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Effective Implementation of a Sedation Weaning Protocol in an Adult Intensive Care Unit

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Abstract

Aim: To evaluate the efficacy of the revised sedation protocol in an adult intensive care unit (ICU).

Materials and Methods: According to the Society of Critical Care Medicine 2013 guidelines, we started to incorporate pain assessment, analgesia-first sedation, and a weaning algorithm into the revised protocol. The target RASS score was −3 to 0 and assessment was performed at 4-hourly intervals. While the choice of medication as directed by a physician, titration of sedation or pain medication was performed by nurses according to the protocol. Midazolam, propofol or dexmedetomidine, and morphine infusion were prescribed at the discretion of the attending physician. After teaching and promulgation, we collected data for 6 months before and after implementation of the change.

Results: 110 patients in the pre- and post-implementation phases were analyzed. There was a reduction in mechanical ventilation (MV) duration (166 hours vs 121 hours; P = 0.012), ICU length of stay (LOS) (10.9 days vs 7.4 days; P = 0.011), average infusion rate of midazolam (0.028 mg/kg/hr vs 0.021 mg/kg/hr; P = 0.008), propofol (0.596 mg/kg/hr vs 0.447 mg/kg/hr; P = 0.019) and morphine (0.026 mg/kg/hr vs 0.019 mg/kg/hr; P = 0.012). There were no differences in the rate of spontaneous breathing trials, consumption of alternative analgesia or adverse outcomes.

Conclusions: Analgesia-first sedation, weaning algorithm, and close collaboration between physicians and nurses are crucial in sedation weaning that effectively reduces MV duration and ICU LOS.

Key words: Analgesia-first sedation; Sedation weaning protocol; Weaning algorithm, Adult intensive care unit, Critical care pain observation tool.

INTRUDUCTION

Association between the duration of sedation administration and that of mechanical ventilation (MV) has been reported and minimizing sedation among intensive care unit (ICU) patients provides clinical benefits [1-5]. A sedation weaning protocol was adopted in our ICU in 2010. We used the Richmond Agitation–Sedation Scale (RASS) [6] as an assessment tool and aimed for a range of −3 to 0. Spontaneous breathing trials (SBT) were attempted when patients were fit for liberation from MV.

In 2016, we took the initiative to review the sedation practice as part of a larger project to reduce the ventilator-associated pneumonia rate in the ICU. The revision of our protocol was based on the application of new knowledge on sedation management in ICU [2,3,5,7]. Changes were promulgated to doctors, and training sessions were organized for nurses, aiming to lighten sedation and allow quicker weaning from MV.

The aim of this study was to evaluate the impact of the revised sedation weaning protocol on the duration of MV, consumption of sedatives and analgesic medications, length of stay, and the occurrence of any adverse outcome in the adult ICU.

MATERIALS AND METHODS

Study Setting

This study was conducted at the ICU of Queen Elizabeth Hospital, which is a tertiary referring hospital in Hong Kong with 1972 acute beds. The ICU is a closed unit with 21 mixed medical and surgical beds with an annual admission of around 1100.

Study Design

We conducted a 'before and after' protocol revision study with a series of measurements over time. Approval was obtained from the ethics committee to extract data for the 6 months before (1st September 2016 to 28th Feb February 2017) and the 6 months after (1st April 2017 to 30th September 2017) implementation of the revised sedation protocol.

With reference to the 2013 Society of Critical Care Medicine (SCCM) Pain, Agitation and Delirium (PAD) guidelines,7 three major changes were incorporated:

1. Inclusion of regular pain assessment by introducing the Critical-Care Pain Observation Tool (CPOT) assessment tool [8].
2. Focus on analgesia-first sedation with analgesics used before sedation to reach the sedative goal.
3. Inclusion of algorithms for the management of pain and over-and under-sedation.

Even if the patient fell on the target RASS score, nurses were encouraged to reduce sedation to ensure the lowest possible sedation was used to achieve the target.

Patients over 18 years of age and mechanically ventilated for > 24 hours were included in this study. Exclusion criteria were patients with raised intracranial pressure; a neurological disease that might affect use of sedation and sedation assessment, e.g. myasthenia gravis, high cervical spinal cord injury, stroke, coma, or dementia; patients requiring deep sedation and neuromuscular blocking agents to facilitate a high level of support, e.g. prone ventilation. Other exclusion criteria included alcohol withdrawal, drug overdose, pregnancy, and known allergies to the sedative agents. Lastly, patients who had been ventilated for more than 48 hours before ICU admission, elective surgery patients on MV < 24 hours, and those in palliative care or treatment limitations were also excluded.

After commencement of MV, all patients received a combination of continuous infusions of sedative (midazolam or propofol) and morphine. Once considered suitable, the sedation was switched to propofol or dexmedetomidine by the attending physician; morphine infusion was switched to intermittent boluses. Sedation assessment was done by nurses at 4-hourly intervals, with a target RASS score of −3 to 0. When patients were sedation-free, the physician proceeded either with SBT or direct extubation.

After revising the sedation protocol, a pain assessment was also performed; the target CPOT score was ≤ 2. Remifentanil was included as part of the armamentarium for analgesia management in the revised sedation protocol. The attending physician continued to take the lead in deciding the choice of sedatives or pain medication and when to switch. After protocol revision, the nurses titrated the pain and sedation medication according to a weaning algorithm to manage over- and under-sedation. For over-sedated patients (RASS −5 to −4) not responding to a decrease in sedation, the infusion was stopped. Even when the target RASS score (−3 to 0) was reached, nurses would continue to wean until complete cessation of sedation. For patients who were weaned off sedation but not ready for extubation, bolus sedation or infusion was started if they became agitated. Oral quetiapine was prescribed as needed.

Data Collection

Patients' demographics, ideal body weight, primary disease category for ICU admission, APACHE II and IV scores, ICU length of stay (LOS), and outcome were collected. MV duration (defined as the time from first intubation to extubation or up to the time of tracheostomy) and daily consumption and duration of sedation and analgesia medication, as well as total dose and sedation-free period, were recorded. Use of alternative drugs for pain relief, medication for delirium, and RASS and CPOT scores were also recorded. Complications related to sedation weaning were recorded. These included self-extubation or removal of medical devices, unstable haemodynamics, ventilator dyssynchrony, agitation, and pain.

The primary endpoint was the MV duration. Secondary endpoints included ICU LOS; consumption of sedation and analgesic medication; the percentage of time the target sedation range was achieved; and complication rate related to sedation/analgesia weaning. All data were extracted from patients' computerized medical records (Philips IntelliSpace Critical Care and Anesthesia, ICCA) and the local clinical information system (CIS).

Statistical Analysis

Based on the findings from a previous study of a 30% reduction in MV duration [9], a power of 80%, 1:1 sample size ratio, and alpha of 5%, the calculated sample size was 198. All analyses were performed using the Statistical Package for Social Sciences for Windows, version 20 (SPSS Inc., Chicago, IL). Means and standard deviations were reported for continuous variables and percentages and frequencies for categorical variables. Continuous variables were compared using a Student's t-test while categorical variables were compared using Pearson chi-square tests or Fisher's exact test as appropriate. All p-values are two-sided. Time to extubation was plotted using Kaplan–Meier survival analysis, and differences between groups were compared with the log-rank test.

RESULTS

Five hundred and eighty-seven patients were admitted during the 6-month period before the protocol was implemented, and 634 were admitted in the 6 months after implementation. In the pre-and post-implementation periods, 178 and 183 patients respectively required MV. Of these 361 patients who required MV, 220 fulfilled the inclusion criteria, 110 in each phase. The two groups were comparable in terms of their age, body weight, gender, primary disease category, and severity of illness as expressed by APACHE II and IV scores (Table 1).

Primary Outcome and Secondary Outcome

The mean MV duration was significantly reduced from 166 to 121 hours (P = 0.012) after revision of the sedation protocol (Table 2). Time to extubation was shorter as shown by the Kaplan–Meier survival analysis (Figure 1). ICU LOS was reduced from 10.9 to 7.4 days (P = 0.011) (Table 2).

Other Secondary Outcomes

Consumption of sedation and analgesia medication

Midazolam, propofol, and dexmedetomidine were the most common sedation medications used; morphine was the mainstay of analgesia control in our ICU.

Among patients receiving midazolam infusion, the mean total dose (Pre: 120 mg vs Post: 70 mg; P = 0.009), infusion duration (Pre: 61 hours vs Post: 38 hours; P = 0.003) and average infusion rate (Pre: 0.028 mg/kg/hr vs Post: 0.021 mg/kg/hr; P = 0.008) were significantly lower in the post-implementation phase (Table 2).

Among patients receiving propofol infusion, the mean average infusion rate (Pre: 0.596 mg/kg/hr vs Post: 0.447 mg/kg/hr; P = 0.019) was significantly lower in the post-

Table 1: Patients' baseline characteristics.

Parameters	Total (N = 220)	Pre (N = 110)	Post (N = 110)	P value
Age (years)	62 ± 15	62 ± 14	62 ± 15	0.982
Body weight (kg)	61 ± 12	62 ± 12	60 ± 12	0.272
Gender male	129 (58.6)	67 (60.9)	62 (56.4)	0.494
Primary diagnosis				
Cardiac	20 (9.1)	10 (9.1)	10 (9.1)	
Gastrointestinal	8 (3.6)	5 (4.5)	3 (2.7)	
Metabolic	6 (2.7)	3 (2.7)	3 (2.7)	
Renal	11 (5.0)	4 (3.6)	7 (6.4)	0.613
Respiratory	69 (31.4)	38 (34.5)	31 (28.2)	
Sepsis	25 (11.4)	8 (7.3)	17 (15.5)	
Emergency postop	75 (34.1)	39 (35.5)	36 (32.7)	
Others	6 (2.7)	3 (2.7)	3 (2.7)	
Speciality				
Medical	93 (42.3)	56 (50.9)	37 (33.6)	
Surgical	99 (45.0)	42 (38.2)	57 (51.8)	
Cardiothoracic	7 (3.2)	3 (2.7)	4 (3.6)	0.144
Ear, nose and throat	10 (4.5)	3 (2.7)	7 (6.4)	
Orthopaedic	8 (3.6)	4 (3.6)	4 (3.6)	
Others	3 (1.4)	2 (1.8)	1 (0.9)	
APACHE IV				
Score	77 ± 31	75 ± 30	78 ± 32	0.433
Risk of death	0.29 ± 0.23	0.28 ± 0.22	0.31 ± 0.25	0.359
APACHE II				
Score	21 ± 8	21 ± 8	21 ± 8	0.682
Risk of death	0.39 ± 0.25	0.40 ± 0.26	0.38 ± 0.25	0.574

Data are presented as mean ± standard deviation or number (percentage) unless otherwise specified.

AED: Accident and Emergency Department; APACHE: Acute Physiology and Chronic Health Evaluation.

Table 2: Patient outcomes and medication consumption

Parameters	Total (N = 220)	Pre (N = 110)	Post (N = 110)	P value
Clinical outcome				
Total MV duration (hours)	143 ± 135	166 ± 163	121 ± 95	0.012
ICU length of stay (days)	9.1 ± 10.1	10.9 ± 12.4	7.4 ± 6.7	0.011
SBT attempts	90 (40.9)	44 (40.0)	46 (41.8)	0.784
Medication consumption				
Midazolam				
Total dose (mg)	95 ± 142	120 ± 164	70 ± 110	0.009
Infusion duration (hours)	50 ± 58	61 ± 64	38 ± 49	0.003
Average infusion (mg/kg/hr)	0.025 ± 0.021	0.028 ± 0.023	0.021 ± 0.018	0.008
Morphine				
Total dose (mg)	92 ± 139	111 ± 159	74 ± 114	0.048
Infusion duration (hours)	51 ± 61	60 ± 68	41 ± 52	0.024
Average infusion (mg/kg/hr)	0.023 ± 0.019	0.026 ± 0.023	0.019 ± 0.016	0.012
Propofol				
Total dose (mg)	2277 ± 3912	2782 ± 4828	1772 ± 2630	0.056
Infusion duration (hours)	50 ± 72	58 ± 89	43 ± 50	0.115
Average infusion (mg/kg/hr)	0.523 ± 0.473	0.596 ± 0.533	0.447 ± 0.392	0.019
Dexmedetomidine (N = 71)				
Total dose (μg)	255 ± 649	279 ± 619	232 ± 679	0.591
Infusion duration (hours)	14 ± 31	15 ± 28	12 ± 34	0.402
Average infusion (μg/kg/hr)	0.279 ± 0.112	0.274 ± 0.114	0.286 ± 0.111	0.647
Use of methadone	8 (3.6)	8 (7.3)	0 (0)	0.007
Use of quetiapine	31 (14.1)	19 (17.3)	12 (10.9)	0.175
Use of other sedatives	7 (3.2)	6 (5.5)	1 (0.9)	0.119
Use of tramadol	85 (38.6)	41 (37.3)	44 (40.0)	0.678
Use of paracetamol	102 (46.4)	46 (41.8)	56 (50.9)	0.176

Data are presented as mean ± standard deviation or number (percentage) unless otherwise specified.

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; MV: mechanical ventilation; SBT: spontaneous breathing trials.

** Weaning decision data available for 212 (96.4%) patients only.

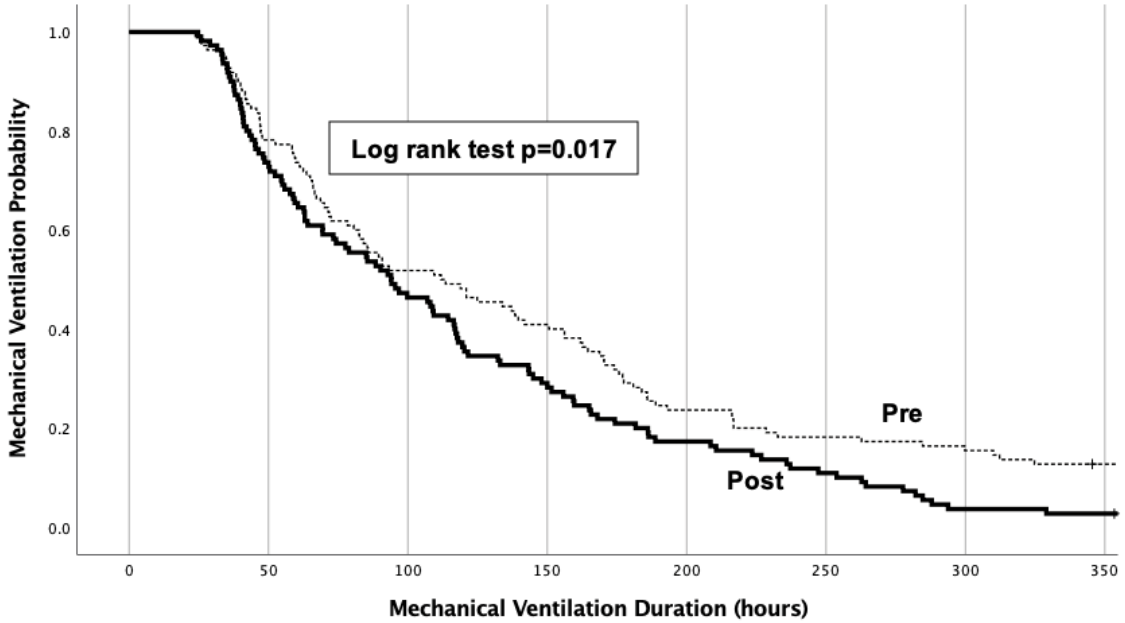

Figure 1: Time to extubation (patients remaining on mechanical ventilation longer than 14 days were censored after day 14).

implementation phase. The mean total dose and infusion duration both decreased but the difference did not reach statistical significance (Table 2).

The consumption of dexmedetomidine was similar in the pre-and post-implementation phases (Table 2).

Among patients receiving morphine infusion, the mean total dose (Pre: 111 mg vs Post: 74 mg; P = 0.048), infusion duration (Pre: 60 hours vs Post: 41 hours; P = 0.024) and average infusion rate (Pre: 0.026 mg/kg/hr vs Post: 0.019 mg/kg/hr; P = 0.012) were significantly lower in the post-implementation phase (Table 2).

A total of eight patients required methadone, all in the pre-implementation phase. The number of patients requiring quetiapine was lower in the post-implementation phase, though the difference was not statistically significant. The number of patients requiring alternative analgesia, e.g. tramadol or paracetamol, was similar in the pre- and post-implementation phases. The duration of the sedation-free period was not statistically different between the two groups.

Percentage of Time a RASS Score in the Target Range was Achieved

The percentage of time during which the RASS score fell within the target range (−3 to 0) was not different between the pre-and post-implementation phases (Pre: 76% vs Post: 77%; P = 0.627) (Table 3). During the initial 14 days of the study period, there seemed to be a higher percentage of RASS score being within the target range in the post-implementation phase, though it was not consistent (Figure 2).

Table 3: Target RASS score and adverse outcomes.

Parameters	Total (N = 220)	Pre (N = 110)	Post (N = 110)	P value
Percentage of RASS readings within the range −3 to 0	77 ± 23	76 ± 22	77 ± 24	0.627
Total sedation-free duration (hours)	28 ± 49	27 ± 50	29 ± 47	0.778
Total sedation-free duration before extubation (hours)	28 ± 49	27 ± 50	29 ± 47	0.778
Adverse outcomes				
Self-extubation	2 (0.9)	1 (0.9)	1 (0.9)	1.000
Self-removal of medical device	4 (1.8)	3 (2.7)	1 (0.9)	0.622
Unstable haemodynamics	9 (4.1)	7 (6.4)	2 (1.8)	0.171
Ventilator dyssynchrony	23 (10.5)	16 (14.5)	7 (6.4)	0.047
Anxiety or agitation	61 (27.7)	35 (31.8)	26 (23.6)	0.175
Pain	6 (2.7)	1 (0.9)	5 (4.5)	0.212

Data are presented as mean ± standard deviation or number (percentage) unless otherwise specified.
ICU: intensive care unit; MV: mechanical ventilation; RASS: Richmond Agitation–Sedation Scale.

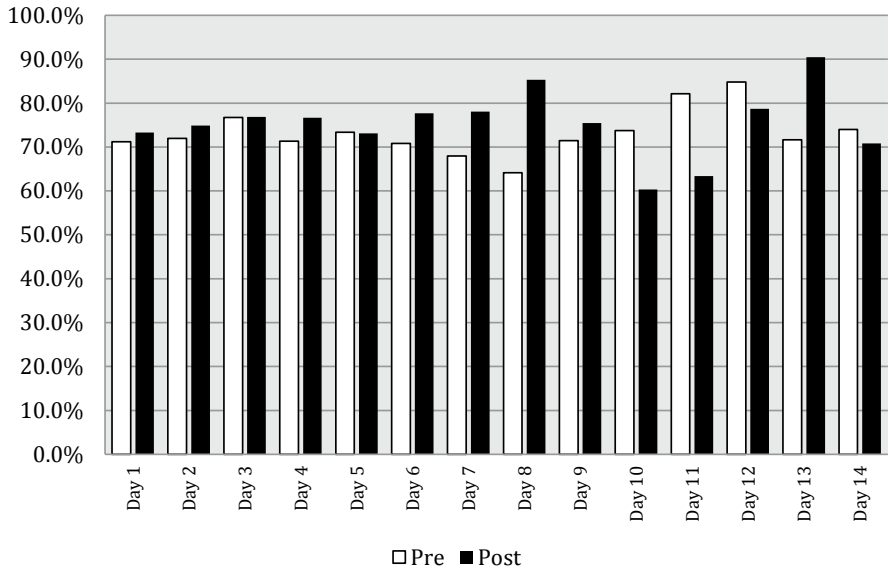

Figure 2: Percentage of RASS scores at target level (0 to −3) for the first 14 days.

Adverse Outcomes

There was no difference in adverse outcomes, including self-extubation, self-removal of medical devices, unstable haemodynamics, anxiety, or agitation. There was a significantly higher incidence of ventilator dyssynchrony in the pre-implementation phase (16 vs 7 episodes; P = 0.047) (Table 3).

DISCUSSION

The 2002 SCCM clinical practice guidelines on sedation [10] were expanded from the first protocol published in 1995 [11] to include 28 recommendations covering analgesia, sedation, and delirium management. Daily sedation interruption became a key strategy in the 2002 guidelines after Kress et al. reported a reduction in ventilation days from 7.3 to 4.9 [1]. This study was further reinforced by two clinical trials, the Awakening and Breathing Controlled Trial in 20085 and the No Sedation in Intensive Care Unit Patients trial by the Demark group in 2010 [2].

Two important recommendations from the 2013 SCCM PAD guidelines [7] are the analgesia-first concept and the benefits of a light level of sedation. To further improve neurological and functional outcomes in MV patients, PAD guidelines were implemented through a care bundle, from the initial ABCDE bundle [12,13] to ABCDEF (Assess, prevent and manage pain (A), Both spontaneous awakening (SAT) and breathing trials (SBT) (B), Choice of analgesia and sedation (C), Delirium: assess, prevent and manage (D), Early mobility and Exercise (E), and Family engagement and empowerment (F)) [14,15]. Finally, two important topics were included in the 2018 PADIS (Pain, Agitation/sedation, Delirium, Immobility and Sleep disruption) guidelines: rehabilitation/mobilization and sleep [16].

A nurse-driven sedation protocol promotes a consistent approach to sedation, improves communication, and eliminates the need for physician orders. The strongest data came from Brook et al., showing MV duration decreased by 1.5 days, and ICU and hospital LOS by 1 and 6 days respectively [17]. A similar benefit of shortening MV and ICU duration was reported in some other studies with the use of nurse-driven protocols [18-20]. However, usage of protocols does not guarantee an improvement in outcome [21]. At least two studies did not show differences in MV duration or ICU LOS, although they might have been underpowered to do so [22,23]. Our sedation protocol differed by having close collaboration between physicians and nurses. The role of the physician was to direct the appropriate choice of sedatives, while nurses were responsible for maintaining the target RASS score. In this study, we achieved a 26.5% decrement of MV duration and a 32.1% reduction of ICU LOS.

Our sedation protocol adjustment also resulted in a significant decrement of midazolam (41.6%), propofol (36.3%), and morphine (33.3%) consumption. We achieved that by adopting the concept of analgosedation in which treatment of pain is the priority before considering sedation for agitated patients. Second, we adopted a sedation algorithm as a tool for nurses to manage over- and under-sedation. More importantly, nurses could wean patients, with a target sedation score of −3 to −0 until the cessation of sedation. Therefore, the patient was given the minimum amount of sedative required. Lastly, physicians' input on the choice of sedation matched the weaning phase of the patient and hastened the whole weaning process.

Instead of using daily interruption of sedation (DIS) to lighten the sedation, we optimized the sedation weaning strategy, especially for those falling in the target sedation range. DIS awakening has been shown to be associated with increased heart rate, blood pressure, and circulating catecholamines [24]. Besides that, DIS has not been consistently associated with reduced MV duration or ICU LOS [25,26]. In one study, DIS was associated with more MV days and resulted in premature termination by the data monitoring committee [27]. Besides that, an increase in nursing workload is another barrier for implementation of DIS [25,28].

The short-acting benzodiazepine midazolam was used in our ICU. Its main indication was in patients requiring deep sedation during the initial ICU admission to facilitate high-level support. Once the patient was fit for weaning from MV, the sedation was changed to propofol or dexmedetomidine which have been shown to shorten time to extubation when compared with midazolam [29-35]. After implementation of the revised sedation protocol, the mean infusion rates of midazolam and propofol were reduced to 0.021 mg/kg/hr (or 0.35 μg/kg/min) and 0.447 mg/kg/hr (or 7.45 μg /kg/min) respectively, low when compared with other published studies [1,33,35,36].

For the choice of sedation, the use of benzodiazepines is associated with more delirium [33,37] while the use of dexmedetomidine-based sedation is associated with

less delirium and physical restraint when compared with standard sedation [33-35]. Early studies comparing dexmedetomidine vs lorazepam in mechanically ventilated patients showed more days alive without delirium or coma (median days, 7.0 vs 3.0; P = 0.01) [34]. Later, the Safety and Efficacy of Dexmedetomidine Compared With Midazolam (SEDCOM) and Dexmedetomidine Versus Midazolam for Continuous Sedation in the ICU (MIDEX) studies showed a similar improvement in reducing MV duration, [33,35] less delirium [33] and an improvement in patients' ability to communicate pain [35]. However, no superiority of dexmedetomidine was shown in a systematic review comparing the efficacy of dexmedetomidine with that of midazolam in ICU patients [38]. A recent large randomized controlled trial comparing early use of dexmedetomidine as the sole sedation agent against the usual care consisting of propofol and midazolam was unable to show any decrease in 90-day mortality, delirium-free days, or ventilator-free days [39]. In our study, we could not demonstrate any relationship between dexmedetomidine and a reduction of MV days, as the doses used in the pre-and post-implementation phases were similar.

We combined the use of morphine infusion with midazolam for a better analgesia and sedation effect. Studies have demonstrated that analgosedation is associated with decreased sedative use, MV duration, and ICU LOS [40-44]. Compared with midazolam-only sedation, co-sedation with midazolam and fentanyl results in fewer hours per day for which the sedation target is not reached and fewer episodes of patient-ventilator asynchrony [45]. Although our unit did not routinely use short-acting opioids like fentanyl or remifentanil, morphine remains popular in most ICUs based on its availability, familiarity, and cost-effectiveness.

Compared with other published studies, the sedation target we adopted was more conservative. A lighter sedation target of −2 to +1 has been promulgated in other studies as well as in the latest 2018 PADIS guidelines [3,16,33]. Lighter sedation is associated with a shorter time to extubation [3,46] and a reduced tracheostomy rate [1]. One would expect an increase in the occurrence of ventilator dyssynchrony once sedation is lightened. We observed an opposite trend. We postulated that it was partly related to the analgesia-based sedation, and partly due to the incorporation of the sedation algorithm to manage under-sedated patients. Lastly, the nurses were more liberal in titrating analgesia and sedation after reinforcement of sedation training.

Our study has several limitations. Firstly, it was a retrospective, 'before and after study from a single-center, thus results could possibly be influenced by factors other than the protocol revision. Nevertheless, there was no change in general patient care or ventilatory strategies between the two study periods. Second, our target sedation range was too conservative. The target RASS score was achieved only 75% of the time and over-sedation might have occurred. A short-acting benzodiazepine was still used for sedation during initial ICU admission and we have not assessed any long-term neuropsychological consequences in our patients. Lastly, we have not assessed the nursing workload after the implementation of these changes.

CONCLUSION

Incorporation of analgesia-first sedation, use of a weaning algorithm, and close collaboration between physician and nurses are important components of an effective sedation weaning protocol. All these decrease MV duration, ICU LOS, and sedative/analgesic consumption in critically ill mechanically ventilated patients.

CONFLICT OF INTEREST

All authors declared no conflict of interests.

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REFERENCES

1. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342(20):1471-1477.
2. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet. 2010;375(9713):475-480.
3. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study*. Crit Care Med. 2013;41(8):1983-1991.
4. Reade MC, Finfer S. Sedation and delirium in the intensive care unit. N Engl J Med. 2014;370(5):444-454.

5. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371(9607):126-134.

6. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal P V., Keane KA, et al. The Richmond Agitation–Sedation Scale. Am J Respir Crit Care Med. 2002;166(10):1338-1344.

7. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263-306.

8. Gelinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420-427.

9. Skrupky LP, Drewry AM, Wessman B, Field RR, Fagley RE, Varghese L, et al. Clinical effectiveness of a sedation protocol minimizing benzodiazepine infusions and favoring early dexmedetomidine: A before-after study. Crit Care. 2015;19(1):1-12.

10. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002;30(1):119-141.

11. Shapiro BA, Warren J, Egol AB, Greenbaum DM, Jacobi J, Nasraway SA, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. Crit Care Med. 1995;23(9):1596-1600.

12. Morandi A, Brummel NE, Ely EW. Sedation, delirium and mechanical ventilation: the 'ABCDE' approach. Curr Opin Crit Care. 2011;17(1):43-49.

13. Pandharipande P, Banerjee A, McGrane S, Ely EW. Liberation and animation for ventilated ICU patients: the ABCDE bundle for the back end of critical care. Crit Care. 2010;14(3):157.

14. Marra A, Ely EW, Pandharipande PP, Patel MB. The ABCDEF Bundle in Critical Care. Crit Care Clin. 2017;33(2):225-243.

15. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at Seven California Community Hospitals: Implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med. 2017;45(2):171-178.

16. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825-e873.

17. Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med. 1999;27(12):2609-2615.

18. Mascia MF, Koch M, Medicis JJ. Pharmacoeconomic impact of rational use guidelines on the provision of analgesia, sedation, and neuromuscular blockade in critical care. Crit Care Med. 2000;28(7):2300-2306.

19. Quenot J-P, Ladoire S, Devoucoux F, Doise J-M, Cailliod R, Cunin N, et al. Effect of a nurse-implemented sedation protocol on the incidence of ventilator-associated pneumonia. Crit Care Med. 2007;35(9):2031-2036.

20. Arias-Rivera S, Sanchez-Sanchez M del M, Santos-Diaz R, Gallardo-Murillo J, Sanchez-Izquierdo R, Frutos-Vivar F, et al. Effect of a nursing-implemented sedation protocol on weaning outcome. Crit Care Med. 2008;36(7):2054-2060.

21. Wall RJ, Dittus RS, Ely EW. Protocol-driven care in the intensive care unit: a tool for quality. Crit care. 2001;5(6):283-285.

22. MacLaren R, Plamondon JM, Ramsay KB, Rocker GM, Patrick WD, Hall RI. A prospective evaluation of empiric versus protocol-based sedation and analgesia. Pharmacotherapy. 2000;20(6):662-672.

23. Bucknall TK, Manias E, Presneill JJ. A randomized trial of protocol-directed sedation management for mechanical ventilation in an Australian intensive care unit. Crit Care Med. 2008;36(5):1444-1450.

24. Kress JP, Vinayak AG, Levitt J, Schweickert WD, Gehlbach BK, Zimmerman F, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. Crit Care Med. 2007;35(2):365-371.

25. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: A randomized controlled trial. JAMA. 2012;308(19):1985-1992.

26. Augustes R, Ho KM. Meta-analysis of randomised controlled trials on daily sedation interruption for critically ill adult patients. Anest Inten Care. 2011;39(3):401-409.

27. de Wit M, Gennings C, Jenvey WI, Epstein SK. Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients. Crit Care. 2008;12(3):1-9.

28. Tanios MA, de Wit M, Epstein SK, Devlin JW. Perceived barriers to the use of sedation protocols and daily sedation interruption: a multidisciplinary survey. J Crit Care. 2009;24(1):66-73.

29. Carrasco G, Molina R, Costa J, Soler JM, Cabre L. Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients. A cost-benefit analysis. Chest. 1993;103(2):557-564.

30. Zhou Y, Jin X, Kang Y, Liang G, Liu T, Deng N. Midazolam and propofol used alone or sequentially for long-term sedation in critically ill, mechanically ventilated patients: A prospective, randomized study. Crit Care. 2014;18(3):1-9.

31. Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. Crit Care Med. 1997;25(1):33-40.

32. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. JAMA. 2000;283(11):1451-1459.

33. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489-499.

34. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. JAMA. 2007;298(22):2644-2653.

35. Jakob SM. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307(11):1151.

36. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med. 2012;186(8):724-731.

37. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21-26.

38. Adams R, Brown GT, Davidson M, Fisher E, Mathisen J, Thomson G, et al. Efficacy of dexmedetomidine compared with midazolam for sedation in adult intensive care patients: A systematic review. Br J Anaesth. 2013;111(5):703-710.

39. Shehabi Y, Howe BD, Bellomo R, Arabi YM, Bailey M, Bass FE, et al. Early Sedation with Dexmedetomidine in Critically Ill Patients. N Engl J Med. 2019;380(26):2506-2517.

40. Devabhakthuni S, Armahizer MJ, Dasta JF, Kane-Gill SL. Analgosedation: a paradigm shift in intensive care unit sedation practice. Ann Pharmacother. 2012;46(4):530-540.

41. Payen J-F, Bosson J-L, Chanques G, Mantz J, Labarere J. Pain assessment is associated with decreased duration of mechanical ventilation in the intensive care unit: a post Hoc analysis of the DOLOREA study. Anesthesiology. 2009;111(6):1308-1316.

42. Chanques G, Jaber S, Barbotte E, Violet S, Sebbane M, Perrigault P-F, et al. Impact of systematic evaluation of pain and agitation in an intensive care unit. Crit Care Med. 2006;34(6):1691-1699.

43. Faust AC, Rajan P, Sheperd LA, Alvarez CA, McCorstin P, Doebele RL. Impact of an Analgesia-Based Sedation Protocol on Mechanically Ventilated Patients in a Medical Intensive Care Unit. Anesth Analg. 2016;123(4):903-909.

44. Rozendaal FW, Spronk PE, Snellen FF, Schoen A, van Zanten ARH, Foudraine NA, et al. Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: a centre randomised, cross-over, open-label study in the Netherlands. Intensive Care Med. 2009;35(2):291-298.

45. Richman PS, Baram D, Varela M, Glass PS. Sedation during mechanical ventilation: a trial of benzodiazepine and opiate in combination. Crit Care Med. 2006;34(5):1395-1401.

46. Treggiari MM, Romand J-A, Yanez ND, Deem SA, Goldberg J, Hudson L, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med. 2009;37(9):2527-2534.