Research Article

No-Sedation in Mechanically Ventilated Chronic Obstructive Pulmonary Disease Patients; A Randomized Controlled Trial.

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Abstract

Purpose: To compare no-sedation versus daily interruption of sedation (DIS) in COPD patients receiving mechanical ventilation upon the ventilator-free days. **Martials and methods:** Patients were randomly assigned to either DIS (n=50) or no-sedation (n=47) (intervention group). Patients failed to be managed by no-sedation strategy (n=9, 19.1%) were shifted to DIS, but analyzed in their parent group (intention to treat principle). Ventilator-free days was the primary outcome measure. Secondary outcome measures included: length of stay in the hospital and in intensive care unit (ICU), the incidence of ventilator-associated pneumonia (VAP), and weaning process (simple, difficult or prolonged). Nurse workload was assessed by the visual analogue scale (VAS). **Results:** no significant difference was found in ventilator-free days between DIS and no-sedation (mean 19.9 vs. 21.5 days, P=0.6). As well, we found no significant difference in length of ICU stay (P=0.7) and hospital stay (P=0.4). There was no significant difference in the incidence of VAP (P=1.0) nor in the weaning process (simple, difficult or prolonged) (P=0.328) between the two groups. The no-sedation group showed a higher nurse workload in comparison to the DIS group. (4.38 vs. 5.69, P<0.001). **Conclusions:** No-sedation protocol can be used safely in COPD patients with respiratory failure, but with no influence upon the ventilator-free days.

Keywords: COPD; Sedation; Mechanical ventilation.

Introduction

Mechanical ventilation implies a stressful situation for critically ill patients. Pain and discomfort are commonly encountered in these patients due to many factors, such as cannulation, endotracheal tube, urinary catheter, interventions, cellulitis, and bed sores[1,2]. Furthermore, frequent noises and alarms result in sleep deprivation that has deleterious cofounding effects on such critically ill patients. All these factors can result in anxiety and agitation. Accordingly, sedation is an integral part in the treatment of mechanically ventilated patients[3,4].

The world is moving towards minimizing sedation in critically ill patients. This principle is clearly shown up in the eCASH concept recently suggested by Vincent and colleagues which components include promotion of early comfort, administration of proper analgesia, minimization of sedation, and humane care[3]. There are many protocols for administering sedation in intensive care units (ICUs). Daily interruption of sedation has been first described by Kress and colleagues in 2000[4]. DIS has beneficial effects as decreased duration of mechanical ventilation and ICU stay which have been mentioned in previous literature[5-9]. Previous randomized controlled trials have been done in general ICUs including either medical or surgical patients or both[7-11]. However, the optimum method of sedation administration in patients with COPD is still unknown.

COPD patients represent the majority of patients admitted to our respiratory ICU. This group of patients usually present with hypercapnic (chronic type II) respiratory failure which may result in depression of the respiratory center[10,11]. Administration of sedative, hypnotic and narcotic drugs in such group of patients may aggravate their condition. The safety of using DIS or no-sedation in COPD patients has not known yet.

This study aimed to detect the optimum method of administering sedation in COPD mechanically ventilated patients and to detect the safety and efficacy of no-sedation versus DIS in

this category of patients with ventilatory failure. **Primary outcome** compared the ventilator-free days in each group. **Secondary outcome** included ICU stay, the incidence of complications, the difficulty of weaning, and nursing workload.

Patient and Methods

This study is a prospective randomized controlled trial, adhered to Good Clinical Practice, and declaration of Helsinki. Firstly; local ethics committee approved the study, and then it was registered at Clinicaltrials.gov under the number of (NCT03406936). It was conducted in the respiratory intensive care unit (RICU) of Assiut university hospital, Egypt. (Thirty beds, and nurse patient ratio is 1:2).

One hundred adult patients with COPD (Already were previously diagnosed as COPD patients; Post- bronchodilator FEV1/FVC< 70, and under follow through the department outpatient clinic) exacerbation admitted to the RICU and required invasive mechanical ventilation were recruited. Exclusion criteria included known allergy to midazolam (the sedative which would be used), renal or hepatic impairment, proven or suspected psychiatric or neurological impairment, pregnancy, or if the patients met criteria for weaning from the ventilator (FiO_2 ≤40% and positive end-expiratory pressure of 5cm H_2O). Informed consent was taken from the legal representative of all patients. Randomization was attained through a web-based randomizer, and the patients were assigned equally into one of the two study groups within 24 hours after intubation as following:

Group A (control group): The patients were managed by DIS (Fig.1). Richmond agitation and sedation score (RASS)[12] was used for monitoring of the depth of sedation. Midazolam was started at an infusion rate of 1–2 mg/hr. which was increased by 1–2 mg/hr. till RASS reached - 4 or -5. Sedation interruption was allowed at 7:00 AM. Infusion resumed at 50% of the prior rate if signs of discomfort occurred, with the midazolam infusion rate adjusted to achieve a score of −3 to 0. Signs of discomfort included agitation (RASS ≥ 1), rise in respiratory rate > 35 breaths/min, decrease oxygen saturation < 90%, rise in heart rate > 140 beats/min, or a change ≥ 20% of the baseline, systolic blood pressure > 180 mm Hg, and/or marked anxiety and diaphoresis. Patients receiving neuromuscular blocking agents did not have sedative or analgesic infusions interruption, and the physician made decisions about adequate sedation. Patients were considered to be "awake" when they had the ability to do three out of four simple tasks on request: open their eyes, squeeze the hand, look at the investigator or put out their tongue[10].

Group B (The intervention group): This group of patients was managed with the no-sedation protocol (Fig 2). If agitation occurred, searching for a cause of patient discomfort was carried out (e.g., tube obstruction or migration, hypoxia, and pain), and managed accordingly. The patient was reassured and allowed to see his relatives for psychological support if needed, and physical restraints were never used. If the patient remained agitated, he/she received iv. a bolus of midazolam of 0.5–5 mg as needed to get comfortable and calm. Afterwards, we started a new trial of management with no sedation; if the sedation has to be repeated three times, we kept the patient sedated by DIS protocol according to the control group protocol. We did not allow crossover between the groups. We kept the shifted patients to the DIS protocol after failure of no-sedation protocol in their parent group according to the intention to treat principle[13].

Ventilator-associated pneumonia (VAP) is defined as pneumonia which occurs after 48 hours after endotracheal intubation[14]. Delirium assessment was based on the 5th edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-V)[15]. Medical treatment for COPD patients included: nebulized salbutamol and nebulized ipratropium bromide, which were administered by a connected piece to the ventilator circuit. Patients were weaned from the ventilator at the discretion of the clinical team; however, pressure support with positive end-expiratory pressure (PEEP) could be used for weaning. When the weaning criteria were met, the attending physician was notified and a 1-hr. trial of spontaneous breathing (SBT) was initiated, during which, the ventilatory support was withdrawn and the patient breathed spontaneously at the previous FIO_2, using flow triggering and continuous positive airway pressure of 5 cm H_2O. The SBT was terminated if the patient developed any sign of failure for > 5 minutes.

Outcome measures included ventilator-free days (Number of days from day-1 to day-28) on which the patient did not need assistance to his breathe; however, if death occurred or the patient dependent on ventilator > 28 days, the value was considered 0[16]. Other data collection involved the time to successful extubation, duration of stay in the respiratory ICU, duration of stay in the hospital, total midazolam consumption, ease of weaning process (simple, difficult or prolonged weaning), other complications (VAP, Venous Thromboembolism, and or pneumothorax), delirium, and mortality rate. Visual analogue scale (VAS) was assessed by nurses working in the ICU unit to represent the workload of both protocols.

Statistical analysis

Calculation of sample size was based on our primary outcome (ventilator-free days). A power calculation was estimated to detect an effect size of 0.8 of difference between means of two independent groups with a p-value >0.05 and 99% power, a sample size of 45 patients for each group was needed (G*Power program), so, totally 100 participants were enrolled. All data were recorded in a special chart for every patient and analyzed by computer program IBM, SPSS (Statistical Package for Social Sciences), Version 23, 2015.

Firstly; the data were examined through the Anderson-Darling test for normality and homogeneity variances. We descried categorical variables as a number or a ratio, whereas continuous variables were described as mean and standard deviation (SD) or error (SE), or median and interquartile range. Comparison of continuous variables was performed using independent t-test (Parametric data) or Mann Whitney U test and Wilcoxon Ranks Test (Non-parametric data). Proportions were compared with chi square test. The p-value <0.05 was considered statistically significant.

Results

Ninety-seven patients have been studied and analyzed (Fig. 3). The patients in both groups were comparable as regards demographic data, clinical, and patient characteristics with non-significant differences in between. Midazolam consumption was significantly higher in the DIS group.

The mean ventilator-free days for the no-sedation group was higher (21.45 ± 3.13 days) when compared to the sedation group (19.94 ± 2.82 days), however, it did not reach a significant difference.

Duration of mechanical ventilation, as well as the ease of weaning processes, showed insignificant differences between the groups (Table 2). The ICU stay and hospital stay showed insignificant differences between both groups as well. As regard mishaps and complications, the incidence of self-extubation was significantly higher in non-sedated patients in comparison to DIS group, otherwise, no significant difference was detected between groups as regard to delirium, mortality rate, VAP, VTE or other complications (Fig. 4). Two patients needed tracheostomy in group B.

We recorded a mortality rate within the extubated patients 50% in group A and 16% in group B with non-significant difference p-value of 0.28.

A significantly higher nurse workload in the no-sedation group in comparison to the DIS group was found (4.38 ± (p-value<0.001) (Fig. 5)

Nine patients (19.1%) could not tolerate no-sedation strategy. They were managed by DIS protocol.

Table (1): Demographic data and clinical characteristics of the participants

Variables	**Group A** (n=50) DIS	**Group B** (n=47) No sedation	**P- value**
Gender (Male/ female)	41/9	33/14	0.17
Age (years)	63.5±8	62.4±9	0.08
Residency (Urban /Rural)	13/37	12/35	0.9
Occupational risk*	24 (48%)	21 (44.7%)	0.7
Smoking Status			
▪ Non smokers	10 (20%)	14 (29.8%)	
▪ Current smokers	18 (36%)	21 (44.7%)	0.15
▪ X-smokers	22 (44%)	12 (25.5%)	
Smoking index			
▪ Mild smokers	2 (5%)	0 (0)	
▪ Moderate smokers	11 (27.5%)	8 (24.2%)	0.387
▪ Heavy smokers	27 (67.5%)	25 (75.8%)	
Indications of mechanical ventilation			
▪ CO_2 narcosis	28 (56%)	25 (53%)	
▪ Refractory hypoxemia	10 (20%)	9 (19%)	0.92
▪ Sever respiratory distress	12 (24%)	13 (28%)	
Comorbidities:			
▪ Cor pulmonale	30 (60%)	25 (53.2%)	0.499
▪ DM	5 (10%)	8 (17%)	0.310
▪ Hypertension	9 (18%)	15 (31.9%)	0.112
▪ Ischemic heart	5 (10%)	7 (14.9%)	0.464
▪ Cardiac dysrhythmias	2 (4%)	2 (4.3%)	1.000
▪ Bronchiectasis	3 (6%)	3 (6.4%)	1.000
▪ Obstructive sleep apnoea	3 (6%)	0 (0.00)	0.243
Exacerbation/year median (range)	2 (0-5)	3 (0-6)	0.3
The need for vasopressors	12	13	0.4
Midazolam dose (mg)	17.88 ±1.80	5.75 ±1.32	0.001
SOFA score	7.4±1.6	7.7±1.7	0.6
APACHE score	18.7±0.3	19.6±3.8	0.2
Mortality risk (%)	31±1.5	32±1.7	0.5

Data are expressed as mean ± SD, number, ratio, percentage.
Group A: daily interruption of sedation, Group B: no sedation.
P-value<0.05 is considered statistically significant.
*****Risky occupations include: farmer, worker in construction, cleaner, coffee worker, carpenter, bbaker and animal worker. APACHE: Acute Physiological and Chronic Health score.
DM: Diabetes Mellitus, IHD: Ischemic Heart Disease, OSA: Obstructive Sleep Apnea, SOFA: Sequential Organ Failure Assessment.

Table (2): Primary and secondary study outcomes

Variables	**Group A** (n=50) DIS	**Group B** (n=47) No sedation	p-value
Ventilator free days	19.94 ±2.82	21.45 ± 3.13	0.6
Duration of MV (Days)	5.96 ± 0.53	5.26 ± 0.42	0.5
Simple weaning **Difficult weaning** **Prolonged weaning**	30 (60%) 9 (18%) 4 (8%)	25 (53.2%) 10 (21%) 3 (6.4%)	0.33
ICU stay (Days)	10.60 ± 0.89	9.92 ±0.80	0.7
Hospital stay (Days)	20.44 ± 1.46	17.79 ± 1.05	0.4

Data are expressed as mean ± SE, number and percentage. DIS daily interruption of sedation, MV mechanical ventilation, VAP ventilator associated pneumonia, VTE venous thromboembolism. P-value<0.05 is considered statistically significant.

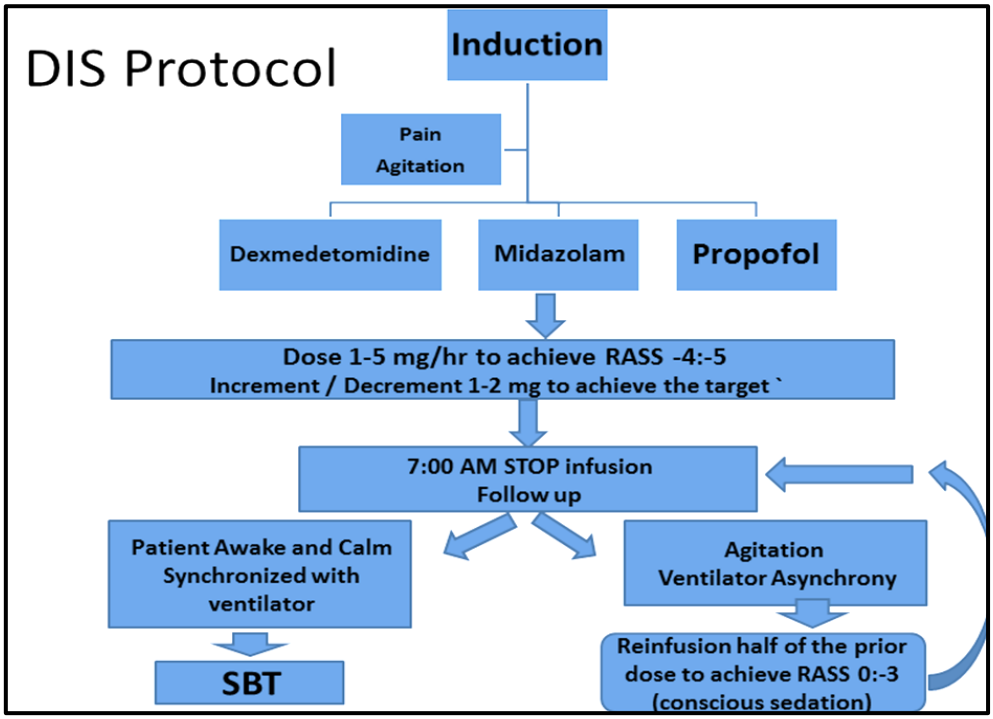

Figure 1: Daily interruption of sedation (DIS) protocol

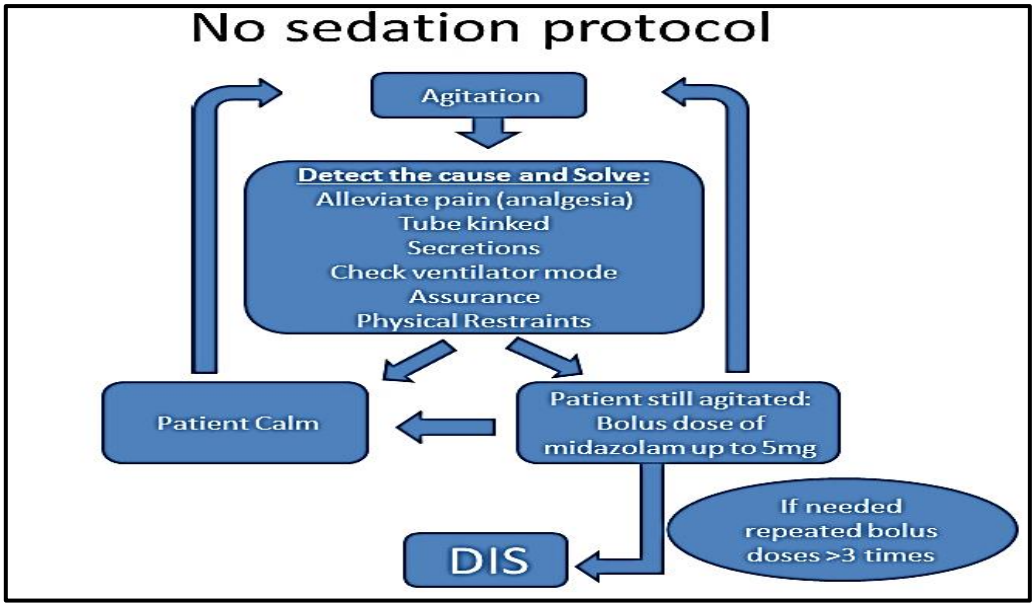

Figure 2: No sedation protocol

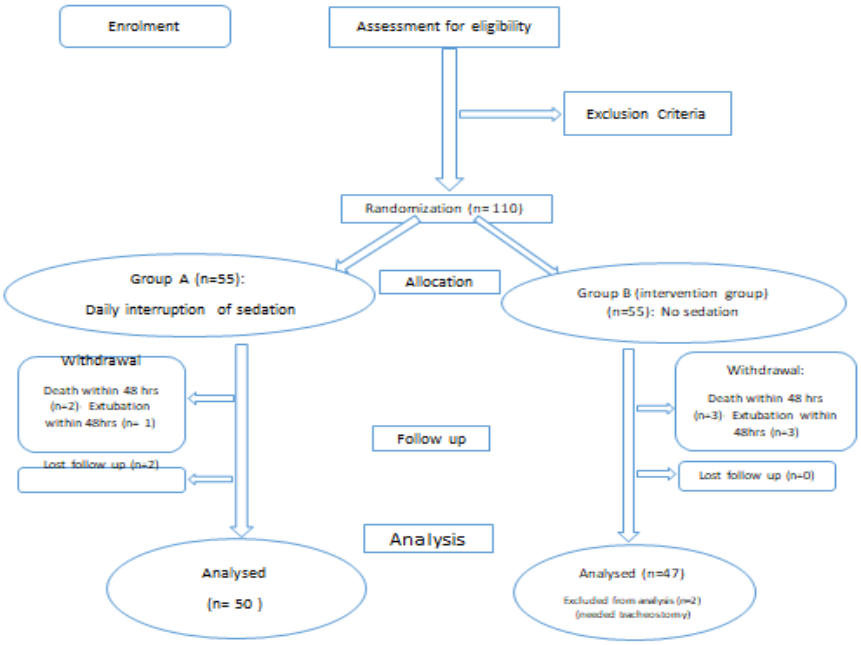

Figure 3: CONSORT flow chart of the participants

Caption: data are expressed as number of the patients. VAP ventilator associated pneumonia, VTE venous thromboembolism

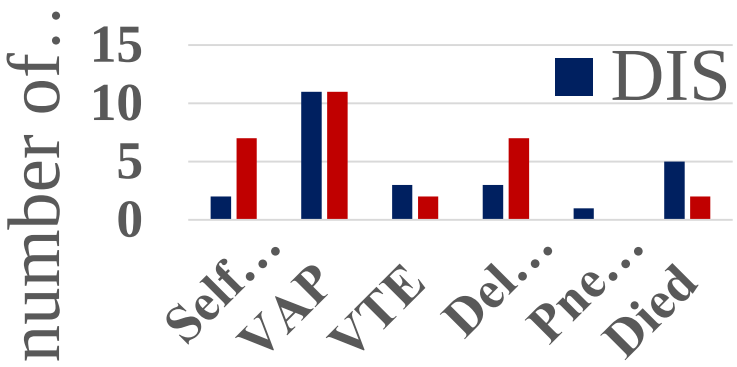

Figure 4: Complications during the study in both groups

Caption: data are expressed as median and interquartile range. VAS visual analog scale. P<0.05 is considered as statistically significant.

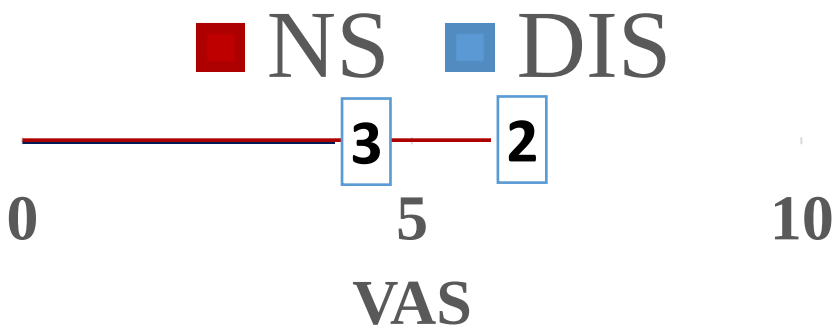

Figure 5: Nurse workload

Discussion

In the present study, we found that in the critically ill COPD patients receiving mechanical ventilation, a protocol of no-sedation offered a higher number of ventilator-free days compared with DIS protocol but with a non-significant difference. The use of no-sedation protocol was also associated with a decrease in the ICU stay and the hospital stay, but still, this difference was not statistically significant.

Daily interruption of sedation and protocolized sedation have been studied for years and shown significant benefits as regards outcome and safety with respect to adverse events such as accidental extubation, extubation failure and long-term psychological outcomes[17-19].

No-sedation protocol has been first suggested by Strøm and colleagues[13]. Their study enrolled 140 patients, 27 patients were excluded from analysis due to early death or extubation (55 analyzed in the no-sedation group, and 58 in the group managed by DIS). They found that no-sedation protocol significantly increased the number of ventilator-free days, despite the increased risk of agitation. The results of the

current study disagree with their study, and this could be explained by the fact that Strøm and his colleagues used an opioid-based sedation protocol, rather than actual no-sedation strategy[20,21]. On the other hand, because our patients were diagnosed as COPD and most of them have hypercapnia, morphine was averted to avoid respiratory center depression. Furthermore, Strøm and colleagues conducted their research on general ICU patients with different medical problems, in contrast to the present study.

Some studies compared DIS with a specified sedation protocol[6,8-11]. Moreover, many studies have suggested that patient outcome and duration of MV is not affected by the type of the protocol used for sedation which agrees with our results[7,8,22].

The results of the current study comes in agreement with another Canadian, multicenter, randomized controlled trial conducted by Mehta and colleagues, which included 423 patients in 16 tertiary care medical and surgical ICUs. They compared protocolized sedation versus DIS. They found no difference in time to successful extubation, ICU and hospital length of stay[8].

The results of this study are in agreement with the Brazilian study conducted by Nassar and coworkers[23]. They compared intermittent sedation and DIS regarding the number of ventilator-free days. This study results stated that there was no difference in the number of ventilator-free days between intermittent sedation and DIS in 28 days. Collected results support that lighter sedation approaches may be feasible and safe even in lower nursing staff level ICUs.
The present study is also in alignment with the meta-analysis conducted by Burry and colleagues that aimed to assess the effectiveness of DIS. They compared both sedation protocols as regards the duration of mechanical ventilation. Their study revealed no differences between both approaches regarding this outcome[22].

Self-extubation is a common fear in protocols which minimize sedation. In the present study, it was found that the accidental removal of the endotracheal tube was significantly higher in the no-sedation group which agrees with this concept. This is not in agreement with the meta-analysis conducted by Junior and Park which suggested a low incidence of accidental extubation[11]. This difference can be explained by the difference in study design between the present study and those included in the meta-analysis. Kress and colleagues found that self-extubation was low and did not differ significantly between the intervention group (DIS) and the control group (continuous sedative infusion)[6].

Regarding incidence of VAP, no significant difference was found in the present study between the two groups, which agrees with Strøm and colleagues' study, where they stated that no-sedation had not increased the risk of VAP (12% vs. 11%)[13]. However, overall rates are higher in our study (22% vs. 23.4%).

In the present study, no significant difference was found in the incidence of venous thromboembolism between the two groups. This is not in agreement with Schweickert and colleagues' study who noted a deceased risk of VTE in patients managed by DIS[24]. The obvious difference in the design between the present study and that of Schweickert (Retrospective study), as well as, the sample size could explain the disagreement.

The incidence of delirium was of higher incidence in the no-sedation group, but with statistical insignificance. Strøm and associates' trial found that the incidence of delirium was significantly higher in the no-sedation group (20%) when compared to DIS (7%)[10]. They have used the same protocol for assessment and diagnosis of delirium we have used; however, the disagreement between the two studies could be due to smaller sample size in our work. The present study agrees with the multicenter trial conducted by Mehta and colleagues in 2012 which found no significant difference in rates of delirium between protocolized sedation and DIS[8,9].

In general, the differences between the present study and others can also be explained by the variation in study characteristics which is recognized from the high statistical heterogeneity revealed in the analysis of different outcomes. Racial, gender and medical differences could affect the metabolism of drugs are described as well[25].

In the current study, it was found that no-sedation strategy increased nurse workload. This agrees with Strøm and colleagues' study, who suggested the need for one more professional nurse per patient in the no-sedation group[13]. Our concept is not with an agreement with the conclusion of the multicenter study which compared no-sedation versus sedation with daily wake up trial (521 patients randomized in 7 centres) and mentioned that no-sedation strategy can be implemented easily in centers with no or limited experience in no-sedation strategy[26]. This can be explained by the high nurse: patient ratio which is available in Scandinavian countries, where their study had been conducted. No-sedation protocol may be not suitable for ICUs in developing countries with a low nurse: patient ratio, especially with limited experience.

The systematic review and meta-analysis which had done by Nassar and coworkers also showed no significant differences in nursing workload between groups during the first five days of mechanical ventilation[23].

In the present study, it was noted that health care professionals including doctors and nurses prefer using sedation with daily interruption rather than no-sedation. Health care professionnals have a good experience with DIS which because it was associated with improved patient compliance on ventilator and better clinical and hemodynamic parameters. This finding is in agreement with Mehta and colleagues who concluded that approval of the sedation protocol was similar for physicians and nurses who participated in the study[8].

Limitations: The relatively small sample size may underestimate the incidence of delirium and the need for tranquillizers. Follow up of cognitive and behavioural changes is recommended in the no-sedation group after hospital discharge.

Conclusions: No-sedation protocol can be used safely in COPD patients with respiratory failure but with no influence upon the ventilator-free days. Meticulous and sufficient nursing care should be offered in such patients to avoid self-extubation and nurse workload.

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