The Effect of Early and Late Tracheotomy on Outcomes in Patients: A Systematic Review and Cumulative Meta-analysis

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Abstract

Objective. To compare the effect of early tracheotomy (ET) and late tracheotomy (LT) on ventilator-associated pneumonia (VAP) incidence and short-term mortality in critically ill patients who received mechanical ventilation.

Data Sources. We searched databases of PubMed, Embase, and others for randomized controlled trials (RCTs) that compared ET (≤8 days after admission to the intensive care unit, initiation of translaryngeal intubation, or initiation of mechanical ventilation) with LT (≥6 days) in critically ill patients.

Review Methods. The overall odds ratio (OR) was estimated by traditional meta-analysis. In addition, cumulative meta-analysis was conducted by adding 1 study at a time in the order of year of publication.

Results. A total of 11 RCTs involving 1436 patients (708 in the ET group and 728 in the LT group) were included in this analysis. Early tracheotomy could significantly reduce the short-term mortality (OR = 0.74; 95% confidence interval [CI] [0.58, 0.95]) but did not reduce the VAP incidence (OR = 0.70; 95% CI [0.47, 1.04]). The cumulative meta-analysis showed that evidence of the benefit of ET on VAP incidence was unstable over time. In contrast, the difference in short-term mortality was stable from the first appearance during the cumulative meta-analysis.

Conclusion. Early tracheotomy could improve short-term mortality but did not alter VAP incidence. Many factors may be responsible for the unstable results during cumulative meta-analysis, and further study is still needed to explore the optimal timing of tracheotomy.

Keywords

early tracheotomy, late tracheotomy, ventilator-associated pneumonia incidence, short-term mortality, meta-analysis

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Tracheotomy is one of the most common procedures conducted in critically ill patients, especially those who always receive long-term mechanical ventilation (MV) due to coma, asphyxia, respiratory muscular paralysis, hypoxia, and so on. The primary reason for tracheotomy is to avoid the complications introduced by prolonged translaryngeal intubation. Moreover, compared with conventional translaryngeal intubation, tracheotomy confers multiple advantages. It can establish an effective artificial airway in a short time, reduce the physiological dead space, protect from further direct laryngeal injury, facilitate nursing care including airway suctioning and mouth hygiene, and improve patients’ comfort.4-6 However, a number of complications resulting from the surgical procedure are implicated, such as stomal hemorrhage, stomal infections, pneumothorax, and occasionally death.5 Therefore, a variable period of translaryngeal intubation prior to tracheotomy is generally employed to balance the benefits and risks of tracheotomy.2,4 The risk of translaryngeal intubation would increase during the intubation, and the timing is a key criterion for performing a tracheotomy.

Unfortunately, the optimal timing of tracheotomy remained disputed. Patient outcomes based on timing of tracheotomy, such as ventilator-associated pneumonia (VAP) incidence, mortality, and time of hospitalization, have been controversial.6 For example, Koch and colleagues7 found that early tracheotomy (ET) could reduce the time of ventilation and hospitalization and decrease mortality. However, the randomized controlled trial (RCT) performed by Terragni and colleagues8 did not show any significant differences in the risk of pneumonia or mortality between ET and late tracheotomy (LT). Some factors, such as number of

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patients, baseline data, and intervention measures, as well as the variable evaluation criterion across different trials, may be responsible for the unstable results. Here, we conducted an updated systematic review and meta-analysis of RCTs on the timing of tracheotomy to comprehensively investigate whether critically ill patients would benefit from ET.

Methods

Search Strategy
Following the guidelines of the PRISMA Statement, we searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, Highwire Press, Springer, CBM, CNKI, Clinical Trials (www.clinicaltrials.gov), and the Chinese Clinical Trial Registry (www.chictr.org) to collect relevant articles in all languages from inception through January 2014, using the keywords early tracheotomy or tracheotomy or early vs late tracheotomy and timing of tracheotomy. The reference documents of the included articles and previous meta-analyses were also checked for additional eligible trials.

Study Selection

Studies were included if they were prospective, randomized, or quasi-randomized trials on tracheotomy in adult patients (older than 15 years) requiring artificial ventilation. The intervention measure was ET compared with LT. Moreover, the studies were all approved by institutional review boards. Studies were excluded if they met 1 of the following criteria: (1) defect of trial design, (2) absence of important data, (3) retrospective cohort study, (4) repeated publication, (5) comments or letters, or (6) other studies not conforming to the selection criteria.

Two authors independently screened the studies to identify eligible ones. Early tracheotomy was defined as a tracheotomy performed up to 8 days after admission to the intensive care unit (ICU), initiation of translaryngeal intubation, or initiation of MV. Late tracheotomy was defined as a tracheotomy conducted 6 days after admission to the ICU, initiation of translaryngeal intubation, or initiation of MV. Disagreements between the reviews were resolved by discussion until a consensus was reached.

Data Extraction and Risk of Bias Assessment

Two authors independently extracted the following data: patient characteristics (ie, sex, age, and disease), grouping method, tracheotomy technique, intervention measure (ie, definitions of ET and LT), diagnostic criteria, main outcomes, and statistical methods. If necessary, we contacted the original authors by email for missing data. Any disagreement was resolved by discussion. The risk of bias was assessed using the method recommended by the Cochrane Collaboration (version 5.1.0) against the following key criteria: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective outcome reporting, and free of other bias. Overall risk of bias for each study was summarized as “low,” “unclear,” or “high” based on the risk of bias across each of the key criteria.

Statistics and Analysis

The incidence of VAP and short-term mortality (28-day or 30-day) were analyzed. Statistical heterogeneity was assessed by the $I^2$ statistic and $x^2$ test. If statistical heterogeneity was evident across studies ($P$ value of $x^2$ test $<.05$ and $I^2 > 50$%), a random-effects model was selected to estimate the overall odds ratio (OR) and 95% confidence intervals (CIs). Otherwise, a fixed-effect model was applied. Sensitivity analysis was conducted by omitting 1 study at a time to investigate the influence of a single study on the overall estimate. In addition, cumulative meta-analysis was conducted to summarize the evidence in the assessment of the timing of tracheotomy. The studies were added at a time in the order of year of publication, and the results were summarized sequentially. Egger’s test was employed to assess the publication bias (if $n \geq 9$). Statistical analyses were carried out using Stata version 12.0 and RevMan version 5.0.

Results

Study Selection and Characteristics

As shown in Figure 1, the initial searches yielded a total of 1898 studies. Of these, 1542 were excluded, since the themes of these studies were not relevant. Then, 127 were excluded to avoid data duplication. After retrieving for more details, 208 were excluded because they did not have an RCT design or they studied tracheotomy technique or VAP only. Moreover, 10 studies were excluded, including 4 reviews, 5 meta-analyses, and 1 study without full text. Hence, we identified 11 trials that fulfilled the inclusion criteria, involving 708 cases in the ET group and 728 cases in the LT group.

The characteristics of the included studies are summarized in Supplemental Table S1 (available at otojournal.org), where they were stratified by chronological order. There were 2 quasi-randomized trials and 9 true randomized trials. All of the included studies were published in English. The patients from the 11 studies were all from Europe and America, including 6 studies from the United States, 2 studies from France, and the other 3 studies from Germany, Italy, and Morocco, respectively. In addition, the eligible studies examined different populations of critical ill patients, including trauma, multiple injuries, head trauma, burn injury, cardiac surgery, neurologic disorders, and medical ICUs. In most of the studies, enrolled patients were older than 18 years, except for 2 studies, in which one enrolled patients $>15$ years and the other $>17$ years. The definition of LT varied among different trials. On the whole, in most studies, ET referred to tracheotomy conducted within 1 to 8 days after admission to the ICU, initiation of translaryngeal intubation, or MV and LT referred to tracheotomy conducted any time. But it should be noted that in the study reported by Koch et al, LT was defined as tracheotomy conducted at or after 6 days of the initiation of translaryngeal intubation. The diagnosis of VAP varied across
the studies, among which 3 studies\textsuperscript{14,15,18} were according to Centers for Disease Control and Prevention criteria,\textsuperscript{19} 3 studies\textsuperscript{3,16,17} were based on bronchoscopy, 2 studies\textsuperscript{7,8} were based on the calculation of the Clinical Pulmonary Infection Score, 2 studies\textsuperscript{12,13} were diagnosed by clinical features and accessory examination, and the remaining 1 study\textsuperscript{11} was according to the infectious disease service. Eight\textsuperscript{3,7,8,13-17} of the 11 studies stated techniques of tracheotomy, which included percutaneous dilatational tracheotomy procedure and surgical technique.

**Evaluation of Risk of Bias**

An overview of the risk of bias is shown in Figure 2A and 2B, from which we found that some studies failed to provide sufficient details to assess the potential risk of bias. Generation of the randomization sequence was adequate in 9 trials\textsuperscript{3,7,8,13-17} but inadequate in the remaining 2 studies.\textsuperscript{11,12} Adequate allocation concealment was reported in 6 studies\textsuperscript{7,8,14-17} but not in the other 5 studies. Blinding design is not available in tracheotomy due to the nature of this intervention measure, so none of the 11 studies applied a blinding method to conduct the experiments or assess the outcomes, although Terragni and colleagues\textsuperscript{8} stated that the choice of technique and the location for tracheotomy were blinded to the study designer. Attrition of the original sample occurred in 1 multicenter study by Sugerman et al.,\textsuperscript{13} since the collaborating investigators in one center moved to other facilities in other cities, leading to the loss of patient data, and in the other 3 centers, data forms of their entered patients were not submitted. In addition, 1 patient in the non-head trauma and 2 in the non-trauma groups in the LT or the continued endotracheal intubation arm of their study did not have completed data on the presence or absence of pneumonia, which might contribute to attrition bias. One\textsuperscript{16} of the studies had a high

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**Figure 1.** Flow chart of study selection.

**Figure 2.** (A) Risk of bias graph: each risk of bias item presented as percentages across all included studies. (B) Risk of bias summary: each risk of bias item for each included study.
risk of reporting bias because the authors did not report all of the outcome data according to the protocol.

**VAP Incidence**

VAP incidence data were available for all of the 11 included studies. Evidence of heterogeneity was observed among these individual trials ($H = 1.43$, $I^2 = 51\%$, $P = .03$), and a random-effect model was applied to pool the results (Figure 3). It seems that the VAP incidence was independent of the timing of tracheostomy ($OR = 0.70$, 95% CI [0.47, 1.04], $P = .05$).

**Short-term Mortality**

All studies except 1 study evaluated short-term mortality as an outcome measure. A fixed-effect model was used to estimate the overall OR since no obvious heterogeneity was found among these individual studies ($H = 1.18$, $I^2 = 29\%$, $P = .19$). In total, there were 144 deaths among 708 patients in the ET group (20.3%) and 185 deaths among 728 patients in the LT group (25.4%). Short-term mortality was significantly reduced in the ET group compared with the LT group ($OR = 0.74$, 95% CI [0.58, 0.95], $P = .02$; Figure 4).

**Cumulative Meta-analysis**

Cumulative meta-analysis was conducted to evaluate the influence of individual study on the overall results. Figure 5 shows a forest plot for the cumulative meta-analysis of VAP incidence after ET and LT treatment. The result indicated that the incidence of VAP between ET and LT was not significantly different until adding a 2010 publication by Terragni et al$^8$ published in 2010 ($OR = 0.740$, 95% CI [0.58, 0.980], $P = .036$). Compared with the result of VAP incidence, the significant difference in short-term mortality remained stable after adding 2 studies published in 2011 and 2012 ($P = .018$ and $P = .019$, respectively).

**Heterogeneity Test**

The Galbraith graph, which describes the accuracy of each individual study versus the standardized effects, was applied to identify the study that contributed to the heterogeneity of VAP incidence. An adjusted regression line and 2 confidence bands are displayed in this graph. A study would be considered to be responsible for heterogeneity when it is located outside the confidence bands. As shown in Figure 9, the trials by Rodriguez et al$^{12}$ and Rumbak et al$^3$ were outside the confidence bands, so they may have outlying results and may be related to the heterogeneity (Figure 9).

**Discussion**

In current study, we identified 11 trials that compared the effect of ET and LT among critically ill patients who received MV. Traditional and cumulative meta-analyses were conducted to estimate the overall VAP incidence and short-term mortality after ET or LT treatment.

**Main Findings**

Our meta-analysis revealed that ET significantly decreased short-term mortality but did not alter the incidence of VAP in critically ill patients. We discussed short-term mortality...
instead since long-time survival data were unavailable. Tracheotomy was considered a time-dependent variable in the retrospective cohort study by Scales et al,\textsuperscript{20} which suggested that each additional delay of 1 day was associated with increased mortality (hazard ratio 1.008, 95% CI 1.004-1.012). A recent meta-analysis performed by Gomes Silva and colleagues\textsuperscript{21} pooled the data of 4 randomized or quasi-randomized controlled studies involving 673 patients and indicated the reduction of short-term mortality in the ET groups. However, several meta-analyses\textsuperscript{22-24} did not observe any favorable impact of ET on short-term mortality.

The effect of timing of tracheotomy on VAP incidence was also disputed. In a prospective study by Gandia-Martinez and colleagues\textsuperscript{25} evaluating the practice of tracheotomy in 118 patients in France, a lower VAP incidence was found in patients who were subjected to ET (<9 days; \( P < .001 \)). Consistent with our result, the meta-analysis by Wang et al\textsuperscript{22} also suggested that ET could not reduce the risk of VAP (relative risk = 0.94, 95% CI [0.77, 1.15], \( P = .54 \)).

With regard to VAP incidence and mortality, there has always been a dispute, which can be partly attributed to the different definition of “early tracheotomy.”\textsuperscript{26} Although a consensus conference recommended that tracheotomy should be performed at 21 days after endotracheal intubation, which can be an important index of tracheotomy timing,\textsuperscript{27} surgeons always choose tracheotomy timing according to their experience. Moreover, the optimal timing of tracheotomy varies greatly across different studies. Early tracheotomy in the trials included in our meta-analysis was defined as \(<8\) days after admission to the ICU, initiation of translaryngeal intubation, or initiation of MV, and LT was defined as \(\geq 6\) days. Thus, a tracheotomy might be considered “early” in some trials but “late” in other trials, and the crossed definitions reflect the flexibility in the timing of tracheotomy and might weaken our conclusion.

In addition to VAP incidence and short-term mortality, timing of tracheotomy seems to be associated with other outcomes, such as duration of artificial ventilation and
length of stay in the ICU. The meta-analysis conducted by Griffiths et al\(^\text{23}\) (in which ET was defined as ≤7 days after intubation or admission to the ICU) indicated that ET significantly reduced the duration of artificial ventilation and length of stay in the ICU. However, in the meta-analysis by Wang et al\(^\text{22}\) (in which ET was defined as ≤8 days after intubation or admission to the ICU), the timing of tracheostomy did not show a significant association with these outcomes. Among the 11 included studies in the current meta-analysis, 6 studies\(^\text{3,7,12,17,18,28}\) indicated that ET could reduce the duration of artificial ventilation and length of stay in the ICU in the ET groups. However, another 4 studies\(^\text{8,14-16}\) and 3 studies\(^\text{8,13,15}\) did not find an improvement effect of ET on duration of artificial ventilation and length of stay in intensive care, respectively. Thus, the association between timing of tracheotomy and these 2 outcomes was also controversial, and more studies are needed to evaluate the association.

**Limitations**

There are several limitations of the current study. First, the number of studies and patients available for the analysis are small, which affect the accuracy of our results. Second, there are multiple heterogeneities among the included trials. The included studies in our meta-analysis were from different countries, including countries in Europe, North America, and Africa. Racial differences and various body mass indexes might be reasons leading to heterogeneity. Furthermore, the types of injury cannot be restricted rigorously. Patients were from head trauma, trauma, burns, medical ICU, cardiac surgery, and neurologic ICU, and thus, various disease states also might contribute to heterogeneity. Third, the definitions of ET and LT were crossed, which may influence the solidity of the final conclusion. Although the definitions were crossed, both cumulative meta-analysis and sensitivity analysis showed that the crossed definitions of ET and LT did not reverse the result of the study. In conclusion, the current meta-analysis suggests that there is no advantage to ET with regard to VAP incidence, and cumulative meta-analysis shows that the result is not stable. However, ET markedly reduces short-term mortality, and this result was stable during the cumulative meta-analysis. Since long-term follow-up data about mortality are scarce, the long-term effect of ET is debatable. It is necessary to carry out a series with a larger sample, critical randomized control, long-term follow-up, and multicenter trials for further exploration, and further study will help us choose and judge the optimal time of tracheotomy.

**Author Contributions**

Xiao Liu, conception of the work, revising the manuscript, final approval, accountability for all aspects of the work; Hong-Chao Wang, design of the work, revising the manuscript, final approval, accountability for all aspects of the work; Ya-Wei Xing, data analysis, revising the manuscript, final approval, accountability for all aspects of the work; Yan-Ling He, data interpretation, revising the manuscript, final approval, agreement to be accountable for all aspects of the work; Ze-Feng Zhang, data analysis, drafting, final approval, accountability for all aspects of the work; Tao Wang, data interpretation, revising the manuscript, final approval, accountability for all aspects of the work.

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Supplemental Material

Additional supporting information may be found at http://otojournal.org/supplemental.

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