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Review Article

Efficacy of Nurse-Led Sedation Protocols in Preventing Ventilator-Associated Pneumonia in Mechanically Ventilated ICU Patients: A Systematic Review

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Abstract

Background: Ventilator-associated pneumonia (VAP) remains a significant challenge in intensive care units, especially among mechanically ventilated patients. Sedation protocols, particularly nurse-led interventions, have been suggested to improve patient outcomes by reducing the incidence of VAP. This study evaluated the effectiveness of such protocols on VAP incidence, mechanical ventilation duration and ICU length of stay.

Methods: A comprehensive search of electronic databases, including MEDLINE, EMBASE and Cochrane CENTRAL from inception to 30 August 2024 was conducted following PRISMA guidelines. Nurse-led sedation protocols and their impact on VAP outcomes were selected for meta-analysis. Data extraction included sample size, interventions, control measures and primary outcomes. Statistical analysis was performed using a fixed-effects model to calculate risk differences and odds ratios with heterogeneity assessed using the I^2 statistic.

Results: The systematic review comprised 15 studies, with 7 studies meeting the criteria for meta-analysis. Nurse-led sedation protocols were associated with a significant reduction in the duration of mechanical ventilation (Risk Difference: -0.21; 95% CI: -0.37 to -0.04, P=0.01). However, analyzing VAP-related mortality, the odds ratio (OR: 0.80; 95% CI: 0.60 to 1.07) indicated no statistically significant difference between intervention and control groups (P=0.14).

Conclusion: Nurse-led sedation protocols show promise in reducing the duration of mechanical ventilation, impact on VAP-related mortality remains inconclusive. Future research should focus on refining these protocols and further evaluating their long-term effects on VAP prevention and patient outcomes.

Keywords: Ventilator-associated pneumonia; Sedation protocols; Nurse-led intervention nurse practice pattern; Intensive care unit; Mechanical ventilation interactive ventilatory support

Introduction

Ventilator-associated pneumonia (VAP) is a serious clinical concern in intensive care units (ICUs) across the world. VAP is the most prevalent hospital-acquired illness, particularly in mechanically ventilated patients, with an estimated frequency of 10% to 30%, depending on the patient demographic and diagnostic criteria (1, 2). The development of VAP is related to greater morbidity, longer ICU hospitalisations, higher healthcare expenses and much higher fatality rates, making

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its prevention a critical care priority (1, 3). One of the primary goals of VAP preventive measures is to improve sedation control in mechanically ventilated patients. Sedation is frequently required to maintain patient comfort, safety, and ventilator synchronization (4). However, severe or prolonged sedation has been associated with some negative outcomes, including delayed weaning from mechanical breathing, an increased risk of delirium, and a greater probability of developing VAP. In response to these issues, promote milder sedation and regular sedation breaks, commonly known as sedation vacations (5, 6).

Nurse-led sedation protocols must improve sedation practices while lowering the incidence of VAP (7). These protocols provide standardised sedation management guidelines, allowing nurses to check sedation levels and alter sedation dosages in real time based on specified criteria (8). These protocols attempt to decrease needless sedation and related problems by giving nurses more autonomy and decision-making powers. Nurse-led sedation procedures successfully reduce VAP incidence (5, 9, 10). A systematic analysis showed nurse-led procedures dramatically reduce the duration of mechanical ventilation and the incidence of VAP in ICU patients, highlighting the significance of such protocols in clinical practice (11-13). Despite promising developments in VAP prevention, the influence of these regimens on VAP-related mortality is still being investigated. While some studies demonstrated that nurse-led sedation procedures may improve patient survival, others have found no meaningful changes (14, 15). This disparity emphasises the need for more studies to determine the specific function of sedation procedures in enhancing patient outcomes beyond VAP preventative measures.

This research aimed to enhance the existing literature by conducting a meta-analysis, to examine the impact of nurse-led sedation regimens on VAP incidence and mortality. This study aimed to provide a more thorough knowledge of the clinical impact of these procedures by combining data from numerous studies and generating insights that might affect future recommendations and practices in ICUs throughout the world.

Materials and Methods

Study Design

On meta-analysis, the nurse-implemented sedation protocol was compared with the incidence and mortality rates of VAP in mechanically ventilated patients in the ICU. After a detailed search, studies were selected by inclusion and exclusion criteria specified beforehand.

Search Strategy

The search strategy included published studies obtained from databases such as MEDLINE, EMBASE and Cochrane CENTRAL from inception to 30 August 2024. Some of the keywords included "ventilator-associated pneumonia", "sedation protocols", "nurse-led", "mechanical ventilation, and Intensive care. Boolean Operators and MeSH terms were utilized to break down the search further to incorporate the work required in the studies.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

1. Population: Patients on Mechanical Ventilation in ICU.
2. Intervention: Nurse Sedation Protocol With includes Sedation Interruptions/Vacation.
3. Comparison: Usual care or other sedation methods.
4. Outcomes: Epidemiology of VAP as well as mortality due to VAP.
5. Study Design: Randomized controlled trials (RCTs), Quasi-experimental & Observational studies.

Exclusion criteria included studies that did not specifically address nurse-led protocols, studies without control groups, and studies focusing on pediatric or non-ICU populations.

Extraction of data

Two researchers performed data extraction independently. Excerpts included:
1. Study characteristics: first author, publication year, country, sample size, and study design.
2. Patient characteristics: age, sex, comorbidities, and duration of mechanical ventilation.
3. Description of intervention: Description of sedation, frequency of sedation interruption, and nursing intervention.
4. Outcomes: VAP incidence, mortality, ICU length of stay, and duration of mechanical ventilation.

Quality assessment

Quality assessment of included studies was assessed using the Cochrane risk of bias tool for RCTs and the Newcastle-Ottawa scale for observational studies was classified as high, moderate risk, or lower levels of bias based on criteria such as randomization, blinding, and complete outcome data.

Statistical analysis

The meta-analysis was conducted using Review Manager (RevMan 5.4) software (16). Because of the homogeneity of the included studies, a fixed-effects model was used. 95% confidence intervals (CIs) and odds ratios (ORs) were calculated for binary outcomes (VAP incidence, mortality), and mean differences were calculated for continuous outcomes (length of ICU stay). Differences between studies were assessed using the Chi-squared test and I-squared statistics. A *P*-value of less than 0.05 was considered statistically significant. Subgroup analyzes were performed to examine the effect of sedation protocols and the patient population.

Sensitivity analysis

The sensitivity analysis revolves around variations made for key determinants as the duration of antibiotic drugs, sedation protocol and patients' determinants that have effects on outcomes like VAP mortality. They are changed methodically one by one or together during one-way or multi-way analyses respectively to assess their impact on this model. Then for each case statistical re-estimation is done and results depicted through different tools such as tornado diagrams and threshold diagrams. Other than that, it also employs Monte Carlo simulations which are probabilistic approaches used whenever there is uncertainty to achieve holistic comprehension regarding outcome variability.

Publication bias

Funnel plots and Egger's regression test are used to evaluate publication bias. This creates an asymmetrical data set since smaller studies with nonsignificant findings have fewer chances of being published. To maintain strong conclusions, sensitivity analyses are also done to account for possible biases. Moreover, experiments and meta-analyses from journal articles are compared so that they do not affect the outcome of our study because we would have corrected for any selection bias concerning outcomes. The use of broad searching methods and including unpublished information when possible, helps reduce instances of possible biases.

Results

The described research design combines a focus on nurse-led clinics, sedation, and its impact on acute care outcomes (Table 1). The query begins with an overview of nurse-led hospitals using the term "nurse-led hospitals" MeSH, followed by a comprehensive search that includes hospital policy, strategy, and management methods "protocol", "direct", "guide". The combination of terms such as "algorithm" ensures the capture of appropriate studies of protocol-driven approaches. This is further refined by attaching terms to nurses such as "nurse supervisor." Then, sedation-related articles are extracted using MeSH terms such as "Conscious Sedation" and "Analgesics" and further narrowed down by searching terms such as "sedat*" and "analge*" in the title or abstract using MeSH search terms and keywords on critical care, ICU Research further focuses on structure, mechanical ventilation, and length of stay. Finally, the search includes these aspects together (#7 AND #10 AND #21) provide a comprehensive overview of the designs of nurse-led trials, sedation management, in ICUs and examine the consistency of results.

Table 1: Search strategy

Step	Query
#1	Nurse-Led Clinics [MeSH Terms]
#2	(Algorithms [MeSH Terms] OR Guidelines as Topic [MeSH Terms] OR Clinical Protocols [MeSH Terms] OR Medication Therapy Management [MeSH Terms])
#3	(protocol* [Title/Abstract] OR direct* [Title/Abstract] OR guide* [Title/Abstract] OR algorithm* [Title/Abstract] OR manage* [Title/Abstract] OR assess* [Title/Abstract])
#4	#2 OR #3
#5	(nurs* [Title/Abstract] OR Nurse Administrator [MeSH Terms])
#6	#4 AND #5
#7	#1 OR #6
#8	(Conscious Sedation [MeSH Terms] OR Patient-Controlled Analgesia [MeSH Terms] OR Analgesics [MeSH Terms] OR Hypnotics and Sedatives [MeSH Terms])
#9	(sedat* [Title/Abstract] OR analge* [Title/Abstract])
#10	#8 OR #9
#11	(Critical Care [MeSH Terms] OR Intensive Care Units [MeSH Terms] OR Critical Illness [MeSH Terms] OR Artificial Respiration [MeSH Terms] OR Ventilator Weaning [MeSH Terms] OR Length of Stay [MeSH Terms])
#12	(critical* [Title/Abstract] OR intens* [Title/Abstract] OR emergency* [Title/Abstract])
#13	(intensive care [Title/Abstract] OR critically ill* [Title/Abstract] OR patient* [Title/Abstract] OR unit* [Title/Abstract] OR ward* [Title/Abstract])
#14	#12 AND #13
#15	(mechanical* [Title/Abstract] OR artificial [Title/Abstract])
#16	(ventil* [Title/Abstract] OR wean* [Title/Abstract] OR respirat* [Title/Abstract])
#17	#15 AND #16
#18	(care [Title/Abstract] OR ill [Title/Abstract] OR illness* [Title/Abstract] OR patient* [Title/Abstract] OR unit* [Title/Abstract] OR ward* [Title/Abstract])
#19	#12 AND #18
#20	(length of stay [Title/Abstract] OR ICU [Title/Abstract]) OR #17 OR #19
#21	#11 OR #20
#22	#7 AND #10 AND #21

The systematic review process described in the design framework sought to identify records from the three databases (Fig. 1). After initially removing 21 duplicates, 350 records were examined. Of these, 234 records were excluded based on relevance. Of the remaining 116 reports, 57 were not accepted for further consideration. Overall, 59 reports were screened for eligibility, excluding 44 reports—2 non-English and 42 deemed unreliable. Finally, 15 studies were included in the systematic review, and 7 of those studies were included in the meta-analysis. The systematic review process described in the design framework sought to identify records from the three databases. After initially removing 21 duplicates, 350 records were examined. Of these, 234 records were excluded based on relevance. Of the remaining 116 reports, 57 were not accepted for further consideration. Overall, 59 reports were screened for eligibility, excluding 44 reports—2 non-English, and 42 deemed unreliable Finally, 15 studies were included in the systematic review, and 7 of those studies were included in the meta-analysis.

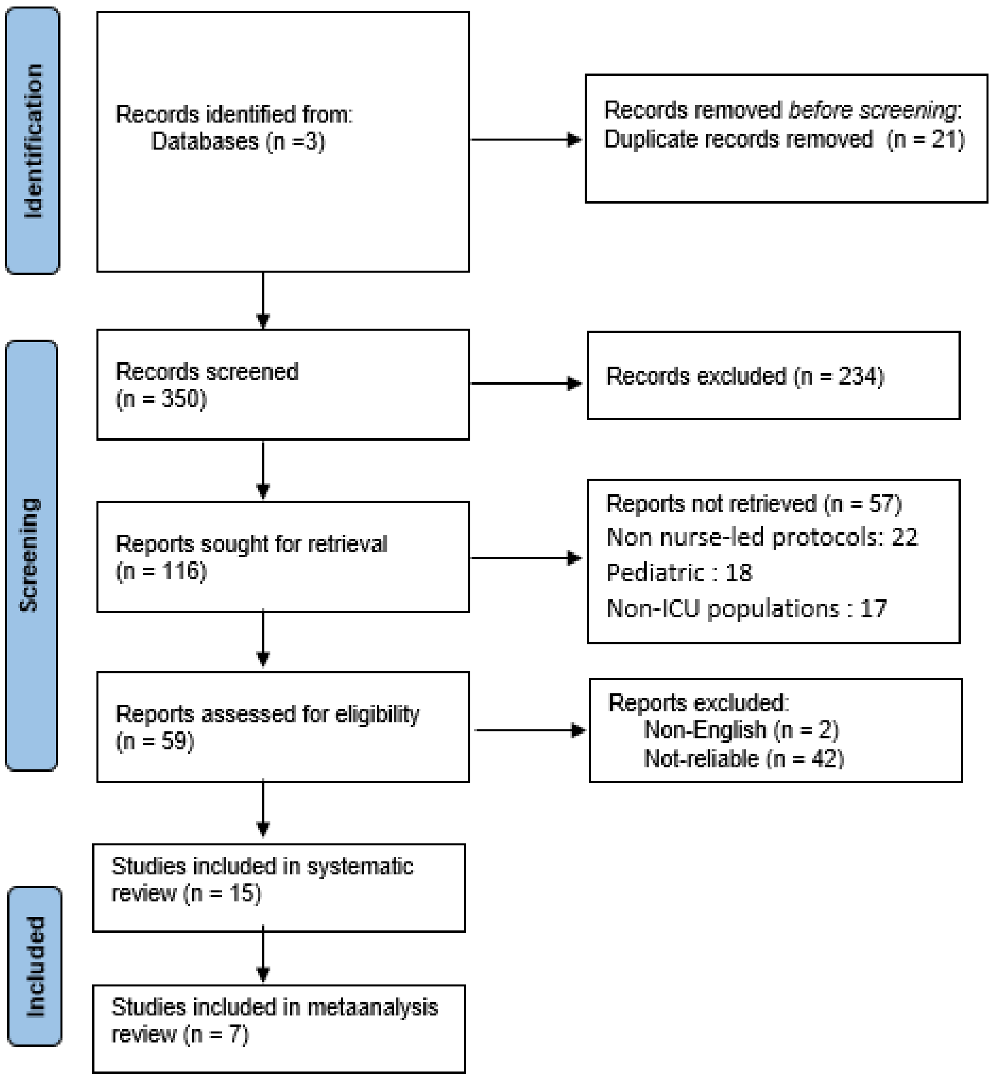

Fig. 1: The PRISMA flowchart clarifies how studies were chosen, including all the stages starting from the first search to the last inclusion. The number of articles discovered, duplicates deleted, as well as studies consisting of screening and after full text review are highlighted

In the studies reviewed (Table 2), Shahabi et al. performed a randomized clinical trial on 80 sufferers, demonstrating that enforcing an everyday sedation holiday protocol considerably reduced early VAP incidence in automatically ventilated patients in crucial care devices (17). Qi et al. analyzed the 1,935 patients in a clinical evaluation, meta-analysis and discovered that nurse-led sedation protocols definitely impacted ICU patients by using reducing the period of mechanical ventilation, although they did now not drastically effect on mortality or ICU period of life (18). Quenot et al. did a two-section, prospective and controlled take a look at involving 423 patients, revealing that a nurse-led sedation protocol decreased VAP prevalence in a clinical intensive care unit (12). Muller et al. studied 39 sufferers and located that goal-directed sedation with propofol-remifentanil reduced extubation time but multiplied self-extubation charges (19). Croce et al. performed a prospective observational take a look at on 630 trauma patients, finding that the ventilator package deal may not effectively prevent VAP, as no sizeable outcome differences were discovered (20). Weheida et al. evaluated the impact of a VAP bundle protocol and found that it progressed nurses' information, compliance, and patient outcomes, leading to shorter ICU stays and decreased ventilation duration (21). Lastly, Aitken et al. conducted a systematic assessment and meta-evaluation, locating inconsistent proof regarding the benefits of lighter sedation on ICU results, limiting the capability to draw definitive conclusions (22).

Comparison of Mechanical Ventilation and ICU Stay Duration

Four studies were analyzed using meta-analysis for evaluating nurse-led sedation protocols on the period of MV and ICU stay (Fig. 2). The pooled risk difference (RD) for MV duration was -0.21 (95% CI: -0.37 to -0.04), indicating a statistically significant reduction (*P*=0.01). These protocols effectively shorten MV duration in critically ill patients. Individual studies showed varying results, with Quenot et al. having the most significant RD of -0.35 (95% CI: -0.69 to -0.02) and others like Muller et al. non-significant findings. The low heterogeneity (I^2 = 0%) across studies supports the consistency of findings made during this analysis. Overall, nurse-led sedation protocols may contribute to improved outcomes by reducing MV duration but further research is needed for confirmation across different settings. For examining publication bias concerning MVP and ICU stay duration, a funnel plot has been created (Fig. 3). The vertical axis is the standard error of the logarithm of the odds ratio and the horizontal axis shows the odds ratio on a logarithmic scale. Each circle indicates a study that was considered while carrying out a meta-analysis. In absence of any kind of publication bias anticipated distribution of studies is represented by a dashed line. Therefore, asymmetry in this funnel.

plot may indicate possibility of presence of some underlying cause for the studies not getting published.

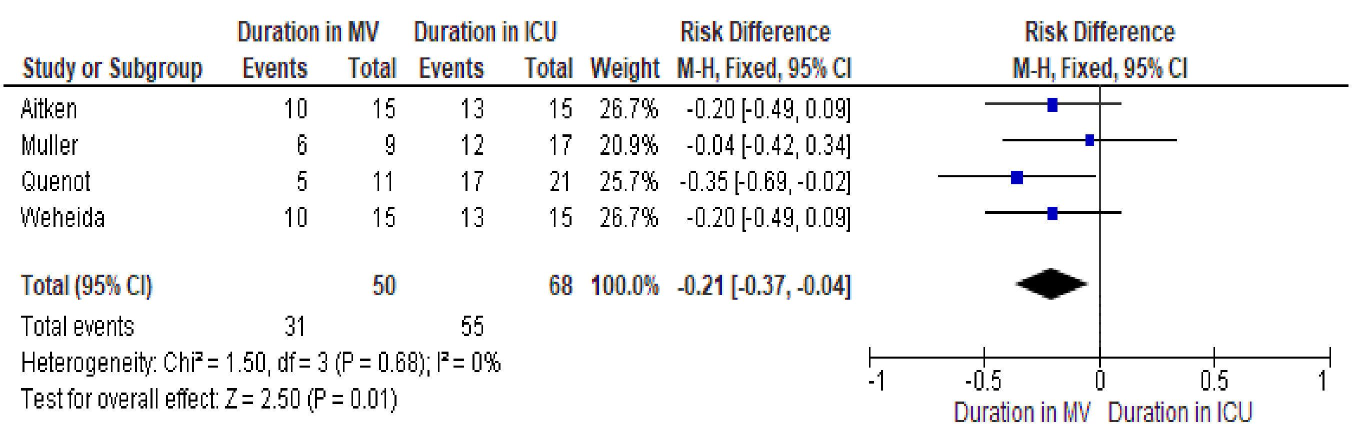

Fig. 2: Forest plot that presents the findings of four separate studies focusing on how long patients spend in the Intensive Care Unit (ICU) and on mechanical ventilation (MV), it is shown that the risk differences with 95% confidence intervals are found for each study, as well as the weights assigned by meta-analysis to every piece of research. Herein, at its bottom-most part, is a combined total effect size that shows a significant outcome (*P*=0.01)

Table 2: Overview of studies on nurse-led sedation protocols for preventing ventilator-associated pneumonia in critically ill patients on mechanical ventilation.

Country	Main Findings	Bias	Conclusion	Ref. no.
Iran	Implementing a daily sedation interruption protocol significantly reduced early VAP incidence in mechanically ventilated patients in critical care units	Blinding in data collection and interpretation introduces potential bias, limiting the overall effort to minimize bias	Daily sedation vacation protocol reduces the incidence of VAP. Recommendation: Nurses should use the daily sedation vacation protocol.	17
China	Nurse-led sedation protocols positively impact mechanically ventilated ICU adults, showing potential benefits in patient care and outcomes.	Intermediate quality in RCTs and low to moderate bias in pre/post-intervention studies	Nurse-led sedation protocols reduce the duration of mechanical ventilation. No significant difference in mortality or length of ICU stay.	11
France	Implementing a nurse-led sedation protocol reduced VAP incidence in critically ill patients, as observed in a medical intensive care unit.	Exclusion of patients receiving analgesics, limiting generalizability, retrospective VAP diagnosis, lack of blinding, and randomization may affect the validity of the results	Nurse-implemented sedation protocol may reduce VAP incidence.	12
France	Goal-directed sedation with propofol-remifentanil reduced time to extubation in ICU patients but increased self-extubation occurrences.	Selection bias, measurement bias, and confounding variables	Propofol-remifentanil sedation decreases extubation time but increases self-extubation rates.	19
USA	Evaluation of the ventilator bundle in trauma patients suggests potential effectiveness in reducing VAP, but the study shows no significant outcome differences between study sites.	Assessing ventilator bundle compliance, particularly due to patient-day calculations favoring longer stays and more severe injuries.	Ventilator bundles may not effectively prevent VAP. Observational study found no statistical outcome differences across sites.	20
Egypt	A designed bundle protocol for VAP improved nurses' knowledge, compliance, and patient outcomes, leading to better care quality and clinical results in the ICU.	Measurement bias could arise from relying on self-reported data for nurses' compliance and knowledge	Bundle protocol training improves nurse performance and patient outcomes, including shorter ICU stays and reduced ventilation duration.	21
UK	The meta-analysis found inconsistent evidence regarding the impact of sedation depth on ICU outcomes, with limited benefits from lighter sedation.	Highly variable bias risks in cohort studies and more consistent bias in RCTs, mainly due to the lack of blinding.	Limited evidence supports lighter sedation benefits. Inconsistencies in study results prevent definitive conclusions.	22

VAP - ventilator-associated pneumonia; ICU- Intensive care units; CI-Confidence intervals; NA-Not available

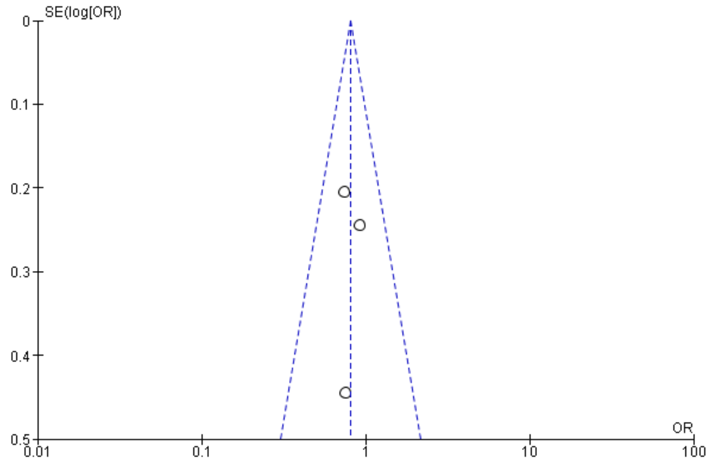

Fig. 3: Assessment of publication bias using a funnel plot for how long patients spend in the Intensive Care Unit (ICU) and on mechanical ventilation (MV), based on the standard error for all included studies. Each circle represents a study in the meta-analysis, with relative risks shown on a logarithmic scale

Comparison of VAP and those without VAP mortality rate

Meta-analysis that assessed three studies (12, 20, 21) comparing patients with VAP and those without VAP (control group) found no significant difference in mortality rates (Fig. 4). The meta-analysis generated an Odds Ratio (OR) of 0.80 [95% CI: 0.60-1.07], with a *P*-value of 0.14, suggesting that VAP did not affect the mortality rate significantly. The individual studies had similar trends and had ORs of 0.92, 0.76, and 0.74, respectively, none reaching statistical significance. The heterogeneity among studies was also found to be negligible (I^2 = 0%) indicating consistent results across them. These findings imply that even though nurse-led sedation protocols can lower the occurrence of VAP and reduce ICU length of stay, their influence on patient survival is still uncertain thus necessitating further investigations into its long-term effects as well as its mechanisms. Funnel plot illustrates publication bias for death among people suffering from VAP as contrasted to control individuals (Fig. 5). The vertical axis stands for the standard error of risk difference and the horizontal axis shows the value for risk difference. The points on each scatter plot are studies that were considered in the meta-analysis. The two dashed lines make an inverted funnel which indicates how studies would be distributed if there was no issue related to publication bias. An asymmetry in this graph would suggest a possible publication bias.

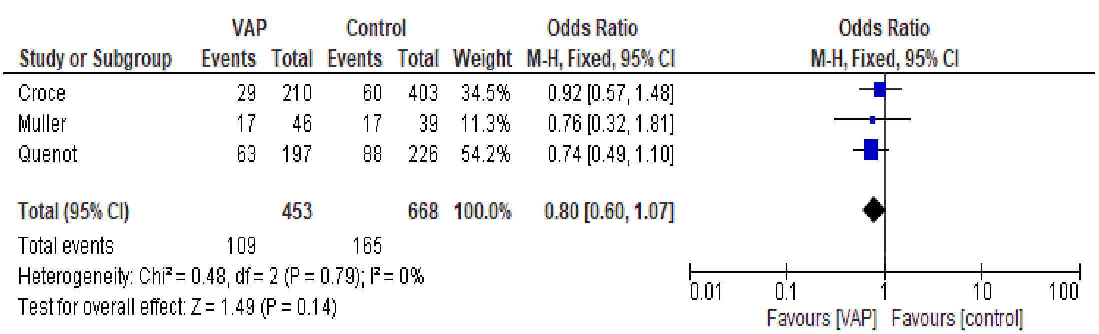

Fig. 4: The Forest plot showing three studies indicates the odds ratios for mortality among people with VAP in comparison to control subjects. The bigger the square, more weight it has in meta-analysis and 95% confidence intervals fall within horizontal lines. The diamond at the bottom represents combined odds ratio which reveals that there is no significant difference between these two groups (Odds Ratio = 0.80 [95% CI: 0.60-1.07], p = 0.14)

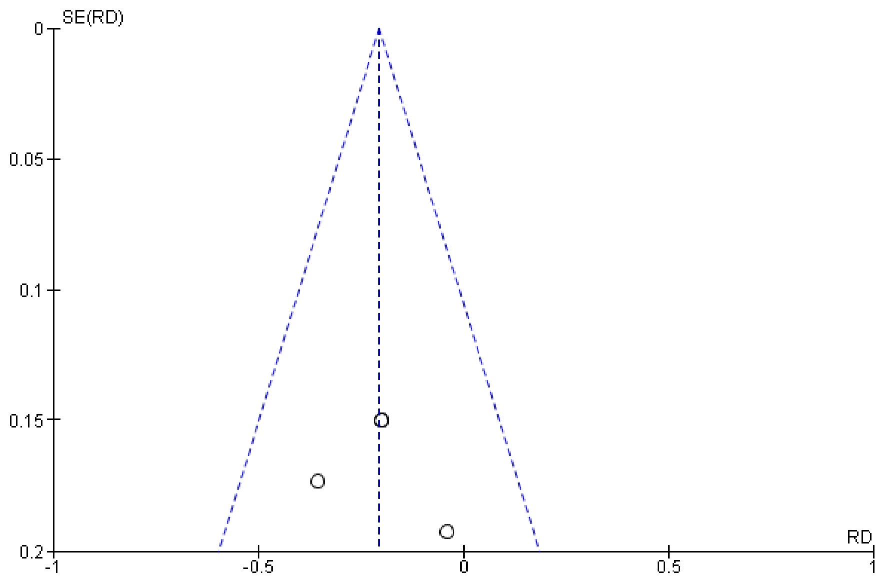

Fig. 5: Assessment of publication bias using a funnel plot for mortality among people with VAP in comparison to control subjects, based on the standard error for all included studies. Each circle represents a study in the meta-analysis, with relative risks shown on a logarithmic scale

Discussion

This study contributes to examining the effectiveness of nurse-led sedation protocols in lowering VAP, especially within critically ill patients. The meta-analysis done in this evaluation included significant studies that investigated both the incidence of VAP and patient mortality rates associated with nurse-led sedation protocols against control groups that did not utilize such interventions. The overall pooled odds ratio of 0.80 (95% CI [0.60, 1.07], P=0.14) indicates that there are tendencies towards lower mortality among intervention groups though they are not statistically significant at this level.

Impact on VAP Incidence

Three studies consistently underline the positive impacts of nurse-led sedation protocols on the reduction of VAP (12,17,18). Randomized clinical trial indicated that the application of a daily sedation interruption protocol there was a considerable decrease in early VAP incidence among mechanically ventilated patients (17). At the same time, a systematic review and meta-analysis carried out nurse-led sedation protocols not only helped reduce VAP incidences but also improved patient outcomes, especially by shortening mechanical ventilation duration (18). In addition, similar results showing lessened VAP cases among critically ill admitted patients within medical ICUs thus emphasize the effectiveness of nurse-led sedative interventions (12). Consequently, these findings are consistent with other broader evidence which avows that well-structured sedation protocols when managed by trained nursing personnel can enhance sedation practices, do away with unnecessary sedation administration policies besides reduce what is called VAP risks. This decrease of VAP incidence is important because it remains one of the most frequent and grave complications among people who are on mechanical ventilation leading to increased morbidity, prolonged stay in ICU as well as elevated healthcare expenditure (1, 23, 24).

VAP-Related Mortality

Nurse-led sedation programs appear to have decreased the incidence of VAP, but evidence on their effect on mortality is inconclusive. No statistically significant difference was observed between intervention and control groups regarding mortality according to the meta-analysis (OR=0.80, 95% CI [0.60, 1.07], *P*=0.14). These findings may be attributed to several reasons such as differences in study designs, patient populations and implementing sedation protocols. Propofol-remifentanil goal-directed sedation methodology reduced extubation time, however it led to an increase in self-extubation cases which could be detrimental to patients' outcomes (19). This emphasizes the intricacy of managing sedatives and the possibility of unintentional side effects when modifying the usage of sedatives. Moreover, a prospective observational study looked at trauma patients and evaluated whether the ventilator bundle was effective in preventing VAPs or not (23). The study suggested some level of effectiveness in preventing VAP; however, no real between-group differences were meaning it is hard to assess mortality effects across various locations. Many factors can cause no significant change in the human death rate as a result of this (VAP) multifactorial nature. The use of sedative protocols can support the prevention of VAP but the other main determinants of mortality include rapid antibiotics delivery, ventilator management & overall care quality during stay in ICU (25, 26). Within these differences, we find heterogeneity among studies (Chi^2 =0.48, *P*=0.79, I^2=0%) which suggests that better standardization would help to achieve appropriate and reliable evidence based on research.

The lack of significant differences in mortality rates across studies can be attributed to a combination of methodological variability, patient diversity and the multifactorial nature of critical care outcomes. Differences in study design, such as sample size, duration and inclusion criteria, contribute to inconsistencies, making it challenging to detect a definitive impact on mortality. Additionally, ICU patients often present with diverse comorbidities and varying severity of illness, complicating the ability to generalize findings or link sedation protocols directly to mortality outcomes. While interventions like nurse-led sedation programs may reduce complications of VAP, their impact on mortality may be indirect or overshadowed by other critical factors, including timely antibiotic administration, ventilator management and overall quality of ICU care.

Clinical Implications

These findings have numerous clinical implications. First, the uniform decline in VAP frequency across studies indicates that nurse-led sedation protocols ought to be incorporated into everyday ICU practices. This concurs with suggestions highlighted that the significance of training and educating nurses on sedation management to optimize patient outcomes through shorter stays in ICU and less time spent on mechanical ventilation (19). Additionally, standardized sedation protocols can increase their effectiveness when accompanied by regular training and monitoring for adherence (26). Nevertheless, it is not clear how they affect VAP-related mortality which suggests that sedation protocols alone may never be enough for total care of VAP (27-29). More extensive strategies using sedative guidelines together with other evidence-based interventions like the ventilator bundle, early mobilization for patients and control of infections might be needed if reduction in mortality is to occur (30). Regarding the nurse-led sedation protocols and prevention of VAP, phytochemistry, nanovaccines and antibacterial research can ability to improve infection prevention in critical care. Phytochemical substances with antimicrobial activities could serve as adjunct therapies, while nanovaccines could help increase the body's defense mechanisms to fight against agents causing respiratory diseases (31-33). In addition, the introduction of new antibiotics would reduce ICU patient susceptibility to infections thus achieving a synergistic effect when combined with sedation protocols to decrease VAP incidences (34).

Limitations and Future Directions

We must recognize some limitations inherent in this study. This meta-analysis is heterogeneous because of differences in design, sample sizes, and patient populations among the included studies. Also, since some of the studies were observational like Croce et al., it was not possible to draw cause-and-effect conclusions between nurse-led sedation protocols and mortality outcomes (21). Furthermore, no data on long-term outcomes or quality of life after ICU discharge makes it difficult to generalize these findings. Large-scale randomized controlled trials that standardize sedation protocols while assessing short-term and long-term effects should be the focus of future research. In addition to this investigative realm, such studies should also look at combining sedation protocols with other VAP prevention strategies to determine what combination of actions is most effective in improving patient outcomes. Further work should also examine how individualized sedation management may play a role based on factors such as patient age, comorbidities, and sedation need.

Conclusion

Nurse-led sedation protocols effectively reduce VAP rates among critically ill patients; however, it is unclear whether these interventions have a significant impact on VAP-related mortality or not. Therefore, every ICU should integrate them into routine care but should also be part of a more comprehensive plan that includes other evidence-based methods for maximizing patient results. Additionally, the need for additional research exists to determine how sedation practices relate to mortality so that critically ill patients get the best and all-encompassing.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of Interest

The authors declare no conflict of interest related to this study.

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