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COMPARING MECHANICAL VENTILATION DURATION BETWEEN DAILY SEDATION INTERRUPTION (DSI) AND PROTOCOLISED SEDATION ON CRITICALLY ILL ADULT PATIENTS WITH MECHANICAL VENTILATION RECEIVING CONTINUOUS PROPOFOL INFUSION.

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Abstract: This study proposes a randomized controlled trial (RCT) comparing the efficacy of daily sedation interruption (DSI) versus protocolized sedation in adult patients requiring mechanical ventilation with continuous propofol infusion. The trial aims to address the gap in existing literature by focusing on non-benzodiazepine sedatives, which are preferred in current clinical practice. Conducted in six medical-surgical ICUs across the United Kingdom and Hong Kong, the RCT will enroll patients based on strict inclusion and exclusion criteria. Patients will be randomized to receive either DSI or protocolized sedation, with blinding of patients and data collectors. The primary outcome measure is the duration of mechanical ventilation, with secondary outcomes including ICU and hospital lengths of stay, level of wakefulness, unintentional device removal, and physical restraint use. Study anticipates enrolling approximately 200 patients per group to detect clinically significant differences in mechanical ventilation duration. This research aims to inform clinical practice and optimize sedation strategies for critically ill patients receiving mechanical ventilation.

Keywords: Daily sedation interruption, Protocolized sedation, Nursing protocolized sedation, Nurse-led sedation, Nursing implemented sedation algorithm, Intermittent sedation, Intensive care unit ICU, Critical care, Mechanical ventilation-Ventilator, Invasive positive pressure ventilation (IPPV)

1. INTRODUCTION

1.1 Background

Continuous sedation infusion is very common for patients with mechanical ventilation in Intensive Care Units (ICUs) because it can reduce the incidence of ventilator dyssynchrony by promoting comfort and analgesia in the patients (Chen et al., 2022). Daily sedation interruption (DSI) and protocolised sedation are two common protocols applied in ICUs to prevent oversedation.

1.2 Search strategy

I am interested in comparing the effects of both protocols and conducted a literature search related to DSI and protocolized sedation with the online database MEDLINE Ovid and PubMed. I used PICO as a framework to identify the relevant keywords and phrases for the literature search (Table 1). I considered different synonyms, alternative terms, acronyms, and variations in spelling for the keywords and phrases (Table 2) during the literature search to get more search results. I used Boolean operators such as "AND" and "OR" to connect the keyword, refine the search, and retrieve more precise results.

After getting the search results, I screened the results to find relevant studies by applying the inclusion and exclusion criteria (Table 3) and expressed the screening progress in the PRISMA flowchart (Figure 1).

Table 1: PICO framework

Population	Adult patients with mechanical ventilation receiving continuous sedation infusion
Intervention	Protocolised sedation
Comparison	Daily sedation interruption
Outcomes	Duration of mechanical ventilation

Table 2: Keywords and synonyms

Keywords	Synonyms
- Daily sedation interruption	- DSI - Sedation interruption - Daily sedation cessation - Sedation cessation - Daily interruption of sedation - -DIS
- Protocolised sedation	- Protocolized sedation - Protocol directed sedation - Nursing protocolised sedation - Nursing protocolized sedation - Nurse-led sedation - Nursing implemented sedation algorithm - Intermittent sedation
- Intensive care unit	- ICU - Critical care
- Mechanical ventilation	- Ventilator - IPPV - Invasive positive pressure ventilation

Table 3: Selection criteria

Inclusion criteria	Exclusion criteria
- Population of the studies was adult patients with mechanical ventilation receiving continuous sedation infusion - Included DSI and protocolised sedation in the intervention and comparison group - Compared the effect of DSI and protocolised sedation	- Duplicated studies - Not published in English - Irrelevant studies related to DSI or protocolised sedation - Not randomised controlled trial (RCT) - No full text available

1.3 Study selection

I found 34 studies in total through the search which eight studies were from MEDLINE Ovid and 26 studies were from PubMed. I exported all the studies to EndNote and started the screening progress. Seven studies were deleted due to duplication. Four and eight studies were excluded as they were irrelevant studies and non-RCT studies respectively. Three studies were excluded because the population of the studies was children aged less than 18. Five studies were excluded because they were not comparing the effect of DSI and protocolized sedation. Seven full-text studies were assessed for eligibility and all seven studies were included in this literature search.

2.CRITICAL APPRAISAL

2.1 Reasons for choosing the following articles for critical appraisal

I will critically appraise two articles using the CASP tool to find the research gap and formulate a research question. I will explain the reasons for choosing the following two articles. First, both studies compared the effect of DSI and protocolized sedation with the same choice of sedative agent, but the results of the studies were different. Second, both studies were the most recent studies published in comparing DSI and protocolized sedation. Third, both studies used a different method, one was unblinded, single-Centre RCT while the other one was single-blinded, multi-Centre RCT.

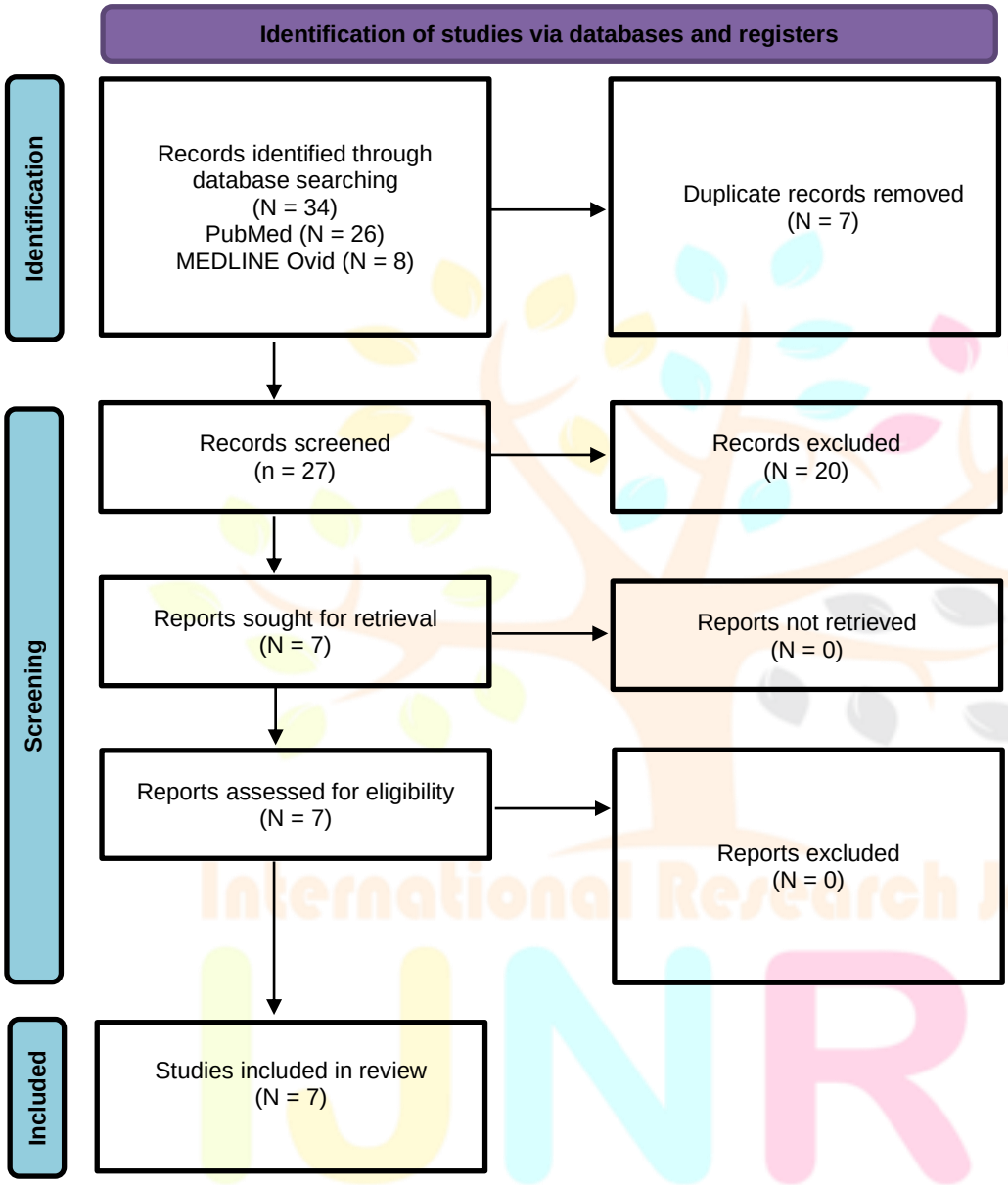
2.2 Critical appraisal of the first article

2.2.1 Summary of the article

The title of the article is "Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients"(de Wit et al., 2008). It was an unblinded, single-Centre RCT conducted in the USA. The article was published in Critical Care in May 2008. The population of the study was adult patients with mechanical ventilation receiving continuous sedation infusion. Patients in the intervention group received daily sedation interruption (DSI), and all sedation and opioid infusions

were discontinued until patients were awake or agitated. Patients in the comparison group received nursing-implemented sedation algorithms (SAs), sedations and analgesics were titrated according to the SAs developed by the local medical ICU physicians, pharmacists, and nurses. The primary outcome was to compare the mechanical ventilation duration of DSI and SA. The results of the study showed patients receiving SAs had shorter mechanical ventilation duration and lengths of ICU stay compared to DSI.

Figure 1: **PRISMA Flow Chart**



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj. n71

2.2.2 Critical appraisal of the article

The study addressed the research question clearly with the method of RCT. RCT is a suitable method for this study because it is the gold standard for measuring the effectiveness of the intervention and is capable of proving the causation relationship between the intervention and outcome (Hariton and Locascio, 2018).

It would be better if the study added one more criterion to the population selection which was patients with expected prolonged mechanical ventilation time of more than 48 hours. It could exclude patients with short expected mechanical ventilation time and draw more accurate results regarding the effectiveness of the intervention. Besides, the study did not mention the ventilator weaning process between groups. It would be better to standardize the weaning process to achieve more comparable results.

Although the study mentioned patients were randomized to the intervention group and comparison group, it did not describe the randomization method used. I was concerned about the possibility of selection bias if the allocation sequence was not concealed from the investigators. The study used intention-to-treat analysis. This method mirrored the real-life clinical scenario and helped to draw an unbiased estimation of the effects of intervention (Gupta, 2011).

Originally, the study planned to recruit 268 patients to detect a two-day difference in mechanical ventilation duration between groups with 80% power and an alpha value of 0.05. However, the study only recruited 75 patients and was terminated after an interim analysis showed a P value ≤ 0.001 in the primary outcome. The study performed the interim analysis early due to safety concerns as there was a patient who experienced study-related adverse events after DSI implementation. Since the interim analysis was performed early and potential selection bias existed due to unexplained allocation sequences during randomization, I was concerned whether the inadequate sample size could demonstrate an accurate causation relationship between intervention and outcome.

The study was unblinded, which is susceptible to performance bias. Operators knew the patients belonged to which group and might provide different levels of care or attention to specific groups of patients affecting the comparison of the effectiveness of the intervention. For the baseline characteristics, there were minimal differences between groups. It can facilitate the comparability and allow for a clearer comparison of the interventions.

The primary and secondary outcomes of the study were specified. The results were reported objectively with words and expressed in tables and graphs. All the data on the outcomes were reported, and no data were missing or incomplete. The p-value of the primary outcome was 0.0003 and the confidence interval reported in the study was 95%.

For the clinical applicability and generalizability of the study to my workplace, some adjustments are needed. First, the DSI process should be performed by ICU nurses instead of investigators because it is not feasible to have extra staff to monitor the awakening trials of the patients in practical clinical situations. Second, the choices of the main sedative agent should be modified to propofol and dexmedetomidine instead of benzodiazepine which was used in the study. This is because benzodiazepines are not preferred as the main

sedative agent in my workplace. Third, the study should mention a standardized ventilation weaning progress to increase the generalizability of the study.

2.3 Critical appraisal of the second article

2.3.1 Summary of the article

The title of the article is "Daily Sedation Interruption in Mechanically Ventilated Critically Ill Patients Cared for With a Sedation Protocol" (Mehta et al., 2012). It was a single-blinded, multi-center randomized trail conducted in 16 ICUs in Canada and USA. The article was published in the Journal of the American Medical Association (JAMA) in November 2012. The population of the study was adult patients requiring mechanical ventilation for at least 48 hours after enrolment with continuous sedation and/or opioid infusion. Patients in both the intervention and comparison group received protocolised sedation as basic usual care, sedation and analgesic infusion were titrated by bedside nurses according to the protocol to achieve a RASS score of -3 to 0. Patients in the intervention group received DSI upon protocolised sedation, sedation and analgesic infusion were daily interrupted by bedside nurses and assessed RASS hourly for wakefulness. The primary outcome of the study was the duration of successful extubation. The results of the study showed no difference between groups.

2.3.2 Critical appraisal of the article

The study appropriately used the method of RCT to address the research question because RCT is the gold standard for measurement of the effectiveness of the intervention (Hariton and Locascio, 2018). It can prove the causation relationship between the intervention and outcome.

The investigators randomized the enrolled patients to the intervention group and comparison group using an automated telephone system. The automated telephone system concealed the allocation sequence from the investigators and helped to minimize selection bias. This randomization method is suitable because it can ensure the balance in the allocation of enrolled patients to the intervention group and comparison group.

The study used intention-to-treat analysis and analysed the patient according to their original group allocation. This method reflects the real-life situation and assists in drawing an unbiased estimation of the effects of intervention (Gupta, 2011). The study performed an interim analysis after they recruited half of the required sample size, and the study did not stop early as no significant difference was detected at the point of interim analysis. Therefore, the study's conclusion accounted for all patients who entered the study.

This was a single-blinded study which can minimize the placebo effect. Patients were blinded from the study and their legal guardian provided written informed consent. Therefore, the patients did not know which group they were assigned to and would not have expectations towards the intervention. It can reduce the bias. However, it was not feasible to blind the operators for safety considerations and it might lead to performance bias as mentioned previously.

The data of the baseline characteristics between groups were similar. It can facilitate the comparability and allow for a clearer comparison of the interventions. However, race and ethnicity of the group were not mentioned which might affect the generalizability of the study.

For the data analysis, the study needed 205 patients per group to detect a two-day reduction in time of successful extubation with a power of 90% and an alpha value of 0.05. The study recruited enough patients for the data analysis, they recruited 214 patients to the intervention group and 209 patients to the comparison group. The primary and secondary outcomes of the study were clearly stated. The study reported all the data of the results and no missing or incomplete data was noted. No differential drop-out between the study groups was identified. The p-value of the primary outcome was 0.52 and the confidence interval reported in the study was 95%.

For the clinical applicability and generalizability of the study to my workplace, it would be better if the study stated the race and ethnicity of the population. Besides, the study did not permit propofol and dexmedetomidine infusions and used midazolam as the primary sedative agent. As mentioned previously, my workplace does not prefer benzodiazepines over propofol and dexmedetomidine as the main sedative agent, more studies with propofol as the primary sedative agent are needed.

3.RESEARCH GAP AND RESEARCH QUESTION

After reading the included studies in the literature search and critically appraising two selected studies, I discovered there were no consistent conclusions regarding the comparison of the effects of DSI and protocolized sedation. All the studies I found comparing DSI and protocolised sedation were using benzodiazepines as sedative agents and were published around ten years ago.

However, sedation with non-benzodiazepine sedatives (propofol and dexmedetomidine) is preferred over benzodiazepines because non-benzodiazepines can improve clinical outcomes in adult patients with mechanical ventilation (Barr et al., 2013). The applicability of the studies is diminished and a new study comparing DSI and protocolised with non-benzodiazepine sedatives should be performed.

Based on this idea, I formulate my research question: Does daily sedation interruption (DSI) has a lower mechanical ventilation duration than protocolised sedation in critically ill adult patients with mechanical ventilation receiving continuous propofol infusion? I will design a study to compare the effectiveness of DSI and protocolised sedation in the following paragraph.

4.STUDY DESIGN

4.1 Methods

4.1.1 Study design

I suggest conducting a single-blinded, multi-Centre RCT to compare the mechanical ventilation duration of DSI vs protocolised sedation for critically ill adult patients with mechanical ventilation receiving continuous propofol infusion. The study will obtain written informed consent from the legal guardians.

4.1.2 Trial Sites and Patient Population

I suggest conducting the trial in 6 adult medical-surgical ICUs in the United Kingdom (UK) and Hong Kong (HK). Both the UK and HK are developed regions with similar hospital settings and different majority of races and ethnicities. Similar hospital settings can minimize performance bias, and diversity in race and ethnicity can increase the generalizability of the study.

Patients who meet the inclusion and exclusion criteria (Table 4) are eligible for the trial.

Table 4: inclusion and exclusion criteria of patient population

Inclusion criteria	Exclusion criteria
- ICU adult patients aged over 18 years - Expected mechanical ventilation time over 48 hours after enrolment with decided use of continuous propofol infusion	- Pregnant women - Patients admitted to ICU due to cardiac arrest or traumatic brain injury - Patients receiving neuromuscular blocking agents - Previously enrolled in the current trial - Incarcerated patients - Patients requiring deep sedation - Patients allergic to sedative agents - Patients received sedation infusion for more than 24 hours at another institution - Patients required benzodiazepines as sedation

4.1.3 Randomization and blinding

I suggest the patients are randomized to the intervention group (DIS) or comparison group (protocolised sedation) using a 1:1 ratio according to a computer-generated list with undisclosed variable block sizes and stratified patients according to the trial site. Therefore, the allocation sequence is concealed, ensuring equal sample size between groups. It can minimize selection bias.

Although blinding caregivers is not feasible due to safety concerns, patients will be blinded in this study. Operators or investigators will not disclose information about grouping to patients or their relatives. However, patients or legal guardians have the right to withdraw their consent and quit the trial.

4.1.4 Trial Interventions

For the comparison group, which is the protocolised sedation group, case nurses will titrate the sedation and analgesic infusions rate according to a protocol modified from (Mehta et al., 2012) (appendix 1). Pain is controlled by morphine and fentanyl bolus or infusion, and propofol is used as the sedative agent. The level of wakefulness is assessed by the case nurse using the Richmond Agitation-Sedation Scale (RASS) and documented by the case nurse hourly. The case nurse will titrate the dosage of the analgesic and sedation against the RASS score to maintain a RASS score of -2 to 0, therefore patients in the comparison group are kept at a light sedation state. When the patients are agitated (RASS score is higher than 0) due to pain, bolus analgesics or propofol can be administered and the propofol infusion rate is titrated up by 10-20 mg/hr. When the patient is oversedated (RASS score is lower than -2), the case nurse will titrate down the analgesic and propofol infusion rate by 10-20mg/hr. The use of benzodiazepines is not permitted in both groups.

For the intervention group, which is the daily sedation interruption group, the case nurse will interrupt propofol sedation daily while keeping an analgesic infusion. It can prevent patients from waking up in pain which might cause discomfort. The level of wakefulness is assessed and documented hourly by the case nurse using RASS. If patients achieve a RASS score of -2 to 0, test the Glasgow Coma Scale (GCS) by assessing the ability to follow simple instructions, for instance, open the eyes, stick out the tongue, and hand squeezing. If patients can perform two of the requested instructions, the case nurse can assess the need for sedation with the physician and stop the sedation infusion if it is no longer required. If patients are agitated after interruption of sedation (RASS score is higher than 0), the case nurse should clarify the need to resume sedation with physicians. Resume the sedation infusion if physicians decide sedation is needed. The case nurse should promptly resume the sedation if patients show signs of ventilator desynchrony, respiratory distress, and tachycardia after interruption of sedation. Physicians are responsible for titrating the rate of sedation infusion in the intervention group. Daily interruption of the sedation can be delayed or canceled if other procedures are needed.

For the ventilator weaning process, physicians will assess the patients' readiness for extubation. Physicians will evaluate patients' condition and ventilator settings at least daily. If patients are fully awake, hemodynamically stable, and receiving low ventilatory support without respiratory distress, the physician should perform a one-hour trial of an unassisted breathing test to the patients. For instance, change the setting of the ventilator to a positive end-expiratory pressure of 5cm H2O. If patients cannot tolerate the unassisted breathing test, resume the original ventilator setting and conduct the trial on the next day until extubation. If patients tolerate the unassisted breathing test, extubation should be carried out by nurses or physicians. If

patients reintubate within 48 hours after extubation, patients will receive the same treatment according to their trial group.

4.1.5 Data Collection

The case nurses of the enrolled patients will document the data using an electronic system including duration of mechanical ventilation, during of sedation interruption, number of sedation interruption attempts, duration of sedative infusion, RASS score during sedation infusion, analgesic and sedation infusion rates, dosages of bolus analgesic and sedation given, number of unintentional device removal, and hours of physical restrain applied. Researchers of the study will be responsible for collecting all the data above and the baseline characteristics of enrolled patients for data analysis.

4.1.6 Outcomes

The primary outcome of the study is mechanical ventilation duration after enrolment. The duration is defined as the time between randomization and extubation, and not reintubating in 48 hours after extubation. The secondary outcomes are the length of ICU and hospital stay, level of wakefulness measured in RASS score, unintentional device removal (self-extubation, self-removal of central venous catheter), and physical restrain use.

4.1.7 Sample size estimation

The sample size estimation takes priori studies conducted to compare DSI and protocolised sedation as a reference (Mehta et al., 2012). Around 200 patients per group are needed to detect a two-day reduction in the duration of mechanical ventilation with a power of 90% and an alpha value of 0.05.

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1. APPENDIX

1.1 Appendix 1