Best Evidence

Journal Scan

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Articles Reviewed:


Objectives: To evaluate the impact of a nurse-driven sedation protocol on the length of mechanical ventilation, total daily doses of sedatives, and complications of sedation.

Design: A single-centre prospective before and after study was conducted from October 2010 to December 2013. Setting: Twelve-bed surgical and medical PICU of the university affiliated hospital in Nantes, France.

Patients: A total of 235 patients, between 28 days and 18 years old, requiring mechanical ventilation for at least 24 hours were included in the study; data from 194 patients were analysed.

Interventions: During the first study phase, no protocol was used. During the second phase, patients were sedated according to a nurse-driven protocol.

Measurements and Main Results: In the whole population, the length of mechanical ventilation did not differ between protocol and control groups (protocol, 4 [3–8] vs control, 5 [3–7.5]; p = 0.44). Analysing age subgroups, the length of mechanical ventilation was significantly shorter in the protocol group than in the control group in children older than 12 months (4 [3–8] vs 5 [2.75–11.25] d; p = 0.04). Daily dose of midazolam decreased during the protocol phase compared with the control phase (1 [0.56–1.8] and 1.2 [0.85–2.4] mg/kg/d, respectively; p = 0.02). No differences were shown regarding other daily dose of drugs. In the control group, 68% of children had more than 20% of COMFORT-behaviour scale (COMFORT-B) assessment under the target (over-sedation) versus 59% in the protocol group (p = 0.139).

Conclusions: Implementation of a nurse-driven sedation protocol in a PICU is feasible and safe, allowed a decrease in daily dose of benzodiazepines, and decreased the duration of mechanical ventilation in older patients.

Reviewer's Comments:

Sedation is routinely used in ventilated patients to ensure their physical safety and minimize psychologic distress. Improper sedation can cause increase in the duration of mechanical ventilation (MV), hospital-acquired infections (particularly VAP) hemodynamic instability, unplanned extubations, withdrawal symptoms, and long term adverse neuropsychological outcomes. While studies in adult patients of nurse driven sedation protocol have reported improved clinical outcomes, including decreased length of MV when compared with usual care, very few pediatric studies have analysed this.

This single centre study was done to assess the effect of sedation on the duration of MV, length of stay (LOS) in the PICU and hospital, occurrence of VAP, any extubation failures, occurrence of hemodynamic failure and withdrawal symptoms. Sedatives and analgesics routinely used was midazolam associated with morphine or sufentanil. While in the controlled phase, sedation was managed as per the physician's choice. In the protocol group, the target level of sedation was nurse driven and adjusted as per the disease severity. COMFORT-B scale was used to compare sedation in the 2 groups. Both the groups had the same predicted risk of mortality. This study did not show any difference between the two groups in length of MV but a subgroup analysis did show a shorter length of MV in patients older than 12 months (p = 0.04) but not in younger patients < 12 months in the protocol group despite being able to decrease the use of daily dose of midazolam. This may be due to other factors (young age, safety, hemodynamics etc) apart from sedation affecting MV.

The study also showed reduced daily doses of epinephrine and norepinephrine in the protocol group. But the study did not show any difference in opioid use. Interestingly no significant difference was highlighted between the two groups in analysis of sedation-related adverse events like occurrence of VAP, extubation failure and withdrawal symptoms.
Major concerns of the present study were, being a single centre study and the questions regarding the quality of the application of the protocol by the nurses because there may be some reluctance to decrease sedatives which may affect the length of MV. No international consensus of ideal sedation exists for PICU. Thus, the protocol followed may not be easily translatable to other PICUs with different populations. There were more postsurgical (cardiac) patients in protocol group in < 12 months of age, hence results may not apply to medical population. Another point to make is that this study was not blinded and there was no randomization, thus introducing a potential bias. Role of daily interruption of sedation (DSI) which has been shown to improve outcomes in pediatric patients has to be assessed in the light of using a protocolized sedation which was not addressed in this study. Delirium assessment was also not done.

A recent trial also, by Curley et al (JAMA. 2015), RESTORE trial, done in 31 PICUs in 2449 children with respiratory failure also failed to show any reduction in the duration of MV with a nurse-implemented goal directed sedation protocol. Primary agents used were morphine and midazolam. There were no group differences in the time to recovery from acute respiratory failure, duration of weaning from MV, or median PICU or Hospital length of stay and sedation-related adverse events including inadequate pain and sedation management, withdrawal symptoms, and extubation failure.

Another study by Neunhoeffer et al (March 2015) showed nurse-driven pediatric analgesia and sedation protocol in critically ill medical pediatric patients reduced total dose of benzodiazepines and the occurrence of withdrawal symptoms significantly. In contrast a meta-analysis by Minhas et al (Mayo clinic proc, May 2015) to assess the effects of protocolized sedation compared with usual care on clinical outcomes in mechanically ventilated adult intensive care unit (ICU) patients reported decreased overall mortality (15%), ICU and hospital lengths of stay (1.73 and 3.55 days, respectively), and tracheostomy (31%).

Nevertheless, the present trial also stressed the feasibility of nurse driven sedation. Conservative sedation benefits patient overall but fails to have any benefit on duration of mechanical ventilation stressing a complex relationship between wakefulness, pain, and agitation. PICU awareness, amnesia, and neurobehavioral outcomes in children needs to be studied in greater detail. Perhaps a protocol using different sedation targets per phase of illness, decisions about sedation adjustment every 8 hours, providing recommendations on when to use secondary agents, and providing a systematic plan to wean high-risk patients will reduce variation in sedation management in various PICUs. Physicians, nurses, pharmacists, and respiratory therapists should collaborate to set sedation goals for an individual patient.

2. Hydrocortisone treatment in early sepsis associated acute respiratory distress syndrome: results of a randomized controlled trial

**Methods:** In this double-blind, single-center (Siriraj Hospital, Bangkok), randomized, placebo-controlled trial, we recruited adult patients with severe sepsis within 12 h of their meeting ARDS criteria. Patients were randomly assigned (1:1 ratio) to receive either hydrocortisone 50 mg every 6 h or placebo. The primary endpoint was 28-day all-cause mortality; secondary endpoints included survival without organ support on day 28. **Results:** Over the course of 4 years, 197 patients were randomized to either hydrocortisone (n=98) or placebo (n=99) and were included in this intention-to-treat analysis. The treatment group had significant improvement in the ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen and lung injury score (p=0.01), and similar timing to removal of vital organ support (HR 0.74, 95% CI 0.51–1.07; p=0.107). After adjustment for significant covariates, day 28 survival was similar for the whole group (HR 0.80, 95% CI 0.46–1.41; p=0.44) and for the larger subgroup (n=126) with...
Acute Physiology and Chronic Health Evaluation II score <25 (HR 0.57, 95% CI 0.24–1.36; p=0.20). With the exception of hyperglycemia (80.6 % vs. 67.7 %; p=0.04), the rate of adverse events was similar. Hyperglycemia had no impact on outcome. **Conclusions:** In sepsis-associated ARDS, hydrocortisone treatment was associated with a significant improvement in pulmonary physiology, but without a significant survival benefit.

**Reviewers Comments:**
Sepsis-associated ARDS, in comparison with sepsis without ARDS is associated with significantly higher morbidity and higher (up to 60%) mortality. Multiple studies have addressed the issue of use of steroid in ARDS. Steroids have been shown to improve oxygenation parameters and reduce markers of systemic inflammation in early ARDS. While some studies have reported beneficial effect of steroids others have refuted the claim and hence, controversies still exist for the steroid efficacy. Notably, Meduri (Chest 2007) reported reduction in duration of mechanical ventilation (MV), ICU stay and mortality by using methylprednisolone infusion in adults with early ARDS. While, a critical appraisal (ICM 2008) of RCTs revealed distinct survival benefit when methylprednisolone was initiated before day 14 of ARDS, a meta-analysis (BMJ 2008) failed to show a convincing treatment effect of steroids in early ARDS. A recent trial by Drago (PCCM 2015) in 35 children reported beneficial effect of low-dose methylprednisolone therapy on oxygenation and ventilation parameters in children but no differences occurred in length of MV, ICU stay, hospital stay, or mortality. Many other trials have shown increase mortality when steroids were initiated after 14 days of MV in ARDS.

Most recently a meta-analysis Meduri et al (ICM 2016) reported beneficial outcomes in patients on prolonged methylprednisolone infusion. A trial analysis with hydrocortisone use was also reported. Mortality reduction, more MV and ICU free days, earlier weaning from MV and no risk for nosocomial infection was reported. This meta-analysis also provides support for longer duration of treatment and incorporates slow tapering (up to 4 weeks) of steroids to prevent clinical deterioration and return to invasive MV.

While there are ample studies on methylprednisolone in ARDS there are fewer studies on hydrocortisone use in ARDS (especially sepsis induced ARDS). Hydrocortisone is a less potent anti-inflammatory agent as compared to methylprednisolone. A previous study (AJRCCM 2005) of hydrocortisone infusion in severe community acquired pneumonia (without ARDS) revealed a significant improvement in Pa02/Fi02 ratio, reduction in C-reactive protein levels, MODS score, delayed septic shock, reduction in length of hospital stay and mortality. The present study is a single centre study evaluating the role of hydrocortisone especially in sepsis (pneumonia) induced ARDS in adult patients. Hydrocortisone group had better short term and long term benefits with Pa02/Fi02 ratios and lung injury score (LIS) which persisted for 7 days (till day 14) even after removal of the study drug. Besides a nonsignificant mortality benefit in subgroup of patients with APACHE score <25, there was no overall significant reduction in mortality, length of MV, MV or vasopressors free days and rate of extubation. The study was probably underpowered for the exploratory analysis to demonstrate a survival benefit. As reported in several studies there were no major side effects except hyperglycaemia. Glucocorticoid treatment of ARDS remains contentious and the available evidence remains contradictory. Despite this, there is a broad consensus that if glucocorticoid treatment is to be initiated, it should be initiated before day 14 of ARDS.

3. **Enteral Nutrition and Acid-Suppressive Therapy in the PICU: Impact on the Risk of Ventilator-Associated Pneumonia**

**Objective:** Enteral nutrition has been implicated as a risk factor for ventilator associated pneumonia. We explored the prevalence of ventilator-associated pneumonia and its association with clinical and nutrition-related therapies in mechanically ventilated children. **Design:** Prospective, multicentre, cohort study. **Setting:** Fifty-nine PICU in 15 countries. **Patients:** Children less than 18 years old, mechanically ventilated for more than 48 hours. **Interventions:** None. Multivariable logistic regression to determine factors associated with
ventilator-associated pneumonia. **Measurements and Major Results:** Data are presented as median (inter quartile range) or counts (%). We enrolled 1,245 subjects (45% female; 42% surgical), age 20 months (4–84mo), and duration of mechanical ventilation 7 days (3–13 d). Culture-positive ventilator associated pneumonia was diagnosed in 80 patients (6.4%) duration of mechanical ventilation for this subgroup was 17 days (8–39d). Enteral nutrition was delivered in 985 patients (79%), initiated within 48 hours in 592 patients (60%), and via post pyloric route in 354 patients (36%). Acid-suppressive agents were used in 763 patients (61%). The duration of enteral nutrition (p = 0.21), route (gastric vs post pyloric) of delivery (p = 0.94), severity of illness (p = 0.17), and diagnostic category on admission (p = 0.31) were not associated with ventilator associated pneumonia. After adjusting for enteral nutrition days, illness severity, and site, ventilator-associated pneumonia was significantly associated with mechanical ventilation more than 10 days (odds ratio, 3.7; 95% CI, 2.2–6.5; p<0.001), PICU length of stay more than 10 days (odds ratio, 1.8; 95% CI, 1.1–3.1; p = 0.029), and the use of acid-suppressive medication (odds ratio 2.0; 95% CI, 1.2–3.6; p = 0.011).

**Conclusion:** Ventilator-associated pneumonia was diagnosed in 6.5% of mechanically ventilated children in a heterogeneous multicentre cohort. We did not find a link between enteral nutrition duration or route of delivery and ventilator associated pneumonia. In addition to duration of mechanical ventilation and length of PICU stay, the use of acid-suppressive therapy independently increased the likelihood of developing ventilator-associated pneumonia in this population. This association must be further explored in clinical trials.

**Reviewer's Comments:**
The enteral route is the preferred mode of nutrient delivery in critically ill pediatric population. Gram negative organisms in GI tract have been recognised as an important source of VAP. A meta-analysis of 8 observational studies (Eur J Ped 2014) reported EN as one of the risk factors for VAP. Several theories like reduced gastric pH, microaspirations, higher gastric residual volumes has been linked to an increased risk of ventilator-associated pneumonia (VAP) in some studies. Post pyloric EN feeding as compared to gastric route was advocated to reduce VAP but recent studies have failed to show a benefit. In the present study EN did not increase the incidence of VAP. Stress ulcer prophylaxis has been advocated in all patients who are on mechanical ventilation (MV) and it has also been endorsed as a part of VAP bundle approach. Stress-related GI bleeding has been associated with a significantly higher mortality rate, compared to patients without evidence of bleeding. But increase in gastric pH may promote bacterial colonization and increase the likelihood of VAP. Acid suppression therapy was also associated with statistically significant increased risk of developing Clostridium difficile infections among children in a recent study by Freedberg et al (Clin Infect Dis. 2015) which was more with proton pump inhibitors (PPIs) than H2 receptor (H2R) blockers. Several adult studies have demonstrated that mechanically ventilated adults receiving pantoprazole have a higher prevalence of VAP than patients receiving ranitidine. A three-fold increased risk of developing VAP using PPIs (pantoprazole) in ICU patients in comparison to H2 receptor blocker (ranitidine) was shown in a recent RCT (Tanaffos, 2013). A meta-analysis of adult studies has questioned the need for acid-suppressive therapies in the ICU, particularly in patients who were on full EN. Continuous enteral feedings cause an increase in gastric pH that tends to negate any differences in stress ulcer prophylaxis upon gastric pH. Most recently (Crit Care 2016) a systematic review and meta-analysis of randomized trials on the efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill adult patients concluded that PPIs were superior to H2RAs in preventing clinically important and overt GI bleeding, without significantly increasing the risk of pneumonia or mortality. Their impact on Clostridium difficile infection could not be confirmed.

In the present study duration of EN, severity of illness, and diagnostic category were not associated with VAP while MV of more than 10 days, PICU length of stay for more than 10 days and the use of acid-suppressive medication was significantly associated with VAP. Multiple acid-suppressive agents were used in this study most commonly used was an H2-antagonist. 20% increase in VAP occurred when all three risk factors were present. 13% patients were found to have VAP when MV was continued for 10 days as compared to 2.8% in whom mechanical ventilation was done for less than 10 days. A recent meta-analysis (Eur Jour of
Ped, 2014) in the NICU identified mechanical ventilation and its duration as one of the risk factors for VAP. The present study being a prospective study and not a RCT, the validity of the results is questionable. Also VAP can itself increase the duration of MV creating a vicious cycle.

Based on these reports and in light of the association with VAP in this study, the rationale and practice of acid-suppression in the PICU population must be further examined. Also whether PPIs or H2RA are safer from VAP point of view is also an unanswered question. EN is safe and feasible in critically ill patients.

4. Effect of hydrocortisone on development of shock among patients with severe sepsis - The HYPRESS randomized clinical trial JAMA 2016 Nov.


Objective: To determine whether hydrocortisone therapy in patients with severe sepsis prevents the development of septic shock. Design, Setting, and Participants: Double-blind, randomized clinical trial conducted from January 13, 2009, to August 27, 2013, with a follow-up of 180 days until February 23, 2014. The trial was performed in 34 intermediate or intensive care units of university and community hospitals in Germany and it included 380 adult patients with severe sepsis who were not in septic shock. Interventions: Patients were randomly allocated 1:1 either to receive a continuous infusion of 200 mg of hydrocortisone for 5 days followed by dose tapering until day 11 (n=190) or to receive placebo (n=190). Main Outcomes and Measures: The primary outcome was development of septic shock within 14 days. Secondary outcomes were time until septic shock, mortality in the intensive care unit or hospital, survival up to 180 days, and assessment of secondary infections, weaning failure, muscle weakness, and hyperglycemia (blood glucose level >150 mg/dl). Results: The intention-to-treat population consisted of 353 patients (64.9% male; mean SD age, 65.0 [14.4] years). Septic shock occurred in 36 of 170 patients (21.2%) in the hydrocortisone group and 39 of 170 patients (22.9%) in the placebo group (difference, −1.8%; 95% CI, −10.7 % to 7.2%; P=.70). No significant differences were observed between the hydrocortisone and placebo groups for time until septic shock; mortality in the intensive care unit or in the hospital; or mortality at 28 days (15 of 171 patients [8.8%] vs 14 of 170 patients [8.2%], respectively; difference, 0.5%; 95% CI, −5.6% to 6.7%; P=.86), 90 days (34 of 171 patients [19.9%] vs 28 of 168 patients [16.7%]; difference, 3.2%; 95% CI, −5.1 % to 11.4% ; P=.44), and 180 days (45 of 168 patients [26.8%] vs 37 of 167 patients [22.2%], respectively; difference, 4.6%; 95% CI, −4.6 % to 13.7%; P=.32). In the hydrocortisone vs placebo groups, 21.5 % vs 16.9% had secondary infections, 8.6% vs 8.5% had weaning failure, 30.7% vs 23.8% had muscle weakness, and 90.9% vs 81.5% had hyperglycemia. Conclusions and Relevance: Among adults with severe sepsis not in septic shock, use of hydrocortisone compared with placebo did not reduce the risk of septic shock within 14 days. These findings do not support the use of hydrocortisone in these patients.

Reviewer’s comment:

Low-dose hydrocortisone is usually added to the treatment regimen for patients with septic shock that is unresponsive to IV fluids and vasopressor therapy. Since septic shock is a continuum of severe sepsis hydrocortisone treatment early in the course may prevent the onset of septic shock. Previous septic shock trials have shown a reduction of ICU length of stay in concordance with earlier weaning off vasopressor therapy and mechanical ventilation. Despite numerous trials, the role of corticosteroids in septic shock remains a controversial issue.

The two landmark trials, Annane et al (2002) and CORTICUS study (2008) revealed similar clinical benefits from steroids (faster shock reversal) although patient population was far sicker in the Annane group. Hence, it could be argued that benefits of steroids did not seem to be restricted to patients with vasopressor-refractory shock. Patients with more severe sepsis might benefit more from steroids than patients with milder sepsis. However, the point at which benefits might outweigh risks is unknown.
The findings in this study is in unison with the surviving sepsis guidelines (2012) that use of hydrocortisone should be restricted to patients with vasopressor-refractory shock. Apart from hyperglycemia there were no other side effects in the hydrocortisone group as compared to a placebo. Interestingly, delirious episodes were less in the hydrocortisone group but this effect may be unreliable. Overall, we continue to use steroids in sickest of the patients and judiciously in less sick patients.


**Importance:** Two previous meta- analyses of nebulized hypertonic saline (HS) on hospital length of stay (LOS) in acute viral bronchiolitis have suggested benefit. Neither study fully addressed the issue of excessive heterogeneity in the cohort of studies, indicating that it may be inappropriate to combine such dissimilar studies to estimate a common treatment effect.

**Objective:** To reanalyse the existing data set for sources of heterogeneity to delineate the population most likely to benefit from HS. **Data Sources:** We used the previously analysed cohort of randomized trials from 2 published meta-analyses comparing HS with normal saline (or, in 1 case, with standard of care) in infants hospitalized for bronchiolitis. We also repeated the search strategy used by the most recent Cochrane Review in the Medline database through September 2015. **Study Selection:** Eighteen randomized clinical trials of HS in infants with bronchiolitis reporting LOS as an outcome measure were included. **Data Extraction and Synthesis:** The guidelines used for abstracting data included LOS, study year, setting, sample size, type of control, admission/ discharge criteria, adjunct medications, treatment frequency, mean day of illness at study enrolment, mean severity of illness scores, and mean age. **Main Outcomes and Measures:** Weighted me and difference in LOS and study heterogeneity as measured by the I^2^ statistics. **Results:** There were 18 studies included of 2063 infants (63% male), with a mean age of 4.2 months. The mean LOS was 3.6 days. Two main sources of heterogeneity were identified.

First, the effect of HS on LOS was entirely sensitive to the removal of one study population, noted to have a widely divergent definition of the primary outcome. Second, there was a baseline imbalance in mean day of illness at presentation between treatment groups. Controlling for either of these factors resolved the heterogeneity (I^2^ = reduced from 78% to 45% and 0%, respectively) and produced summary estimates in support of the null hypothesis (that HS does not affect LOS). There was a weighted mean difference in LOS of −0.21 days (95% CI, −0.43 to +0.02) for the sensitivity analysis and +0.02 days (95% CI, −0.14 to +0.17) for studies without unbalanced treatment groups on presentation. **Conclusions and Relevance:** Prior analyses were driven by an outlier population and unbalanced treatment groups in positive trials. Once heterogeneity was accounted for, the data did not support the use of HS to decrease LOS in infants hospitalized with bronchiolitis.

**Reviewer's Comments:**
Viral bronchiolitis is a common disease affecting infants. Current clinical practice guidelines do not recommend the routine use of any medication for bronchiolitis. 3% hypertonic (HS) saline was previously advocated to affect clinical outcome and shorten length of stay (LOS) in hospital. A Cochrane review (Zhang et al, 2013) suggested nebulised 3% HS may significantly reduce the length of hospital (LOS) stay among infants hospitalised with non-severe acute viral bronchiolitis and improve clinical severity scores in both outpatient and inpatient populations but no effect was shown among the emergency department patients. However, heterogeneity due to selection bias may have affected the results. But, another RCT by the same authors (Zhang et al, JAMA 2014) showed no significant effect on LOS in HS group despite reporting decreased hospital admission rate. While a subsequent systematic review again by the same authors (Zhang et al, Ped 2015) reported 20% reduction in the risk of hospitalization and reduction in LOS by 0.45 days, it acknowledged inconsistency in results between trials and a risk of bias. Silver et al (Ped 2015) in his recent RCT reported no difference in LOS or 7-day readmission rates. Another recent meta-analysis (BMC Pulm Med 2015) reported disparity in the results of effect of HS on LOS and failed to provide a
firm evidence-base for routine use of HS in inpatient acute bronchiolitis. The present study clears some air around the controversy. It also acknowledges inconsistencies in the results of various studies. This study analyzed 18 RCTs to delineate the set of population which can be benefited with use of hypertonic saline nebulization. It enlists causes of heterogeneity in the studies like patient age, day of illness, expected LOS, use of adjunct medications (eg, β-agonists, adrenaline nebulisation), frequency of HS treatments, use of systemic steroids prior to admission, illness severity scores, discharge criteria. All these factors introduce bias and it can lead us to draw false conclusions. After addressing the heterogeneity in various study groups and comparing all for the effect of nebulized hypertonic saline on length of hospital this analysis concluded that it was not beneficial.


**Background:** Potential benefits of subglottic secretion suction for preventing ventilator-associated pneumonia (VAP) are not fully understood. **Methods:** We searched Cochrane Central, PubMed, and EMBASE up to March 2016 to identify randomized controlled trials (RCTs) that compared subglottic secretion suction versus non-subglottic secretion suction in adults with mechanical ventilation. Meta-analysis was conducted using Revman 5.3, trial sequential analysis (TSA) 0.9 and STATA 12.0. The primary outcome was incidence of VAP. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to evaluate the level of evidence. **Results:** Twenty RCTs (N = 3544) were identified. Subglottic secretion suction was associated with reduction of VAP incidence in four high quality trials (relative risk (RR) 0.54, 95 % confidence interval (CI) 0.40–0.74; p < 0.00001) and in all trials (RR = 0.55, 95 % CI 0.48–0.63; p < 0.00001). Sensitivity analyses did not show differences in the pooled results. Additionally, the results of the above-mentioned analyses were confirmed in TSA. GRADE level was high. Subglottic secretion suction significantly reduced incidence of early onset VAP, gram-positive or gram-negative bacteria causing VAP, and duration of mechanical ventilation. It delayed the time-to-onset of VAP. However, no significant differences in late onset VAP, intensive care unit (ICU) mortality, hospital mortality, or ICU length of stay were found. **Conclusions:** Subglottic secretion suction decreased VAP incidence and duration of mechanical ventilation and delayed VAP onset. However, subglottic secretion suction did not reduce mortality and length of ICU stay. Subglottic secretion suction is recommended for preventing VAP and for reducing ventilation length, especially in the population at high risk of early onset VAP.

**Reviewer's comments:**

The VAP bundle approach did not list SSS in its 5 point element but acknowledged it's important in VAP prevention. Depending on the duration of onset, VAP is classified as early (< 4 days of MV) or late (>4 days of MV). Early-onset VAP usually carries a better prognosis, and are more likely to be caused by antibiotic sensitive bacteria while late-onset VAP are more likely to be caused by multidrug-resistant (MDR) pathogens, and are associated with increased patient mortality and morbidity.

Many previous studies (Valles 1995, Kollef 1999, Smulders 2002, Collard 2003, CDC 2004, ATS 2005) have established its effectiveness and have shown reduced incidence (50% risk reduction). Time to onset of VAP was also reduced by 3.1 days. Previous meta-analysis like Dezfulian (2005), Muscedere (2011) have established the beneficial role of continuous SSS and it was recommended for patients expected to require more than 72 hours of ventilation. But, none of these studies showed a beneficial effect on mortality rate, length of stay in the ICU, or duration of MV. This meta-analysis is an updated one and includes recent trials favouring SSS. Data was collected from 20 RCTs with more than 3500 patients. Methodology is quite eloquent. Trial sequential analysis (TSA) was used to determine whether the currently evidence was robust and conclusive. Meta-analysis may result in type 1 errors due to systemic errors or random errors due to sparse data and repeated significance testing when updating meta-analysis with new trials. Bias from trials with low methodological quality, outcome measure bias, publication bias, early stopping for benefit, and small trial bias may result in spurious P-
values. In TSA the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and TSA controls the risks for type I and type II errors and helps to clarify whether additional trials are needed. Additionally, TSA provides us with important information regarding the required sample size for such trials.

The results echoed what was previously known. The SSS significantly prevented the incidence of VAP (RR=0.55, 95 % CI 0.48–0.63; p<0.00001). TSA showed that it is unlikely that further trials will change the conclusion and are not necessary. SSS was significantly associated with a reduction in the incidence of early-onset VAP, gram-positive or gram-negative bacteria causing VAP, and duration of mechanical ventilation. SSS also delayed the time-to-onset of VAP. The reduction in causative pathogens was not analysed in previous meta-analyses, which supports the pathogenesis of VAP that leakage of fluid with bacteria passes the tracheal tube cuff toward the lungs. SSS may greatly reduce incidence of VAP in patients who may have undergone early tracheal extubation. The reduction in the duration of MV which was not seen in previous RCTs.

The absolute risk reduction (ARR) was 0.0953 meaning that SSS can reduce 9.53 % of the absolute rate of VAP. NNT (10.49) meant that for every 11 patients with SSS, one VAP was prevented. Both intermittent and continuous suction can prevent VAP, with no significant difference between subgroups. It was difficult to determine which approach is appropriate because the current evidence was limited. However, no significant difference was detected between SSS and non-SSS in terms of late-onset VAP, ICU mortality, hospital mortality, ICU length of stay, incidence of tracheotomy, or reintubation. The attributable mortality of late-onset VAP is higher than that of early-onset VAP, which weakens the impact of SSS on mortality from VAP. Other reasons quoted were, confounding factors and need for a much bigger sample size (at least 1940–4519 in each arm) to show any significant effect on mortality.

Major concerns regarding SSS were that these are significantly more expensive than ordinary endotracheal tubes. Few studies and reviews suggest poor uptake of SSS based mostly on cost effectiveness (and cost expectations) rather than cost benefit analysis. The aspiration port can clog easily and hamper suction. The narrower inner lumen of the endotracheal tubes may increase the airway resistance. Additionally, the continuous suction has the potential to injure the oropharynx and proximal airway since these tubes are more stiffer than normal tubes.

Limitations were few in this study and were as expected. Firstly, the included RCTs in this meta-analysis were performed in different patient groups and various clinical settings. Therefore, the risk of introducing potential heterogeneity was present, although the detected heterogeneity was not significant. Secondly, because SSS is an obvious clinical manipulation, it could not be blinded for physicians and nurses; this may have lead to unavoidable performance bias. Thirdly, confounding interventions, such as polyurethane, continuous control of cuff pressure, and semi-recumbent position, existed in some included trials. Sensitivity analysis was done excluding these confounding factors and the final outcome still complied with the expected result. Fourthly, data on cost-effectiveness of SSS was unavailable in this meta-analysis as RCTs analysing that are very few. This study reiterates what is known about SSS and may rest any further questions about efficacy of SSS.

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