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Intermittent versus Continuous Sedation during Mechanical Ventilation in Critically Ill Patient

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Abstract
Background:In order to reduce patient pain and agitation during mechanical breathing, sedation has grown to be a crucial component of critical care management (MV). Patients' short- and long-term outcomes will alter as a result of pharmaceutical treatment that is evidence-based. The study's objective is to assess the effects of intermittent and continuous sedation on mechanically ventilated patients' length of stay in the critical care unit, frequency of adverse events, and MV duration. **Methods**:This randomised clinical research included 100 critically sick patients who had recently needed mechanical ventilation and were anticipated to need it for more than 24 hours. The patients were divided into two groups at random: group A, which received midazolam infusions of 1 to 8 mg/hour or 0.01 to 0.1 mg/kg/hour, titrated to the desired level of sedation, and morphine infusions of 2 to 30 mg/hour when they became agitated with a sedation agitation score (SAS) of 5 or higher. Group B, which received intermittent sedation, received morphine when they became agitated **Results**: When compared to patients receiving continuous sedation, those receiving intermittent sedation showed considerably greater SAS (P 0.001). Within 3 days of the follow-up, NAS was substantially different and lower when dealing with patients on intermittent sedation as opposed to those on continuous sedation (P values 0.001). When compared to patients receiving continuous sedation (median duration: 105 hr), those receiving intermittent sedation (median time: 47 hr, HR (95 percent CI): 4.686 (2.799: 7.847)), were on MV for a considerably shorter period of time with a greater HR of being extubated (P 0.001). While tracheostomy was not a predictor, the APACHE II score, being reintubated, and the incidence of delirium all significantly predicted the length of MV (coefficient: 2.361, 95 percent CI: 1.175 to 3.548, P0.001, coefficient: 28.411, 95 percent CI: 10.134 to 46.688, P=0.003, and coefficient: 21.222, 95 percent CI: 10.348 to 32.097, P0.001). **Conclusions**:Patients who had intermittent sedation experienced considerably lower rates of reintubation, NAS, brief MV stays, and longer hospital stays than those under continuous sedation, but significantly greater SAS.

Keywords: Sedation, intermittent, continuous, mechanical ventilation

Introduction

One of the most often employed therapies in the ICU is mechanical ventilation (MV), which is essential for preserving life in critically sick patients with acute respiratory failure [1].

Most ICU patients suffer pain, and neglecting to acknowledge this discomfort also adds to agitation [2].

In order to reduce patient pain and agitation during MV, sedation has grown to be a crucial component of critical care management. A trinity of circumstances, including pain, anxiety, and delirium, may cause agitation. In the intensive care unit, achieving and maintaining the highest degree of comfort and safety is crucial to provide for critically sick patients. Sedation is intended to produce calm, relaxed people who are not readily startled and who are able to bear medical treatments and monitoring [3].

Patients' synchronisation with MV is made easier by sedation, which is routinely utilised to improve the comfort and safety of ICU patients. In the past, it was observed that excessive sedation was often recorded, which is linked to poor clinical results (for example, a lengthy duration of MV). In order to maximise sedation, several sedation methods (such as intermittent sedation and protocolized sedation) have been devised [4]. But in 40 to 60 percent of patients, these medications cause over-sedation, which may result in extended intubation, psychosis, and drug-induced hypotension [5].

The proper sedation of critically sick patients needing MV is a crucial part of their treatment. [6] The patient's comfort is likely to be affected more by the level of sedation than the stability of their physiological condition [7].

Deep levels of sedation are linked to a number of detrimental outcomes, including prolonged ICU stays, delirium, memory impairment, and greater short- and long-term mortality. Longer hospital stays, greater hospital expenses, and worse long-term outcomes are typical in ICU patients, particularly those with MV, where the risk of delirium is as high as 80% [8].

For use in the ICU for the assessment and titration of medication, objective measurements of pain, sedation, and anxiety have been validated [9].

Patients' short- and long-term outcomes will alter as a result of pharmaceutical treatment that is evidence-based. In order to provide an

up-to-date viewpoint on practises for the management of mechanically ventilated adult ICU patients, we investigated a wide range of literature and advancements in the area of ICU sedation for this guideline [10].

The study's objective is to assess the effects of intermittent and continuous sedation on mechanically ventilated patients' length of stay in the critical care unit, frequency of adverse events, and MV duration.

Patients and Methods

From September 2021 to February 2022, the Critical Care Department at Benha University Hospital and the Intensive Care Unit at Damietta Specialized Hospital treated 100 critically ill patients who had recently needed MV, were expected to need MV for longer than 24 hours, and required sedative medications. The Ethics Committee of the Benha University Faculty of Medicine gave its approval to the project.

Patients with the following conditions were excluded: those who were under the age of 18, were pregnant, required deep levels of sedation (for example, those with metastatic cancer, NY functional class IV heart failure, Child C hepatic cirrhosis, oxygen-dependent chronic obstructive pulmonary disease, status epilepticus), and were not expected to survive for more than six months.

The patients were divided into two groups at random: group A received continuous sedation, while group B received intermittent sedation.

The following tests were performed on all patients: a thorough medical history, an APACHE II score of 179, a PaO2/FiO2 ratio of (mmHg), the source of admission, the diagnosis at admission, the reason for intubation, the mean arterial pressure (MAP), the Glasgow Coma Score, a full blood count, liver functions, and renal functions.

Procedures:

Patients in group A continued to be sedated continuously with morphine at a dose of 2 to 30 mg/hour and midazolam at a dose of 0.5 to 5 mg over 2-3 minutes every 1 to 5 minutes (if necessary). They also received daily interruptions of sedation for neurological evaluations until their sedation agitation score (SAS) reached 4 or more, at which point they returned to continuous sedation.

Every six hours, bedside nurses checked the amount of sedation in all patients using a Portuguese version of SAS [11]. Sedation was described as the infusion of sedative medications, namely midazolam, at the attending physician's discretion. If the intubation was done in the ICU, patients in the intermittent sedation group would be retained without a continuous infusion of sedatives, or their infusion would be stopped after randomization if they had been brought from the ER, OR, wards, or another ICU with an intubation.

Patients weren't given any more sedatives till they woke up. Patients who were calm and cooperative upon awakening (SAS of 4) were retained without sedative administration. The doctor (attending or resident) was consulted if the patient appeared uncomfortable or agitated (SAS 5), and potential sources of discomfort (pain, patient-ventilator asynchrony, thirst, hunger, and position on the bed, all of which were investigated using a poster with figures expressing these uncomfortable sensations) were investigated and treated according to a standard procedure. Fentanyl (50–150 mg) boluses were used to alleviate pain.

A continuous infusion of fentanyl was started and titrated by the attending nurse using a numeric pain scale (which measures pain from 0 = no pain to 10 = the worst pain ever experienced), aiming for a value 4. If the pain returned in less than two hours or there was a persistent pain stimulus (for example, surgical scars, drains), the infusion of fentanyl was stopped. When pain was already being empirically managed with a bolus of fentanyl and there was no apparent basis for the agitation, delirium was suspected and haloperidol was given (bolus of 2.5 or 5 mg). If the patient was still uneasy or agitated after 15 minutes, a continuous infusion of midazolam or propofol was started in order to reach an SAS of 3 to 4. The attending physician had the option of administering propofol or midazolam.

Every two hours after then, the dosage of sedatives was adjusted—or sooner if the patient remained agitated—so that SAS 5. Sedative infusions were then stopped during the next shift (morning, afternoon, or night) in an effort to keep the patient awake once again.

Patients in group B were given midazolam at a dose of 0.5 to 5 mg or 0.01 to 0.05 mg/kg over 2-3 minutes, repeated at intervals of 10 to 15 until the desired level of sedation was reached, but only when they became agitated with an SAS of 5 or higher. Patients in group B did not receive any continuous sedation from the time of intubation and/or admission.

To achieve an SAS objective of 3 to 4, which indicates that the patient was awake or quickly aroused by verbal or mild physical stimulation, midazolam would be administered to the daily continuous group. A minimum of three SAS would be recorded per day. Sedative and opioid infusions were stopped by bedside nurses every morning following the shift

change (7 am) until patients were awake and able to follow basic instructions (open their eyes, look at the clinician, squeeze the hand, open their mouth).

Only if the patient became agitated (SAS 5), the sedative infusion was resumed at half the previous dosage. The infusion was also continued at half the previous dosage and titrated to an SAS of 3 to 4 if feasible if the patient became agitated after the sedative was interrupted and was unable to follow instructions. Only if the patient was agitated (SAS 5) throughout that day were sedative infusions adjusted. Every two hours, the numeric scale was used to assess pain. It was handled the same manner as in the group receiving intermittent sedation. Haloperidol was administered as previously mentioned in cases of probable delirium, which is defined as agitation without a clear explanation after the injection of fentanyl.

Positive end-expiratory pressure (PEEP) was set at 5 cmH2O and inspiratory fraction of oxygen was 0.4. If the patient was hemodynamically stable (mean arterial pressure 65 mmHg, no significant use of norepinephrine or dobutamine, respiratory rate 35/min, PaO2/FiO2 ratio > 150), a spontaneous breathing trial (T-tube trial) would be performed. If the patient needed to be reintubated, the preceding randomised group process was followed once again.

Outcomes:

The main goal of this investigation was to determine the entire MV duration (time in days from intubation to successful extubation, defined as no requirement for reintubation).

ICU and hospital mortality, ICU and hospital length of stay, incidence of delirium, nurse workload, rate of re-intubation, percentage of time on target sedation monitored by SAS [11], accidental catheter removal rates, tracheostomy rates, total sedative doses per patient, variations in hemodynamic and ventilator variables, and total sequential organ failure assessment (SOFA) score [12] were the secondary outcomes.

Statistical Analysis

Statistical evaluation was carried out using SPSS version 25. (IBM Inc., Chicago, IL, USA). In order to determine whether parametric or nonparametric statistical testing should be utilised, the distribution of quantitative data was tested using the Shapiro-Wilks normality test and histograms. The three groups' parametric variables were compared using the F test, with the post hoc (Tukey) test used to compare each pair of groups separately. Parametric variables were represented as mean and standard deviation (SD). The paired T test was used to examine comparisons between two variables within the same group. The Kruskal-Wallis test was used to evaluate non-parametric variables, which were reported as the median and interquartile range (IQR). Mann-Whitney (U) test was then used to compare each pair of groups. Wilcoxon test was used to compare two variables within the same group. Categorical variables were statistically examined using the Chi-square test and presented as frequency and percentage. Statistical significance was defined as a two-tailed P value 0.05.

Results

No statistically significant difference was found between both groups regarding baseline characteristics, diagnosis at admission and reasons for intubation (table.1)

Table (1) Baseline characteristics, diagnosis at admission and reasons for intubation of the studied groups

		Group A (n=50)	**Group B (n=50)**	**P value**
Age (years)	**Median (IQR)**	41 (36 - 49)	44 (38 - 50)	0.309
Weight (kg)	**Median (IQR)**	69 (64 - 74.75)	71 (66 - 76.75)	0.544
Sex	**Male**	21 (42%)	27 (54%)	0.23
Serum creatinine (µmol/L)	**Median (IQR)**	161.25 (157.3 - 167.4)	165.8 (158.8 - 171.23)	0.176
Bilirubin (µmol/L)	**Median (IQR)**	34.75 (30.83 - 38.5)	32.6 (28.95 - 36.88)	0.073
APACHE II	**Median (IQR)**	20 (18 - 24.75)	20.5 (18.25 - 25)	0.264
PaO_2/FiO_2 (mmHg)	**Median (IQR)**	184.5 (128.5 - 272.25)	195.5 (110 - 244.75)	0.741

Source of admission	**Emergency department**	27 (54%)	21 (42%)	0.304
	Wards	17 (34%)	26 (52%)	
	Surgical room	4 (8%)	2 (4%)	
	Other ICU	2 (4%)	1 (2%)	
Diagnosis at admission	**Respiratory failure**	25 (50%)	28 (56%)	0.243
	Sepsis syndrome	24 (48%)	18 (36%)	
	Cardiogenic shock	1 (2%)	4 (8%)	
Reasons for intubation	**ARDS**	16 (32%)	13 (26%)	0.247
	Sepsis syndrome	15 (30%)	12 (24%)	
	Pneumonia	9 (18%)	16 (32%)	
	Acute pulmonary edema	6 (12%)	2 (4%)	
	Other	4 (8%)	7 (14%)	

Nurses' workload was evaluated by NAS. By following the score in each group separately at three different days, it was significantly decreased after 2 and 5 days of MV when compared to NAS at day 1 (P<0.05) while it was comparable between the 2nd and 3rd day measurements.By comparing between both groups, NAS was significantly different being lower working with patients on intermittent sedation as compared to those on continuous sedation within 3 days of follow up (P values <0.001) as shown in table.2

Table (2) Evaluation of nurses' workload in the first 3 days of MV according to the type of sedation

		Group A	Group B	P between groups
NAS	**Day 1**	60 (58 - 63) [a]	51 (48 - 57) [a]	**<0.001***
	Day 2	53 (48 - 58) [b]	45 (44 - 52) [b]	**<0.001***
	Day 3	50 (47 - 51.75) [b]	44.5 (43 - 49) [b]	**<0.001***
P between measurements		**<0.001***	**<0.001***	**---**

Patients on intermittent sedation had significantly higher SAS compared to those on continuous sedation (P<0.001). Regarding reintubation, it was performed at a significantly lower rate in patients receiving intermittent sedation as compared to those on continuous sedation [P= 0.016, RR (95%CI): 9 (1.184: 68.423)]. Intermittent sedation was associated with significantly shorter time on MV, hence shorter durations of ICU and hospital stay when compared to continuous sedation (P values<0.001). Other parameters were comparable between both groups. (table.3)

Table (3) Outcome, hemodynamic, ventilator properties, duration of hospital stay, mechanical ventilation and adverse effects of studied patients

		Group A (n=50)	Group B (n=50)	P value
SOFA score	**Median (IQR)**	8.5 (6 - 11)	9.5 (8 - 11)	0.248
SAS	**Median (IQR)**	3 (2 - 4)	4 (3.25 - 4)	**<0.001***
Delirium		23 (46%)	18 (36%)	0.309
Reintubation		9 (18%)	1 (2%)	**0.016***
Accidental removal of catheters		2 (4%)	3 (6%)	1.00
Tracheostomy		6 (12%)	3 (6%)	0.487
Mortality		14 (28%)	16 (32%)	0.663
Ventilatory support	**Pressure support**	37 (74%)	44 (88%)	0.074

	Controlled mode	5 (10%)	11 (22%)	
Hemodynamic support	**Norepinephrine**	18 (36%)	27 (54%)	0.07
	Dobutamine	8 (16%)	15 (30%)	
Mortality		14 (28%)	16 (32%)	0.663
Hospital stay (days)		21 (19 - 24.75)	13.5 (12 - 15)	**<0.001***
Length of ICU stay (days)		10 (5.25 - 14.75)	4.5 (3.25 - 5)	**<0.001***
Duration of MV (hr)		105 (98.25 - 109.75)	47.5 (43 - 94.25)	**<0.001***
Adverse effects				
No adverse effects		44 (88%)	47 (94%)	0.509
Hypoxemia		3 (6%)	2 (4%)	
Bag-mask ventilation		1 (2%)	1 (2%)	
Systolic hypotension		2 (4%)	0 (0%)	

Patients receiving intermittent sedation stayed on MV for a significantly shorter time with higher HR of being extubated [median time: 47 hr, HR (95% CI): 4.686 (2.799: 7.847)] as compared to those on continuous sedation [median time: 105 hr, HR (95% CI): 4.686 (0.127: 0.357)] as (P<0.001). (figure.1)

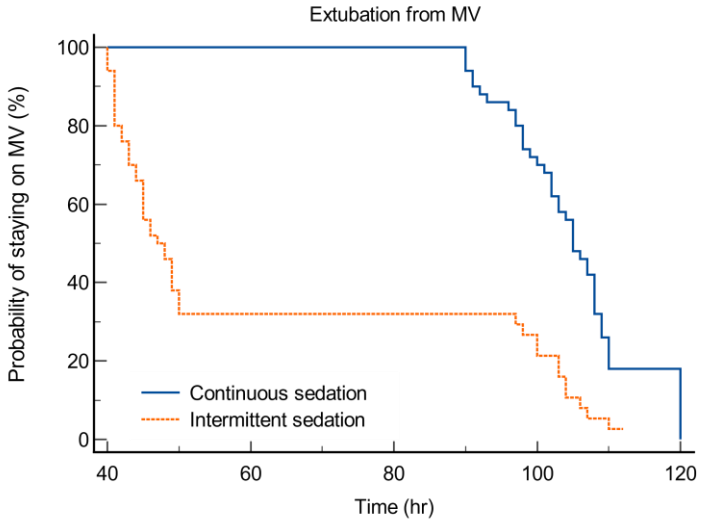

Fig. (1) Kaplan Meier survival analysis of mechanical ventilation according to the type of sedation

By performing simple linear regression for different factors associated with duration of MV: APACHE II score (coefficient: 2.361, 95%CI: 1.175 to 3.548, P<0.001), being reintubated (coefficient: 28.411, 95%CI: 10.134 to 46.688, P= 0.003) and the incidence of delirium (coefficient: 21.222, 95%CI: 10.348 to 32.097, P<0.001) can significantly predict the duration of MV while tracheostomy was not a predictor.

Multiple linear regression showed that APACHE II score (coefficient: 1.436, 95%CI: 0.216 to 2.656, P= 0.022), being reintubated (coefficient: 19.691, 95%CI: 2.335 to 37.047, P= 0.027) and the incidence of delirium (coefficient: 15.742, 95%CI: 5.019 to 26.466, P= 0.004) were significant predictors of MV duration while tracheostomy was not. (table.4)

Table (4) Linear regression of different factors for the prediction of mechanical ventilation duration in the studied patients

	Simple regression			Multiple regression		
	Coefficient	**P value**	**95% CI**	**Coefficient**	**P value**	**95% CI**
APACHE II	2.361	**<0.001***	1.175: 3.548	1.436	**0.022***	0.216: 2.656
Being reintubated	28.411	**0.003***	10.134: 46.688	19.691	**0.027***	2.335: 37.047
Being subjected to tracheostomy	13.813	0.171	-6.063: 33.689	9	0.32	-8.889: 26.89
The incidence of	21.222	**<0.001***	10.348:	15.742	**0.004***	5.019:

delirium	32.097	26.466

Discussion

Regarding reintubation, it was discovered in the current research that patients undergoing intermittent sedation had reintubation at a rate that was much lower than that of patients under continuous sedation. Kollef et alfindings .'s [13] showing reintubation was carried out at a much lower rate in patients undergoing intermittent sedation as compared to those on continuous sedation are consistent with our findings. Carson et alfindings[14] .'s were consistent with our findings in that reintubation was carried out substantially less often in patients receiving intermittent sedation than in those receiving continuous sedation. According to their findings, Nassar and Park et al [15] noted that patients receiving intermittent sedation had reintubation at a considerably lower incidence than those receiving continuous sedation.

As opposed to patients receiving continuous sedation, those receiving intermittent sedation had considerably greater SAS, according to the current research (P 0.001).

Nassar and Park et al.[15] noted that patients receiving intermittent sedation had considerably greater SAS compared to those receiving continuous sedation (P 0.001), which is consistent with our findings.

In the current investigation, it was discovered that there was no statistically significant difference between the two groups in terms of SOFA score, incidence of delirium, inadvertent catheter removal, tracheostomy, or death rate.

Additionally, Schulingkamp et alresearch[16] .'s demonstrated that there was no statistically significant variation in delirium. According to their findings, Carson et al.[14] found that there was no statistically significant difference between the two groups for the SOFA score, incidence of delirium, inadvertent catheter removal, tracheostomy, or death rate. Nassar and Park et al. [15] also noted that there was no statistically significant difference between the two groups for the SOFA score, incidence of delirium, inadvertent removal of catheters, tracheostomy, or death rate, which is consistent with our findings.

In the current research, it was discovered that NAS assessed the workload of nurses. Following each group's score independently on three distinct days revealed that, compared to NAS on day 1, it dramatically dropped after two and five days of MV while being similar between the second and third day assessments. In agreement with our findings, Nassar and Park et al.[15] noted that NAS was equivalent between the second and third day assessments, but dramatically reduced after 2 and 5 days of MV when compared to NAS at day 1. Within 3 days of the follow-up in the current investigation, it was discovered that NAS was considerably different and lower while dealing with patients under intermittent sedation as opposed to those under continuous sedation (P values 0.001). In line with our findings, Nassar and Park et al. [15] noted that, during 5 days of follow-up, NAS was substantially different and lower while dealing with patients under intermittent sedation as opposed to those under continuous sedation (P values 0.001).

It was discovered in the current research that there was no statistically significant difference between the analysed groups in terms of hemodynamic and ventilator characteristics.

Similar to our findings, Nassar and Park et al.[15] emphasised that there was no statistically significant difference between the analysed groups in terms of hemodynamic and ventilator characteristics.

Additionally, Carson et al. [14] noted that there was no statistically significant difference between the study groups in terms of hemodynamic and ventilator characteristics.

It was discovered in the current research that patients receiving intermittent sedation remained on MV for noticeably less time and had a higher HR of being extubated than patients getting continuous sedation (P 0.001).

Kollef et al. [13] also noted that patients receiving intermittent sedation remained on MV for a considerably shorter period of time with a greater HR of being extubated as compared to those receiving continuous sedation (P0.001), which is consistent with our findings.

According to Schulingkamp et al.[16], who found similar findings to ours, patients receiving intermittent sedation remained on MV for a considerably shorter period of time and had a higher HR of being extubated than those getting continuous sedation (P0.001).

In line with our findings, Nassar and Park et al.[15] pointed out that patients receiving intermittent sedation were on MV for noticeably less time and had a higher HR of being extubated than those getting continuous sedation (P0.001).

According to de Wit et al. [17], who conducted research similar to ours, daily interruption of sedatives was linked to a longer duration of MV (almost three days), a prolonged hospitalisation in the intensive care unit (seven days), and a protracted hospital stay (eleven days).

Furthermore, Carson et al [14] noted that patients receiving intermittent sedation (lorazepam) remained on MV for noticeably

less time and had a greater risk of being extubated than patients getting continuous sedation (propofol) (P0.001).

Regarding simple linear regression in the current research for several parameters related to MV duration: While tracheostomy was not a predictor, the APACHE II score may substantially predict the length of MV (coefficient: 2.361, 95 percent CI: 1.175 to 3.548, P0.001). The length of MV for the total research group was shown to be strongly connected with APACHE II scores (Spearman correlation coefficient [SCC]=0.2527, p 0.001), but tracheostomy was not a predictor, according to Kollef at alfindings, .'s which are in accordance with our findings.

Multiple linear regression in the current research revealed that tracheostomy was not a predictor for the length of MV.

According to Kollef at al[13], tracheostomy was not a predictor of the length of MV, which is consistent with our data.

In the current investigation, it was discovered that 3 patients receiving continuous sedation and 2 receiving intermittent type had hypoxemia. Each group only needed one patient who needed bag-mask ventilation. Systolic hypotension occurred in two individuals receiving continuous sedation.

According to their findings (5.3 percent vs. 3.4 percent, p = 0.53), Lee et al.[18]found that four of the 119 patients in the bolus injection group and six of the 113 patients in the continuous infusion of propofol both had hypoxemia. Two patients in each group needed bag mask ventilation, but no patients needed endotracheal intubation (1.8 vs. 1.7 %, p = 1.00).

It is advised that this subject be the subject of further study. As a quality-of-life indicator, we advise measuring the sedation's effectiveness from the patient's viewpoint and offering a long follow-up time. For patients in the ICU receiving MV, the intermediate sedation strategy may be a useful technique since it reduced the amount of time spent undergoing MV, the duration of stay, and the need for medicine without sacrificing sedation level or delirium incidence.

Conclusions

Patients who had intermittent sedation experienced considerably lower rates of reintubation, NAS, brief MV stays, and longer hospital stays than those under continuous sedation, but significantly greater SAS. APACHE II score being reintubated and the occurrence of delirium were shown to substantially predict the length of MV in both simple and multiple linear regression analyses, although tracheostomy was not a predictor. Comparable to the other group, adverse effects included hypoxemia, bag-mask ventilation, and systolic hypotension.

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