm 19.8$ | $66.4 \pm 18.2$    | $71.5 \pm 21.7$    | 0.402      |
| Blood pH                          | $7.27 \pm 0.09$ | $7.30 \pm 0.09$    | $7.25 \pm 0.09$    | 0.087      |
| WBC ($\cdot 10^9/L$)              | $15.8 \pm 5.0$ | $16.4 \pm 5.8$     | $15.1 \pm 3.7$     | 0.389      |
| Percentage of NEU (%)             | $87.9 \pm 4.2$ | $88.3 \pm 5.1$     | $87.4 \pm 2.8$     | 0.446      |
| CRP (mg/mL)                       | $157.6 \pm 46.4$ | $159.4 \pm 48.3$  | $155.4 \pm 45.2$   | 0.779      |

# Inter-group difference was calculated between SMV group and CMV group. SMV: sequential mechanical ventilation, CMV: conventional mechanical ventilation, BMI: body mass index, APACHE: acute physiology and chronic health evaluation, A-aDO$_2$: alveolo-arterial oxygen partial pressure difference, WBC: white blood cell, NEU: neutrophil, CRP: C-reactive protein.
The baseline characteristics were similar in CMV group and SMV group (all *P* value > 0.05). After treatment, all respiratory and inflammatory parameters in each group significantly ameliorated with no any death case occurred. Breathing frequency and heart rate significantly decreased in both SMV group and CMV group. When FiO$_2$ of ventilation reduced to 50%, the patients in SMV group had similar respiratory rate, heart rate, oxygenation index, A-aDO$_2$, PaCO$_2$, blood pH, WBC, percentage of NEU and CRP to those in CMV group (all *P* value > 0.05) (Table 2). Correspondingly, the improvement of oxygenation index, A-aDO$_2$ and PaCO$_2$ in SMV group were paralleled to those in CMV group (Fig. 1).

### Table 2
Comparison of clinical outcomes between the two groups after treatment

| Parameters               | SMV group (n = 24) | CMV group (n = 20) | *P* value |
|--------------------------|--------------------|--------------------|-----------|
| Respiratory rate (/min)  | 25.7 ± 4.3         | 25.0 ± 2.7         | 0.551     |
| Heart rate (/min)        | 99.1 ± 8.4         | 98.6 ± 5.4         | 0.808     |
| Oxygenation index (mm Hg)| 183.3 ± 29.7       | 178.4 ± 34.8       | 0.618     |
| A-aDO$_2$ (mm Hg)        | 27.0 ± 10.8        | 31.4 ± 10.3        | 0.172     |
| PaCO$_2$ (mm Hg)         | 51.7 ± 8.5         | 49.8 ± 9.2         | 0.480     |
| Blood pH                 | 7.38 ± 0.05        | 7.39 ± 0.04        | 0.412     |
| WBC (-10$^9$/L)          | 10.2 ± 2.8         | 9.6 ± 1.7          | 0.390     |
| Percentage of NEU (%)    | 79.3 ± 5.7         | 77.9 ± 3.8         | 0.342     |
| CRP (mg/mL)              | 67.0 ± 36.6        | 66.0 ± 35.5        | 0.924     |

SMV: sequential mechanical ventilation, CMV: conventional mechanical ventilation, A-aDO$_2$: alveolo-arterial oxygen partial pressure difference, WBC: white blood cell, NEU: neutrophil, CRP: C-reactive protein.

There was no significant difference in total ventilation time and the length of ICU stay between the two groups (*P* > 0.05), but SMV group significantly reduced the time of invasive ventilation (50.8 ± 25.3 hrs versus 87.0 ± 32.3 hrs; MD: -36.2 hrs, 95% CI: -53.6, -18.8 hrs, *P* < 0.001) (Table 3). SMV group also dramatically reduced the incidence of VAP (33.3% versus 75.0%; RR: 0.44, 95% CI: 0.24, 0.83, *P* = 0.006) and atelectasis (29.2% versus 60.0%; RR: 0.49, 95% CI: 0.24, 1.00, *P* = 0.040) compared with CMV group. Patients in SMV group were much more comfortable with lower VAS score (6.5 ± 1.1 versus 7.7 ± 1.1; MD: -1.2, 95% CI: -1.9, -0.6, *P* < 0.001). Additionally, in-hospital cost was statistically lower in SMV group than in CMV group (50 ± 22 thousand versus 63 ± 20 thousand; MD: -13 thousand, 95% CI: -25, -1 thousand, *P* = 0.045).
Table 3  
Comparison of in-hospital outcomes between the two groups

| Parameters                        | SMV group (n = 24) | CMV group (n = 20) | MD or RR | 95% CI         | P value |
|-----------------------------------|--------------------|--------------------|----------|----------------|---------|
| Ventilation time (hrs)            | 87.7 ± 36.0        | 87.0 ± 32.3        | 0.7      | -19.5, 20.9    | 0.946   |
| Invasive mechanical ventilation time (hrs) | 50.8 ± 25.3        | 87.0 ± 32.3        | -36.2    | -53.6, -18.8   | < 0.001 |
| VAP (%)                           | 8 (33.3)           | 15 (75.0)          | 0.44     | 0.24, 0.83     | 0.006   |
| Atelectasis (%)                   | 7 (29.2)           | 12 (60.0)          | 0.49     | 0.24, 1.00     | 0.040   |
| ICU stay (d)                      | 5.5 ± 2.6          | 4.4 ± 1.4          | 1.1      | -0.1, 2.3      | 0.086   |
| VAS score                         | 6.5 ± 1.1          | 7.7 ± 1.1          | -1.2     | -1.9, -0.6     | < 0.001 |
| Total cost (thousand RMB)         | 50 ± 22            | 63 ± 20            | -13      | -25, -1        | 0.045   |

SMV: sequential mechanical ventilation, CMV: conventional mechanical ventilation, MD: mean difference, RR: relative risk, CI: confidence interval, VAP: ventilator-associated pneumonia, VAS: visual analogue scale.

Discussion

The present study showed SMV was an effective strategy to reverse respiratory function in tuberculosis patients and was comparable to CMV in improving oxygenation index and A-aDO\(_2\). To some extent, our results were consistent with some former studies. Frat et al. [11] evaluated the clinical efficacy of humidified oxygen using SMV (which included high-flow nasal cannula alternated with non-invasive MV) in acute hypoxemic respiratory failure. The results showed better improvement in oxygenation and tachypnea in SMV compared to standard oxygen therapy. Burns et al. [12] reviewed relevant randomized controlled trials (RCT) to explore the efficacy of non-invasive MV as a weaning strategy for ventilation in patients with respiratory failure. Compared to continued invasive MV, non-invasive weaning reduced the mortality and the incidence of pneumonia, without increasing the risk of weaning failure or reintubation. Osadnik et al. [13] performed another systemic review to compare the efficacy of non-invasive MV in conjunction with usual care versus usual care without MV in acute hypercapnic respiratory failure. Their results showed that non-invasive MV was beneficial to reducing the mortality and endotracheal intubation, and it could be regarded as a first-line intervention in conjunction with usual care for patients with respiratory failure. All evidence proved the non-invasive MV as an efficient weaning strategy for ventilation.

Although there was no significant difference in ventilation time and the length of ICU stay between the two groups, our study detected SMV was able to reduce the incidence of VAP and atelectasis, mainly due to the reduced time of invasive ventilation. A recent meta-analysis performed by Huang et al. also
assessed the safety of SMV versus CMV in the treatment of acute exacerbation of COPD (AECOPD) [14]. Their results showed the application of SMV at the pulmonary infection control window significantly decreased VAP incidence (RR: 0.20, 95% CI: 0.16–0.26), mortality (RR: 0.38, 95% CI: 0.26–0.55), reintubation (RR: 0.39, 95% CI: 0.27–0.55) and reduced the invasive ventilation time (MD: -9.23, 95% CI: -10.65, -7.82), ventilation time (MD: -4.91, 95% CI: -5.99, -3.83), and the length of ICU stay (MD: -5.10, 95% CI: -5.43, -4.76). Poor tolerance to non-invasive MV accounted for 5%-25% intubation in the hypoxemic patients [15–18]. Our data showed the patients in SMV group were much more comfortable than those in CMV, representing a better tolerance of non-invasive MV than invasive MV. However, some research reported a reversed result. Frat et al. [11] showed high-flow nasal cannula was better tolerated than non-invasive MV with a lower VAS score. Moreover, we found SMV was a cost-effective strategy, which was also confirmed by other investigations [19]. These advantages in comfort and economy will highly improve the acceptance of SMV by patients.

It has been discussed that non-invasive MV is not suitable for patients with severe bronchial infections and heavy sputum, since they are unable to cough and unconscious to severe hypercapnia. In these conditions, invasive MV with intubation is usually needed to facilitate sputum drainage and improve respiratory function. During invasive MV, however, it is more likely to get repeated VAP due to implementation of the artificial airway [20,21]. Once VAP occurs, the patients’ condition usually get worse, and weaning of ventilation is difficult to be performed [22, 23]. Therefore, the key to reduce the incidence of VAP is to shorten the time of intubation or remove the implementation. We previously found fiber optic bronchoscope (FOB) was not only useful in the diagnosis of suspected pneumonia, but could be also applied to locate and suction sputum [24]. Song et al. [25] reported the application of FOB was effective and safe in AECOPD during weaning of SMV, which decreased the total ventilation time, the length of ICU stay, reintubation rate, incidence of VAP. The application of FOB may further improve the tolerance of non-invasive MV.

The limitations of the present study should be also noticed. First, it was designed as a pilot study and the sample size was relatively small. Second, we only included patients with APACHE II score ≤ 16, which meant patients with severe chronic diseases were excluded. Hence, we are unable to estimate the real mortality. Third, we have only provided data to compare the short-term clinical outcomes between the two groups, but failed to assess the mid-term or long-term efficacy and safety by follow-up. Fourthly, VAS score was evaluated subjectively, though the nurses and doctors were trained to follow to standard criteria. In addition, it may be not suitable to compare our data with former studies, since most of them focused on patients diagnosed with COPD. Finally, we failed to detect the best time point for switching from invasive MV to non-invasive MV, which is important for clinical work and therefore badly needed for further investigations.

**Conclusions**

SMV was effective and safe to improve respiratory function with advantages in reducing invasive ventilation time and ventilator-associated adverse events. SMV can be regarded as an optional strategy
to treat tuberculosis patients with respiratory failure.

**Abbreviations**

MV: mechanical ventilation, SMV: sequential mechanical ventilation; CMV: conventional mechanical ventilation, IPPV: invasive positive pressure ventilation, CPAP: continuous positive airway pressure, A-aDO$_2$: alveolo-arterial oxygen partial pressure difference, MD: mean difference, CI: confidence interval, VAP: ventilator-associated pneumonia, RR: relative risk, SARS: severe acute respiratory syndrome, COPD: chronic obstructive pulmonary disease.

**Declarations**

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**

Study design: NMK, LL, Study conduct: all authors, statistical analysis: NMK, LL. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The research protocol was approved by the Human Ethics Committee of Beijing Chest Hospital (2019-clinic-64).

**Consent for publication**

Not applicable.

**Competing interests**

All authors declare that they have no competing interests.

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