VENTILATOR-ASSOCIATED PNEUMONIA IN INTENSIVE CARE PATIENTS: AN EVALUATION USING META-ANALYTIC TECHNIQUES

JOHN VICTOR PETER, BINILA CHACKO, JOHN L. MORAN*

BACKGROUND: Ventilator-associated pneumonia (VAP), a frequent nosocomial infection in the intensive care, is associated with considerable morbidity. Endotracheal suctioning is routinely performed in mechanically ventilated patients to clear secretions. This study assessed if there were advantages of closed endotracheal suctioning (CES) over open endotracheal suctioning (OES) with respect to clinical outcomes. MATERIALS AND METHODS: Trials comparing CES with OES were identified by search of MEDLINE (1966-July 2006) and bibliographies of relevant articles. Only trials reporting VAP and/or mortality were considered. Studies reporting only physiological outcomes were excluded. STATISTICAL ANALYSIS USED: A meta-analysis of randomized controlled trials (RCTs) was performed using the random-effects estimator. The effect of suctioning type on VAP and mortality was reported as risk difference (RD) and duration of mechanical ventilation (MV) as mean weighted difference (MWD). RESULTS: Nine RCTs fulfilled criteria for inclusion. There was no differential treatment effect of suctioning type (closed versus open, n = 9 studies) on VAP (RD - 0.01; 95% CI - 0.05, 0.03; P = 0.63) or on mortality (n = 5; RD 0.01; 95% CI - 0.04, 0.05; P = 0.8). Although OES was associated with a shorter duration of MV (n = 4; MWD - 0.64; 95% CI 0.21, 1.06; P = 0.004), one study contributed significantly to the estimates. Heterogeneity of treatment effects was not observed. CONCLUSIONS: This meta-analysis has not demonstrated a superiority of CES over OES with respect to VAP or mortality. Thus the decision for the use of CES may be based on possible benefits in patients requiring high respiratory supports, reduced costs in those needing prolonged MV or occupational health and safety concerns with OES.

Key words: Endotracheal suctioning, meta-analysis, publication bias, random effects

Ventilator-associated pneumonia (VAP) is a common nosocomial infection in the intensive care unit (ICU) with an incidence ranging from 6.8 to 44%. VAP increases costs, length of hospital stay and mortality, and any strategy to reduce its occurrence is worthy of consideration. Endotracheal suctioning is performed in intubated mechanically ventilated patients as a routine essential part of care to clear endotracheal secretions. Two methods of endotracheal suctioning are in practice: the open endotracheal suctioning (OES) system, where suctioning is performed after disconnecting the respiratory circuits and using sterile single-use suction catheters. This technique of suctioning has been reported to be associated with arterial desaturation, inability to maintain PEEP and cardiac arrhythmias, particularly in patients with cardiorespiratory instability. In the closed endotracheal suctioning (CES) system, which was developed to minimize these complications, suctioning is performed without disconnecting the respiratory circuit and uses multi-use in-line catheters that are enclosed in a sheath along with the respiratory circuit. This mode of suctioning has comparatively fewer physiological disturbances and consequences during suctioning, and provides ease of use, given that only one operator is required for suctioning. Further, CES is postulated to reduce VAP rates by decreasing environmental contamination during suctioning. These potential advantages have led to the conduct of several randomized controlled trials (RCTs) that compared CES and OES. These individual trials failed to show a superiority of one type of suctioning over the other. This evaluation was undertaken to assess if there was any advantage of CES over OES with respect to the development of VAP. The hypothesis was that there would be no difference in the incidence of VAP between CES and OES suctioning. Secondary outcomes assessed in the study were mortality, duration of ventilatory support, as well as hospital and ICU length of stay (LOS).

MATERIALS AND METHODS

Selection of trials
RCTs comparing CES with OES in mechanically ventilated patients were considered for inclusion. CES was defined as endotracheal suctioning performed without disconnection from the respiratory circuit, employing a multi-use-in-line suctioning catheter. OES was defined as endotracheal suctioning done after disconnection of the respiratory circuit and employing a single-use suction catheter under aseptic precautions. Only trials reporting VAP rates and/or mortality were considered for inclusion. Studies reporting only physiological endpoints, those performed in children or infants and non-English articles were excluded.

Search strategy
A computerized literature search was performed using PubMed and OVID Medline for the period 1966-July 2006. The search was restricted to studies on adult human population and was carried out using the search terms: suction or suctioning or endotracheal suctioning or tracheal suctioning or open suctioning or closed suctioning AND randomised or randomized trials or clinical trials or controlled trials. Abstracts of trials generated by electronic search were reviewed, and trials pertaining to open and closed suctioning were retrieved for detailed evaluation. The references of identified articles were reviewed to identify other relevant articles. The Cochrane Central Register of Controlled trials was also searched to identify other trials on this topic. A systematic review was identified at the completion of this study. A second meta-analysis on the same subject was also published following submission of this article for journal review. Personal correspondence...
with authors was not sought.

Quality assessment
Quality assessment was performed in an unblinded fashion by two investigators using a quality score modified for this study and adapted for ventilated patients. This score assessed composite aspects of study quality (10 aspects in total, with scores 0 or 1; minimum total score 0 and maximum total score 10). Differences in opinion were settled by consensus.

Data abstraction
Two investigators independently abstracted data using standardized data collection forms. The extracted variables were predefined and differences in data abstraction were settled by consensus.

Outcome measures
The primary outcome assessed was number of patients developing VAP. This was defined in various studies as new onset of purulent bronchial secretions, body temperature of >38°C or <35.5°C (definitions of body temperature were variable), white cell count (WCC) of >10,000 or <4,000/mm³ (cut off values for WCC were variable), chest radiography showing new or progressive infiltrates and a (quantitative in some studies) radiography showing new or progressive infiltrates and mortality. Publication bias was not reported, as the ability to adequately detect bias is limited when the number of trials included is less than 10 and when the sample size in the individual studies is small. A cumulative meta-analysis was also performed to study possible time trends in treatment effects.

RESULTS
Preliminary search identified 731 trials on suctioning in the adult population. A single investigator reviewed these abstracts, and 48 articles were identified for detailed evaluation by two authors. Forty-two articles were excluded [Figure 1]. Six articles fulfilled criteria for inclusion, and a further three articles were identified by hand-search and review of other articles. The study cohort thus consisted of 9 RCTs from 1966-2006 that compared CES with OES [5,6,12,24-29]. Table 1 summarizes the study characteristics as well as the quality scores. A breakdown of the quality scores for the different studies is provided in the Appendix.

The CES group consisted of 644 patients; and the OES group, 648 patients. The two groups were matched [Table 2] for age, sex, APACHE II score; and the number of medical, surgical or trauma patients (inverse variance weighted differences, \( P \geq 0.26 \)).

VAP rates
All studies reported VAP rates. VAP rates differed between groups. Differences in data abstraction were settled by consensus.

The duration of ICU stay was evaluated using means of the Q statistic, considered significant at \( P \leq 0.1 \) and (ii) the impact (upon the variation of pooled treatment effect) by means of the 1 measure, where an 1 of <30% indicates mild heterogeneity, 30-50% moderate, and substantially >50%, severe heterogeneity. Meta-regression analysis was undertaken to assess the (potential) effect of average age; percent male patients; average percent of medical, surgical and trauma patients on the development of VAP and mortality.

Publication bias was not reported, as the ability to adequately detect bias is limited when the number of trials included is less than 10 and when the sample size in the individual studies is small. A cumulative meta-analysis was also performed to study possible time trends in treatment effects.

Figure 1: Process of identification of trials flow diagram depicting the process of identification of trials that were included in the meta-analysis.

Figure 2: Effect of type of suctioning on ventilator-associated pneumonia rates forest plot representation - fixed-effects model. The vertical straight line denotes null effect; and the dotted line, the overall mortality effect of treatment with early enteral nutrition compared with early parenteral nutrition. The individual boxes denote the risk difference of each study; and the lines on either side, the 95% confidence intervals. There is no effect of the type of suctioning (open or closed) on VAP rates.
the random-effects estimator due to heterogeneity of treatment effects; this was not different in the two studies reporting ICU LOS [Table 4]. The duration of mechanical ventilation, in four studies, assessed by the fixed-effects estimator was significantly lower in the OES group [Figure 4]; however, one study\(^9\) contributed substantially (93%) associated pneumonia.

### Table 1: Summary of the included studies

<table>
<thead>
<tr>
<th>Study (ref)</th>
<th>Year</th>
<th>Country</th>
<th>I/E criteria</th>
<th>Type of closed suctioning</th>
<th>Randomisation</th>
<th>Allocation concealment</th>
<th>Definition of ventilator-associated pneumonia</th>
<th>OS</th>
<th>Number of aspirations/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deppe(^{26})</td>
<td>1990</td>
<td>USA</td>
<td>Y/N</td>
<td>Trachcare(^{™}) Random number table</td>
<td>Nil</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>16.6 12.4</td>
</tr>
<tr>
<td>Johnson(^{26})</td>
<td>1994</td>
<td>USA</td>
<td>Y/N</td>
<td>Trachcare(^{™}) Randomly assigned</td>
<td>Randomly allocated</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
<td>9.0 16.0</td>
</tr>
<tr>
<td>Adams(^{26})</td>
<td>1997</td>
<td>UK</td>
<td>Y/N</td>
<td>Trachcare(^{™}) Randomly assigned</td>
<td>Randomly allocated</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
<td>9.0 16.0</td>
</tr>
<tr>
<td>Coombers(^{26})</td>
<td>2000</td>
<td>France</td>
<td>Y/N</td>
<td>Stericath(^{®}) Randomly assigned</td>
<td>Randomly allocated</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>NA NA</td>
</tr>
<tr>
<td>Zeiuton(^{26})</td>
<td>2003</td>
<td>Brazil</td>
<td>Y/Y</td>
<td>Hi-Care(^{®}) Alternate day Randomization</td>
<td>Randomized (sealed envelopes)</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
<td>8 8</td>
</tr>
<tr>
<td>Rabitsch(^{26})</td>
<td>2004</td>
<td>Austria</td>
<td>Y/Y</td>
<td>Trachcare(^{™}) Randomly assigned</td>
<td>Randomly allocated</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
<td>NA NA</td>
</tr>
<tr>
<td>Topel(^{26})</td>
<td>2004</td>
<td>Turkey</td>
<td>Y/Y</td>
<td>Stericath(^{®}) Randomly assigned</td>
<td>Randomly allocated</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
<td>NA NA</td>
</tr>
<tr>
<td>Lorenz(^{26})</td>
<td>2005</td>
<td>Spain</td>
<td>Y/N</td>
<td>Hi-Care(^{®}) Random number</td>
<td>Nil</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>8.13±3.54* 8.32±3.71*</td>
</tr>
<tr>
<td>Lorenz(^{26})</td>
<td>2006</td>
<td>Spain</td>
<td>Y/N</td>
<td>Hi-Care(^{®}) Randomly assigned</td>
<td>Randomly assigned</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>8.13±2.7 7.9±2.6*</td>
</tr>
</tbody>
</table>

I/E - Included / exclusion criteria defined, NA - Not available, *Mean and standard deviation provided in the text,  #Quality score (minimum score 0, maximum score 10)

### Table 2: Summary of baseline characteristics of the two treatment groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of studies</th>
<th>CES group</th>
<th>OES group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>6</td>
<td>548</td>
<td>548</td>
<td>0.15</td>
</tr>
<tr>
<td>Age (Mean ± SD years)</td>
<td>6</td>
<td>52.3 (14.0)</td>
<td>54.8 (13.2)</td>
<td>0.01 (-0.04, 0.05)</td>
</tr>
<tr>
<td>Male: Females</td>
<td>6</td>
<td>398:177</td>
<td>388:198</td>
<td>0.80</td>
</tr>
<tr>
<td>Number (%) of medical patients</td>
<td>4</td>
<td>284 (53.0)</td>
<td>289 (57.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Number (%) of surgical patients</td>
<td>4</td>
<td>178 (37.7)</td>
<td>184 (38.1)</td>
<td>0.84</td>
</tr>
<tr>
<td>Average APACHE II score (Mean ± SD)</td>
<td>4</td>
<td>17.5 (3.5)</td>
<td>16.5 (3.5)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

CES - Closed endotracheal suctioning, OES - Open endotracheal suctioning, Continuous variables analyzed by t-test, categorical results by Fisher Exact (*).

### Table 3: Incidence of ventilator-associated pneumonia and mortality rates in the individual studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>CES</th>
<th>OES</th>
<th>CES</th>
<th>OES</th>
<th>CES</th>
<th>OES</th>
<th>CES</th>
<th>OES</th>
<th>CES</th>
<th>OES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deppe(^{26}) 1990</td>
<td>46</td>
<td>38</td>
<td>12</td>
<td>26.1</td>
<td>11</td>
<td>28.9</td>
<td>12</td>
<td>26.1</td>
<td>11</td>
<td>28.9</td>
</tr>
<tr>
<td>Johnson(^{26}) 1994</td>
<td>16</td>
<td>13</td>
<td>8</td>
<td>50.0</td>
<td>10</td>
<td>52.6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Adams(^{26}) 1997</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Coombers(^{26}) 2000</td>
<td>50</td>
<td>54</td>
<td>4</td>
<td>8.0</td>
<td>9</td>
<td>16.7</td>
<td>13</td>
<td>26.0</td>
<td>15</td>
<td>27.8</td>
</tr>
<tr>
<td>Zeiuton(^{26}) 2003</td>
<td>23</td>
<td>24</td>
<td>7</td>
<td>30.4</td>
<td>11</td>
<td>45.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rabitsch(^{26}) 2004</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>0.0</td>
<td>5</td>
<td>41.7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Topel(^{26}) 2004</td>
<td>41</td>
<td>37</td>
<td>13</td>
<td>31.7</td>
<td>9</td>
<td>24.3</td>
<td>27</td>
<td>65.9</td>
<td>25</td>
<td>67.6</td>
</tr>
<tr>
<td>Lorenz(^{26}) 2005</td>
<td>210</td>
<td>233</td>
<td>43</td>
<td>20.5</td>
<td>42</td>
<td>18.0</td>
<td>52</td>
<td>24.6</td>
<td>50</td>
<td>21.5</td>
</tr>
<tr>
<td>Lorenz(^{26}) 2006</td>
<td>236</td>
<td>221</td>
<td>43</td>
<td>14.0</td>
<td>31</td>
<td>14.0</td>
<td>31</td>
<td>13.1</td>
<td>30</td>
<td>13.6</td>
</tr>
</tbody>
</table>

CES - Closed endotracheal suctioning, OES - Open endotracheal suctioning

### Table 4: Outcomes

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Number of studies reporting</th>
<th>Number of patients</th>
<th>Difference % (95% CI)</th>
<th>P value</th>
<th>Heterogeneity (P)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with ventilator-associated pneumonia</td>
<td>9</td>
<td>644/648</td>
<td>-0.01 (-0.05, 0.03)*</td>
<td>0.63</td>
<td>0.16</td>
<td>32</td>
</tr>
<tr>
<td>Mortality (number)</td>
<td>5</td>
<td>583/583</td>
<td>0.01 (0.04, 0.05)*</td>
<td>0.76</td>
<td>0.84</td>
<td>0</td>
</tr>
<tr>
<td>Duration of ventilation (days)</td>
<td>4</td>
<td>457/457</td>
<td>0.64 (0.21, 1.06)*</td>
<td>0.004</td>
<td>0.39</td>
<td>1.1</td>
</tr>
<tr>
<td>Intensive care unit, length of stay (days)</td>
<td>2</td>
<td>91/91</td>
<td>-0.90 (-5.61, 3.81)*</td>
<td>0.71</td>
<td>0.09</td>
<td>66</td>
</tr>
</tbody>
</table>

- | F - variation in risk difference attributable to heterogeneity, CI - Confidence interval, Number of patients - Number in the closed suctioning group, Number in the open suctioning group, Risk difference, Weighted mean difference, Fixed-effects estimator used in the above estimates except for Intensive care unit length of stay, where random-effects estimator was used

### Figure 3: Effect of type of suctioning on mortality.

The effect of suctioning on mortality represented as risk difference using the fixed-effects model. There is no difference in mortality when closed endotracheal suctioning was compared with open endotracheal suctioning.

### Figure 4: Effect of open and closed endotracheal suctioning on duration of ventilation.

Forest plot representation - fixed-effects model. The vertical straight line denotes null effect; and the dotted line, the overall treatment effect of the type of suctioning on ICU length of stay represented as mean weighted difference. The individual boxes denote the risk difference of each study, and the lines on either side, the 95% confidence intervals. Open suctioning was associated with a significant reduction in the duration of ventilation when compared to closed suctioning.

### The cost of suctioning

The cost of suctioning was provided in four studies. Two studies\(^{26-28}\) reported higher costs with closed suctioning, one study reported similar cost\(^{26}\) and in one study cost was marginally higher with open suctioning.\(^{26}\)

### Cumulative meta-analysis

Cumulative meta-analysis [Figure 5] did not demonstrate any substantial variation in the point estimates for VAP, although there was a retraction in the confidence intervals over...
time with the addition of the more recently published studies.

The effect of trial quality score, assessed as "quality-weights," on treatment outcomes (VAP and mortality) was minimal with no change in the point estimates or level of significance. Similarly, there was no substantial effect of the quality score on the duration of ventilation (P value remaining significant at 0.001).

**DISCUSSION**

This meta-analysis has not demonstrated an advantage of CES over OES in the primary outcome (VAP rates). Given that no difference was established between the two methods of endotracheal suctioning (CES and OES) on primary outcome, the expectation would have been a translation of this "lack of difference" to secondary outcomes. No difference was established with respect to mortality or ICU length of stay; but a statistically significant reduction in the duration of ventilation, favoring CES, was found. However, the number of studies reporting these secondary outcomes varied from two to five [Table 4], reflecting intra-study publication bias, and the estimates of these outcomes are therefore uncertain. However, if one were to speculate a reason for the observed reduction in the duration of ventilation with OES, more effective clearance of respiratory secretions with OES compared with CES might have effected this difference.

CES is postulated to have several advantages over OES, which include lower gasometrical and hemodynamic impairment, lower risk of contamination of the endotracheal system due to a protective sheath and decreased environmental exposure, as well as ease of use and reduced nursing time. These potential advantages have not been demonstrably translated into improvements in clinically meaningful outcomes (incidence of VAP, mortality and ICU LOS). The disadvantages of CES - higher costs and reduced effectiveness in clearing secretions - may actually favor the use of OES in the routine suctioning of patients in different ICU environments.

Despite the theoretical advantages of CES, failure to demonstrate a clinical benefit may be due to several reasons - a true effect, the meta-analysis being under-powered to detect a difference or a relatively low incidence of VAP in the cohorts included in these studies. The VAP rates of 18.6% (120/644) and 19.8% (128/648) in the CES and OES groups respectively are considerably lower than other studies, where incidences of up to 44% have been recorded. With the use of conventional power calculations, as suggested by Flather and colleagues, we observed that this meta-analysis was actually under-powered (power 63%) to detect a difference between the groups. In order to demonstrate a 5% difference in VAP assuming a baseline VAP rate of 20%, 1,252 patients would need to be evaluated in each treatment arm for 80% power. It is also interesting to note, in the cumulative meta-analysis [Figure 5], that the effect-line favored CES suctioning, albeit the 95% CI always extended beyond unity.

Although a similar meta-analysis was published at the time of completion of this meta-analysis, as well as a second one during the review process of this article, the current meta-analysis is more comprehensive: the systematic process of trial identification and data abstraction is formally presented; other clinically relevant endpoints (mortality, ICU length of stay and duration of MV) have been canvassed and the question of use of CES in patients on high respiratory supports was not addressed in the current meta-analysis. Several other studies have suggested that there is less desaturation with CES in patients on high respiratory support, in whom the CES may be preferred. The favorable effect of CES on arterial oxygen saturation in the smaller studies has not translated to a benefit in the recent meta-analysis. The same meta-analysis also reported significant differences in heart rate (6 beats/min) and mean arterial pressure (3.5 mmHg) in favor of CES. These differences are however unlikely to be clinically significant or meaningful.

Costs are also vital, more so in developing countries such as ours, where any increase in cost without a definitive improvement in clinical endpoints cannot justify the use of CES. Until definitive clinical benefit is demonstrated in further trials, OES may continue to be favored in these nations.

Other issues may impact upon the question of CES versus OES. In developing countries where the space allocated to individual beds may be restricted (picture), close proximity of beds may lead to environmental contamination of the respiratory tract. The high incidence of pulmonary tuberculosis in developing countries such as ours poses greater risk to the health personnel, and the mode of suctioning assumes greater...
importance. Thus, studies comparing CES with OES may be more relevant in the developing world. These issues may not be paramount in countries where occupational health and safety concerns preclude the use of OES and where the ease of use as well as reduced nursing time with CES may override cost concerns.

We submit therefore that the question of open or closed endotracheal suctioning in mechanically ventilated patients is still very much an ‘open’ issue.

ACKNOWLEDGMENTS

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Announcement

Dr. J. C. Patel Birth Centenary Celebration Committee

The year 2008 is the Birth Centenary Year of Dr. J. C. Patel. Some of his students/admirers felt that it would be a good idea to celebrate this Centenary Year by organizing CMEs, Orations/Lectures, Conferences, etc. during the year. He was associated with many professional bodies, which meet regularly every year; during these annual meetings/conferences, a lecture/symposium, etc can be organized as a part of Centenary celebrations. We would like to form a Dr. J. C. Patel Birth Centenary Celebrations Committee. All his past students/admirers are invited to join the committee (without any financial commitment). Kindly communicate your name, designation, postal address, telephone number and E-mail ID to Dr. B. C. Mehta at Flat 504, Prachi Society, Juhu-Versova Link Road, Andheri (W), Mumbai 400 053 (drmehta.bc@gmail.com).