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Research Article

Sedation versus Nonsedation among Critically-Ill Patients Receiving Mechanical Ventilation: A Meta-Analysis and Systematic Review

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1. Abstract

1.1. Background: At present, sedation in patients on mechanical ventilator remains the standard of care. However, many trials have shown that sedation was associated with worse outcomes (i.e. more days on mechanical ventilation and higher mortality rates). We explored the use of nonsedation protocols as compared to conventional sedation in order to determine its effect on the mortality and number of days free from the ventilator among critically-ill patients on mechanical ventilation. This is the first meta-analysis of its kind.

1.2. Methods: We searched electronic databases (PubMed, Medline, EMBASE, Cochrane Central Register of Controlled Trials, Google Scholar, and Research Gate) from 1966 to March 2020 complemented with manual searches. The validity of included studies was assessed using the Cochrane Handbook for Systematic Reviews of Interventions; and analysis using the random-effects model in Review Manager Version 5.3.

1.3. Results: Two of 89 trials comprised of 813 patients were included in the final analysis. All studies included compared two groups of critically ill patients on mechanical ventilation sedation versus non-sedation. The nonsedation groups in both studies only received boluses of morphine as needed. There was no difference between both groups in terms of mortality [1.14 (0.86 to 1.51, 95% CI, Z = 0.93, I2 = 59%) P = 0.35] and number of days free from the ventilator [1.95 (-1.27 to 5.17, 95% CI, Z = 1.19, I2 = 64%) P = 0.24]. However, there were more adverse events reported in nonsedated patients in one study.

1.4. Conclusions: There is no significant difference between the nonsedation and sedation groups in terms of mortality and number of days free from the mechanical ventilator. However, there were more adverse events in the form of accidental self-extubations requiring reintubation and removal of other equipment in the non-sedation. In light of these findings, sedation remains to be preferred

2. Introduction

Currently, the standard of care of patients on mechanical ventilation was to provide sedation [1]. Even though mechanical ventilators are now more advanced and sophisticated that they are less uncomfortable to patients, sedation is still recommended [2]. However, there have been trials which showed that sedation was associated with worse outcomes in patients on mechanical ventilators (i.e. longer hospital stay, more days on mechanical ventilation, higher mortality rates) [3-5].

A disadvantage when sedating critically ill patients is the inability of clinicians to assess their mental status. It was noted in the study by Kress et al. the there were lesser Computed Tomography (CT) scans of the brain among patients who were in the group that was woke-up daily compared to the study's control group (i.e. patients on continuous sedation infusions only interrupted at the clinician's discretion) [4]. Another study by Kress et al. reported that daily interruption of sedation was associated with lower incidences of post-traumatic stress disorder [6].

In one of the studies included in the study, they compared mechanically-ventilated patients not on sedation versus those on sedation. They reported that the nonsedation group was had more days off the ventilator and shorted length of stay in the intensive care unit (ICU) compared to the sedation group. However, that trial lacked statistical prowess to show a mortality benefit [7]. There was a post-hoc analysis done of that trial, and it showed that the nonsedation groups had a lower incidence of acute renal failure [8].

Additionally, the common risks arising from mechanical ventilation such as bacteremia, ventilator-associated pneumonia, barotraumas, upper gastrointestinal bleeding, venous thromboembolic disease, sinusitis, and cholestasis were lower in patients having daily interruption of sedation compared to those who were not [9]. Naturally, a development for sedation protocols would be to use it less as much as possible with the expectation that the protocol could lessen the duration that the patient is on the ventilator [10].

The aim of this study was to systematically review studies that compared sedation with nonsedation among critically-ill patients receiving mechanical ventilation, and to perform a meta-analysis with the data presented in these studies. To our knowledge, this is the first meta-analysis comparing the two groups mentioned.

3. Objectives

The main objective of this meta-analysis is to determine the effect of sedation and nonsedation among critically-ill patients receiving mechanical ventilation on mortality. This meta-analysis aims to:

- Determine the effect of nonsedation versus sedation with regards to the number of days the patient is off the mechanical ventilator.
- Determine the effect of nonsedation versus sedation with regards to the number of days the patient is admitted in the ICU.
- Determine the adverse events from patients on the sedation and nonsedation groups.

4. Methodology

4.1. Study Selection

Studies included in the final analysis were randomized controlled trials which included adult patients (aged more than or equal to 18 years) who were critically-ill and receiving mechanical ventilation. The intervention group consisted of patients who did not receive any sedatives but could receive boluses of morphine analgesia as needed only. The control group consisted of patients receiving continuous infusion of sedatives. Outcomes of interest in this meta-analysis are all-cause mortality, number of mechanical ventilator-free days, and length of stay in the ICU. Articles selected were in English. There was no restriction on the date of publication of the trial.

4.2. Data Search, Search Methods, and Identification of Studies

The researchers searched for studies published in PubMed, NEJM, Cochrane, Web of Science database and Google scholar. Citations in the articles found were also searched. Unpublished articles were also sought by searching for ongoing trials or recently finished trials that have not yet been submitted to journals through ClinicalTrials.gov. For studies without complete text published online, correspondence with the author were made in order to obtain a copy of the complete text to enable a comprehensive analysis of the study.

In the comprehensive search done, the following search terms were utilized: "Sedation", "Nonsedation", "Critically-ill Adults", "Mechanical Ventilation", "Mortality", "Mechanical Ventilator-Free Days", "Length of Stay", "randomized controlled trials". A MESH search was done to include all possible iterations of these terms.

4.3. Data Collection and Analysis

4.3.1. Selection of studies: Two independent reviewers identified trials for inclusion by applying the selection criteria. The inclusion criteria consist of adult critically-ill patients receiving mechanical ventilation. Exclusion criteria included those younger than 18 years-old, the presence of other conditions or diseases that necessitated the use of sedation (i.e. those with status epilepticus or hypothermia after cardiac arrest), pregnant patients, and those with severe head trauma.

4.3.2. Data extraction: Two independent reviewers extracted pertinent data using a standardized Data Collection Form, which is the Cochrane Data Collection Form. After completing the review of articles, the reviewers independently assessed the internal validity of each article using the validity assessment tool. The reviewers were blinded to the authors and institutions of the trials undergoing review. Disagreement on the validity of a study being analyzed was

resolved through a third independent reviewer.

4.3.3. Assessment of Treatment Effect: In the trials analyzed, treatment effect was determined through a change in the all-cause mortality among patients given continuous sedation and those who did not receive it. This was reported in both studies with one study reporting mortality in the ICU and hospital overall (did not specify how many days after randomization), while another study reported mortality 90 days after randomization. For the outcome of mechanical ventilator-free days, the effect of the treatment on the number of days the patient was off the mechanical ventilator was assessed. The other secondary outcome of length of ICU stay was also assessed based on the number of days that the patients in both groups were admitted in the ICU. The adverse events arising from the sedatives and/or the boluses of morphine were also identified and assessed.

4.3.4. Assessment of Risk Bias: Risk bias was assessed by determining allocation sequence generation, allocation concealment, blinding, complete outcome data reporting. The Cochrane validity assessment tool was utilized for all the included studies. The PRISMA Checklist for Meta-analysis was also employed.

4.3.5. Data Analysis: The Revman software version 5.3 was the tool used to analyze the outcomes in this meta-analysis. Primary Outcome of interest, which is the all-cause mortality in percent, was in the form of dichotomous data. While the secondary outcomes of interest, which were the number of mechanical-ventilator-free days and length of stay in the ICU, which were continuous data, were assessed through the use of mean difference and standard deviation at the 95% confidence interval. The Forest plot was generated through the Revman software. A funnel plot was also produced to check for outlier studies. A comparison of the table of characteristics of both studies was employed to assess treatment heterogeneity. The test for heterogeneity was quantified through the I^2 statistic, which was produced from the Revman software.

5. Results

5.1. Data Collection

A thorough search, accompanied by a MESH search, using the terms "Sedation", "Nonsedation", "Critically-ill Adults", "Mechanical Ventilation", "Mortality", "Mechanical Ventilator-Free Days", "randomized controlled trials" of the databases of Pubmed, Medline, Cochrane, Web of Science Database and Google Scholar yielded a total of 89 articles. Two trials of acceptable quality were selected as part of the analysis. The search flow diagram is found below [11] (Figure 1).

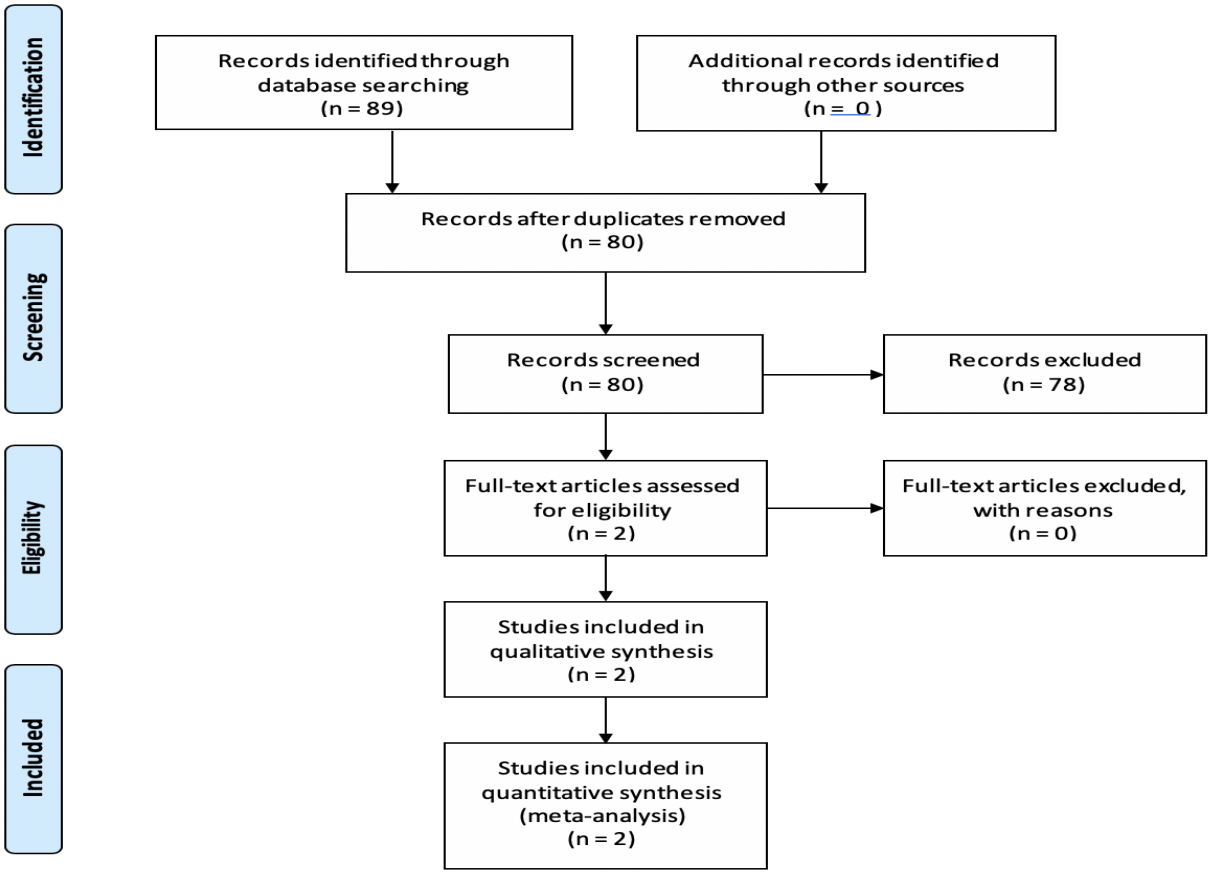

Figure 1: Search flow diagram

5.2. Description of Studies

All trials found had their intervention group not on sedation but were on boluses of morphine which were given on a "as needed" or "as deemed by the physician" basis were included. Whereas the control group were patients who were given sedation (specific sedatives given are shown in the (Table 1) below).There were two trials featuring the outcomes of interest? Below is the table of included studies [12].

Table 1: Characteristics of Included Studies

Study	Methods	Participants	Interventions		Outcomes
			Experimental group (Nonsedation)	Control group (Sedation)	
Strøm et al. (2010)[7]	Single-Center, Randomized, Controlled Trial	-Patients aged more than or equal to 18 years-old -Critcally-ill (admitted to the ICU) on Mechanical Ventilation (regardless of length), but they were recruited within 24 hours of admission to the ICU.	-Patients received intravenous boluses morphine (2.5 or 5 mg) as needed.	-Patients received intravenous boluses of morphine (2.5 mg or 5 mg) or Haloperidol (1-5 mg) as needed; and -Sedated with an infusion of propofol (20 mg/ml) titrated to reach a Ramsay score of 3-4.	-Primary: the number of days without mechanical ventilation (after successful extubation, or removal of ventilator support for patients with tracheostomies) in a 28-day period; the total length of stay in the intensive care unit and in hospital, where data were available; and mortality in the intensive care unit and hospital. -Secondary: occurrences of need for CT or MRI brain scans, accidental removal of endotracheal tube, and ventilator-associated pneumonia.
Olsen et al. (2020)[12]	Multi-Center, Randomized, Contorlled Trial	-Patients aged more than or equal to 18 years-old Critically-ill (admitted to the ICU) who had undergone endotracheal intubation within 24 hours before screening; and who are expected to be on mechanical intubation for more than 24 hours.	-Patients received intravenous boluses of morphine as needed.	-patients received continuous infusion of sedatives with a goal of achieveing light sedation (Richmond Agitation and Sedation Scale of -2 to -3); Propofol was used in the first 48 hours, then shifted to Midazolam thereafter.	-Primary: all-cause mortality 90 days after randomization Secondary: Number of days until death up to 90 days after randomization, number of thromboembolic events up to 90 days after randomization, number of days free from coma or delirium within 28 days after randomization, the highest score on the Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease (RIFLE) assessment, which classifies acute kidney injury according to severity, within 28 days after randomization, the length of stay in the ICU up to death or 28 days after randomization, whichever occurred first; and the number of days without mechani- cal ventilation within 28 days after randomization. Days free from coma or delirium were re- corded during the ICU stay, and days alive after discharge from the ICU up to day 28 were counted as delirium-free days.

5.3. Quality Assessment of Included Studies

Based on the criteria set by Cochrane Group, the quality of the retrieved studies was assessed independently by the two authors (Figure 2). The assessment done was then checked by a third party (senior co-author) to amend the differences. Both the clinical trials included lacked blinding but this has minimal effect on the final analysis because this will not change the outcomes of interest (Mortality, Number of days on Mechanical Ventilation, Length of Stay in the ICU), which are an objective findings.

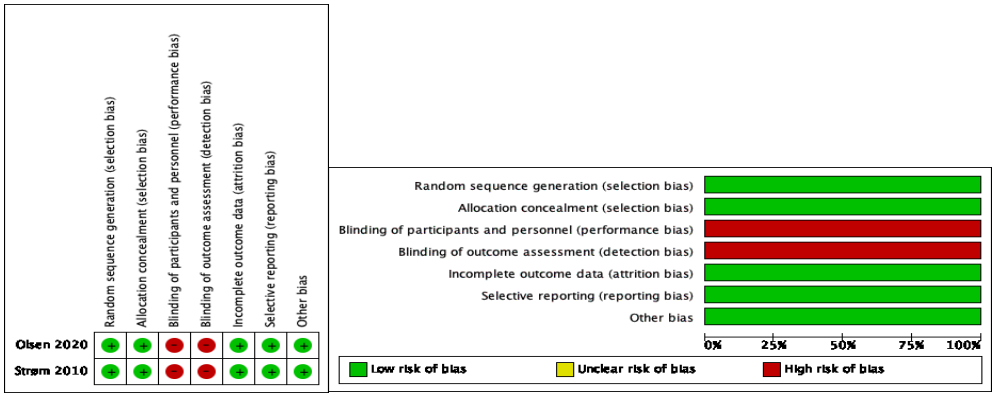

Figure 2: Quality Assessment of the studies included in the Meta- Analysis

5.4. Effects on Intervention on Outcomes of Interest

5.4.1: The effect of Nonsedation on the mortality rate of critically ill patients receiving mechanical ventilation: The relative risk of both studies analysed was 1.14 (0.86 to 1.51, 95% CI, Z = 0.93, I^2 = 59%). This revealed that there was a reduction in mortality favoring the group receiving sedation (Figure 3); however, this had a P of 0.35 which meant that this benefit is statistically not significant. Also, there was noted to be high heterogeneity with I^2 at 59%.

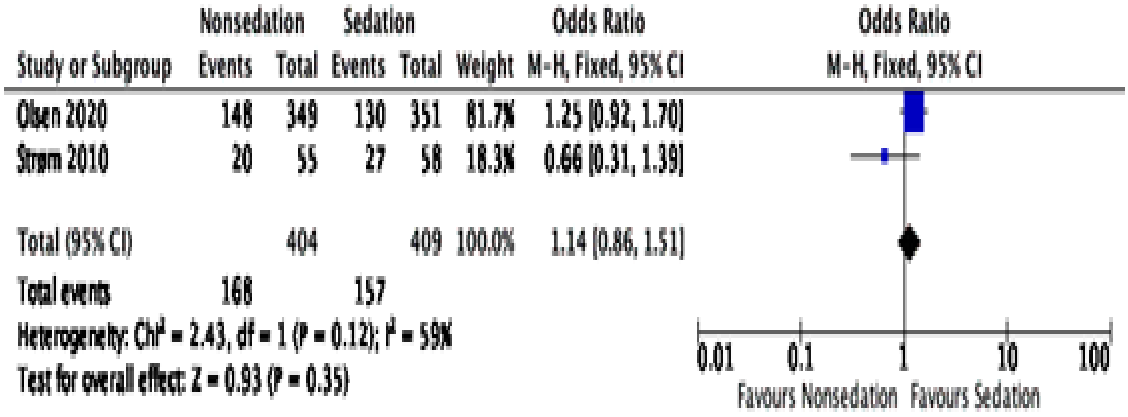

Figure 3: Forrest plot showing the effect of nonsedation and sedation on mortality rate

5.4.2. The Effect of Nonsedation on the Number of Days That the Patients in the Study were Ventilator-Free: The relative risk reported is 1.88 (-0.80 to 4.56, 95% CI, Z = 1.38, I^2 = 54%). Similarly, the benefit of sedation here lacks statistical power as the P is 0.17 and this is highly heterogenous with I^2 at 54% (Figure 4).

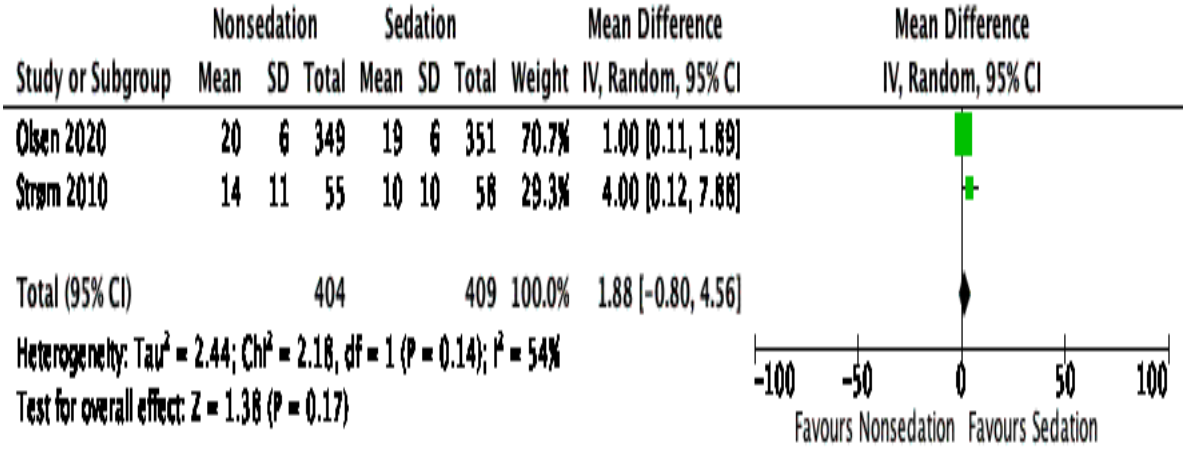

Figure 4: Forrest plot showing the effect of Nonsedation on the number of days that the patients were ventilator-free.

5.4.3. The Effect of Nonsedation on the Length of Hospital Stay in the ICU Expressed as Number of Days: The relative risk reported in this analysis is -5.21 (-13.73 to 3.31, 95% CI, Z = 1.20, I^2 = 95%). This is not statistically significant with P at 0.23 and is highly heterogenous with I^2 at 95% (Figure 5).

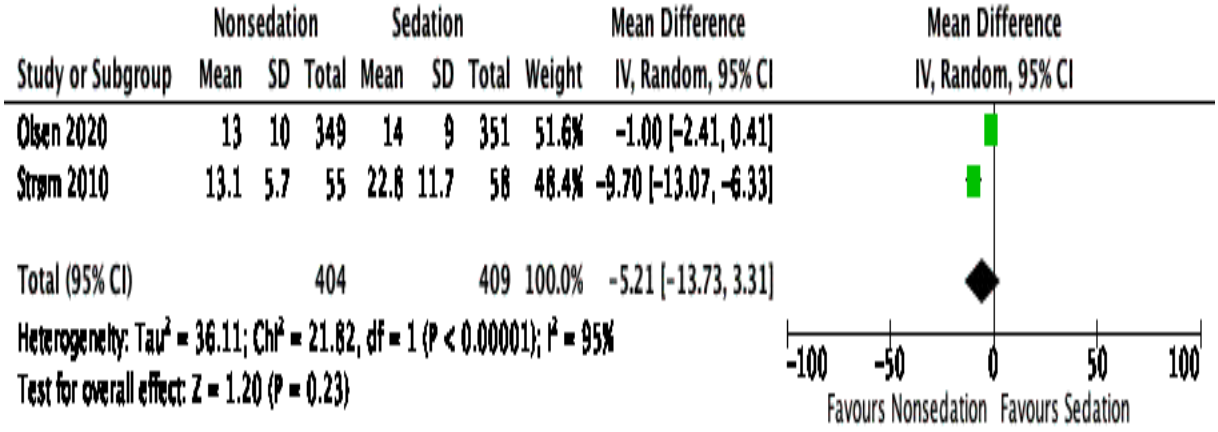

Figure 5: Forrest plot showing the effect of Nonsedation on the number of days that the patients were admitted in the ICU.

5.4.4. Adverse Effects Nonsedation and Sedation: The study by Strom et al. did not report any adverse event. However, the study by Olsen et al. did. The table below (Table 2) reports the adverse events from both the nonsedation and sedation groups.

Table 2: Adverse effects Nonsedation and Sedation

	Non-Sedation (n=349)	Sedation (n=351)	Difference (95%)	P-Value
Serious Adverse Events				
Accidental self-extubation requiring re-intubation within one hour n (%)	4 (1.1%)	1 (0.3%)	0.8 (-0.7%; 2.6%)	0.20
Adverse Events				
Accidental self-extubation requiring re-intubation within 24 hours n (%)	31 (8.9%)	14(4.0%)	4.9% (1.3%; 8.7%)	0.01
Accidental self-removal of central venous line n (%)	3 (0.9%)	3 (0.9%)	0% (-1.8%; 1.8%)	1.00
Accidental self-removal of peripheral IV line n (%)	9 (2.6%)	10 (2.8%)	0.2% (-2.4%; 2.8%)	0.87
Accidental self-removal of other equipment (gastrointestinal tube, arterial line, etc.) N (%)	53 (15.2%)	32 (9.1%)	6.1% (1.3%; 11%)	0.01

It was reported that those belonging in the nonsedation group had reported more serious adverse and adverse events. However, only the accidental self-extubation requiring reintubation with 24 hours and the accidental self-removal of other equipment showed statistically significant differences favoring the sedation group.

6. Discussion

The earlier trial comparing nonsedation with sedation by Strom et al. showed there was a benefit with regard to the number of days free from mechanical ventilation; this however was not replicated in the newer multicenter trial ten years after by Olsen et al. The later study

showed no difference between both groups. In the meta-analysis, all outcomes of interest showed no difference in both groups also. This was due to the lack in statistical power and the highly heterogenous data.

It was also noted that the baseline characteristics of the patients under the sedation group in the study by Strøm had more patients with respiratory disorders, sepsis, and pancreatitis. There was no statistical tool to show that there were no significant differences in their baseline characteristics. Also, in the later study by Olsen, they used the RASS scores and their goal was to achieve light sedation unlike the other study which aimed to achieve of a Ramsay score of 3-4. Both trails used different scales for sedation which are no equivalent to each other. The light sedation in the later study was achieved with a RASS of -2 which corresponds to brief awakening to voice. This is not a big difference between the two groups studied.

The literature mentioned earlier that sedation was associated with poorer outcomes (i.e. mortality, longer hospital and ICU stay, and more days on the mechanical ventilator). The study by Olsen et al. suggests that putting a patient on light sedation is safe with no differences in outcomes; however, light sedation was associated with lower serious adverse and adverse events. The light sedation in the later study more or less suggests that further reduction in sedation may no longer be beneficial. In both trials, the use of morphine on a "as needed" basis suggests that boluses instead of continuous infusions may suffice in the care of those patients.

The other outcomes of interest are the adverse events. The earlier study did not report those, but the later study did. And there was a significant difference favoring the sedation group (light sedation). The adverse events were all accidental events brought about by the patient being anxious or agitated, and the light sedation achieved in the study by Olsen proved that those events were lessened, thus leading to less complications.

7. Conclusion

Among critically ill patients receiving mechanical ventilation, nonsedation had no difference on the mortality, number of days free from the mechanical ventilator, and length of stay in the ICU compared to those given sedation. However, light sedation (arousable to verbal command) did show a statistical difference (favoring light sedation) over those with no sedation. There is more benefit in giving light sedation to patients than not as there is no difference in the other outcomes.

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