Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicenter cohort study

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Abstract

Introduction: Sedation overuse is frequent and possibly associated with poor outcomes in the intensive care unit (ICU) patients. However, the association of early oversedation with clinical outcomes has not been thoroughly evaluated. The aim of this study was to assess the association of early sedation strategies with outcomes of critically ill adult patients under mechanical ventilation (MV).

Methods: A secondary analysis of a multicenter prospective cohort conducted in 45 Brazilian ICUs, including adult patients requiring ventilatory support and sedation in the first 48 hours of ICU admissions, was performed. Sedation depth was evaluated after 48 hours of MV. Multivariate analysis was used to identify variables associated with hospital mortality.

Results: A total of 322 patients were evaluated. Overall, ICU and hospital mortality rates were 30.4% and 38.8%, respectively. Deep sedation was observed in 113 patients (35.1%). Longer duration of ventilatory support was observed (7 (4 to 10) versus 5 (3 to 9) days, \( P = 0.041 \)) and more tracheostomies were performed in the deep sedation group (38.9% versus 22%, \( P = 0.001 \)) despite similar PaO2/FiO2 ratios and acute respiratory distress syndrome (ARDS) severity. In a multivariate analysis, age (Odds Ratio (OR) 1.02; 95% confidence interval (CI) 1.00 to 1.03), Charlson Comorbidity Index >2 (OR 2.06; 95% CI, 1.44 to 2.94), Simplified Acute Physiology Score 3 (SAPS 3) score (OR 1.02; CI 95%, 1.00 to 1.04), severe ARDS (OR 1.44; CI 95%, 1.09 to 1.91) and deep sedation (OR 2.36; CI 95%, 1.31 to 4.25) were independently associated with increased hospital mortality.

Conclusions: Early deep sedation is associated with adverse outcomes and constitutes an independent predictor of hospital mortality in mechanically ventilated patients.
Introduction
Sedation is an important component of care for patients under mechanical ventilation (MV) in the ICU. Significant distress is related to MV itself or to routine procedural interventions [1] and minimizing pain, anxiety and distress is a major recommendation in recent guidelines [2]. Pain and anxiety control is usually obtained with analgesics and sedatives that ensure comfort, improve synchrony with the ventilator and decrease work of breathing [3]. Some studies, however, have shown that oversedation is associated with poor outcomes, including delirium, prolonged MV, ventilator-associated pneumonia, long ICU and hospital length of stay [3-6], posttraumatic stress disorder [7] and cognitive impairment [8,9] as well as increased costs [10-12]. Nevertheless, the issue of early sedation has seldom been evaluated, especially in randomized controlled studies.

Despite the current recommendations [2], there is still a significant gap between evidence from recent trials and implementation in clinical practice [2,6,13,14]. Moreover, to date no large randomized controlled trials of sedation strategies used mortality as the primary outcome. In addition, clinical trials of sedation have until now enrolled patients mostly after 24 to 48 hours following initiation of MV, resulting in inadequate assessment of early sedation practice and its association with clinically relevant outcomes [15-17].

The aim of this study is thus to describe the association of early sedation strategies (sedation depth and sedative choice) with clinical outcomes of mechanically ventilated adult ICU patients, with hospital mortality as the primary outcome.

Materials and methods
Study design, patient selection and definitions
This study was a secondary analysis of a multicenter prospective cohort conducted in 45 Brazilian ICUs (from the Brazilian Research in Intensive Care Network) from 12 states between 1 June 2011 and 31 July 2011 [18]. Additional file 1 presents the participating ICUs in more detail. In the present study, adult patients (≥18 years old) requiring invasive ventilatory support in the first 48 hours of ICU admission using sedatives on the second day of MV were included.

We excluded patients submitted exclusively to noninvasive MV and those presenting with primary neurological disorders. We also excluded those with missing data regarding sedation depth on the second day of MV. Demographic, clinical and laboratory data were collected during the ICU stay and included cause of respiratory failure, chronic health status, Charlson Comorbidity Index [19], Simplified Acute Physiology Score 3 (SAPS3) [20] and the Sequential Organ Failure Assessment (SOFA) score [21]. Data regarding the need for vasopressors, tracheostomy and renal replacement therapy were also reported. Sepsis diagnosis was made based on current definitions [22]. A patient was considered to have an infection when presenting with suggestive clinical, laboratory, radiographic and microbiological findings that justified the administration of antibiotics (excluding prophylaxis) [23]. Acute respiratory distress syndrome (ARDS) was defined and classified according to the Berlin definition [24].

As the primary study was not designed to evaluate sedation strategies [18], the Glasgow Coma Scale (GCS) – originally reported for SOFA score calculation – was used as a surrogate for sedation depth. Light sedation was defined as GCS ≥9 whereas those patients with GCS <9 were considered deeply sedated. Reliability of GCS as a surrogate for the Richmond Agitation–Sedation Scale (RASS) as well as selection of GCS = 9 as the cutoff value were based on the study by Ely and colleagues that demonstrated an excellent correlation ($r = 0.91$, $P <0.001$) between the GCS and RASS, where GCS = 9 would be equivalent to RASS = −2 [25].

Our primary hypothesis was that early sedation strategies, namely sedation depth, could be associated with clinical outcomes including hospital mortality, so we chose to evaluate the sedation level on the second day of MV.

The study was approved by the institutional review board of Hospital Sírio-Libanès at the coordinating center (Comitê de Ética em Pesquisa; approval number HSL 2010/51) and subsequently by local review boards. Additional file 1 describes the local review boards by participating hospital. Due to the observational nature of the study, the following institutions waived the need for informed consent: Comitê de Ética em Pesquisa – Hospital São Camilo; Comitê de Ética em Pesquisa – Hospital Sírio-Libanès; Comissão de Ética para Análise de Projetos de Pesquisa – HCFMUSP; Comitê de Ética em Pesquisa – Hospital das Clínicas de Niterói; Comitê de Ética em Pesquisa – HCor; Comitê de Ética em Pesquisa – Hospital Israelita Albert Einstein; Comitê de Ética em Pesquisa – HCFMRP – USP; Comitê de ética do Hospital São Jose; Comitê de Ética em Pesquisa do Vitória Apart Hospital; Comitê de Ética em Pesquisa do Hospital Madre Teresa; Comitê de Ética em Pesquisa do Hospital da Mulher Heloneida Studart; Comité de Ética em Pesquisa – Hospital Moinhos de Vento; Comité de Ética em Pesquisa do Hospital Mater Dei; Comité de Ética em pesquisa – Hospital Mario Lioni; Comité de Ética e Pesquisa do Hospital Espanhol; Comité de Ética em Pesquisa – Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz; Comité de Ética em Pesquisa – UNIFESP/EPM; Comitê de Ética em Pesquisa – Hospital Copa D’or; Comité de Ética em Pesquisa – Beneficiência Médica Brasileira S/A Hospital São Luiz; Comité de Ética em Pesquisa do Hospital do Trabalhador; Comité de Ética em Pesquisa da Fundação de Medicina Tropical do Tocantins; and Comité de Ética em Pesquisa – FMUSP.
Statistical analysis
Continuous variables are reported as the median (25 to 75% interquartile range). Univariate and multivariate analyses using a binary logistic regression were used to identify factors associated with the dependent variable (hospital mortality). Variables yielding $P < 0.2$ by univariate analysis, or those considered clinically relevant despite $P$ values, were entered into the multivariate analysis to estimate the independent association of each covariate with the dependent variable. Results are presented as the odds ratio with 95% confidence interval. A Kaplan–Meier curve with log-rank test was used to compare patients with light versus deep sedation for hospital mortality (censored at day 30). Two-tailed $P < 0.05$ was considered statistically significant. All statistical tests were carried out using the commercial SPSS19.0 package for Windows (SPSS Inc., Chicago, IL, USA).

Results
Characteristics of the study population
From 773 patients derived from the original cohort, a total of 322 patients fulfilled the eligibility criteria (Figure 1). Patients excluded for missing data about sedation depth on day 2 ($n = 51$) were comparable with the included population regarding demographic data, comorbidities, physiologic and disease severity variables and outcomes (data not shown). The main patient characteristics are presented in Table 1. Median (25 to 75% interquartile range) age was 59 (41 to 74) years. The median SAPS3 was 61 (50 to 72) and SOFA score was 8 (6 to 11) on the first day in the ICU. Overall ICU and hospital mortality rates were 30.4% and 38.8% respectively. When comparing nonsurvivor and survivor subgroups, we observed that nonsurvivors showed higher median age (68 (52 to 77) years vs. 53 (34 to 69) years, $P < 0.001$), higher SAPS3 and SOFA score (68 (57 to 79) vs. 57 (48 to 67), $P < 0.001$ and 10 (7 to 12) vs. 8 (5 to 10), $P < 0.001$) and higher percentage of patients with a Charlson Comorbidity Index >2 (37.6% vs. 16.2%, $P < 0.001$). Those who died during hospital admission also had a higher frequency of moderate/severe ARDS (24% vs. 9.6%, $P = 0.004$), need for vasopressors (85.6% vs.71.1%, $P = 0.003$) and renal replacement therapy (33.6% vs.13.7%, $P < 0.001$).

Sedative choice and sedation depth
The most frequently used sedatives were the association of midazolam and fentanyl (39.4%) or of propofol and fentanyl (14%) and the use of fentanyl (12.4%) or midazolam (8.1%) as single drugs. Sedative drug type was also associated with sedation levels: the sole administration of fentanyl and dexmedetomidine was more frequent in lightly sedated patients (15.3% vs. 7.1% for fentanyl, $P = 0.033$; 8.6% vs. 0.9% for dexmedetomidine, $P = 0.005$).

Deep sedation was observed in 113 patients (35.1%) and was associated with a higher overall disease severity, as demonstrated by higher median SAPS 3 (65 (54 to 78) for deep sedation vs. 59 (48 to 70) for light sedation, $P = 0.001$) (Table 2). Moreover, longer duration of ventilatory support was observed (7 (4 to 10) vs. 5 (3 to 9) days, $P = 0.041$) and more tracheostomies were performed in the deep sedation group (38.9% vs. 22%, $P = 0.001$) despite similar arterial partial pressure of oxygen/fraction of inspired oxygen ratios and ARDS severity. Finally, trends to increased ICU and hospital mortality (37.2% vs. 26.8%, $P = 0.054$ and 46% vs. 34.9%, $P = 0.051$ respectively) were also associated with deep sedation (Table 3). A survival curve comparing patients with deep and light sedation is shown in Figure 2.

In a multivariate analysis, age, Charlson Comorbidity Index >2, SAPS3, severe ARDS and deep sedation were independently associated with increased hospital mortality (Table 4).

Discussion
In the present multicenter cohort study we evaluated the association of early sedation strategies with outcomes of adult mechanically ventilated patients in the ICU. Deep sedation in the first 48 hours of MV is a common
Table 1 General characteristics of study patients according to survival status

| Characteristic                              | Survivors (n =197) | Nonsurvivors (n =125) | P valuea |
|---------------------------------------------|--------------------|-----------------------|----------|
| Age (years)                                 | 53 (34 to 69)      | 68 (52 to 77)         | <0.001   |
| Male gender                                 | 114 (58)           | 73 (58)               | 0.925    |
| Admission SAPS3 (points)                    | 57 (48 to 67)      | 68 (57 to 79)         | <0.001   |
| SOFA score day 1 (points)                   | 8 (5 to 10)        | 10 (7 to 12)          | <0.001   |
| Charlson comorbidity index                  |                    |                       |          |
| 0                                           | 106 (53.8)         | 30 (24)               |          |
| 1 to 2                                      | 59 (29.9)          | 48 (38.4)             | <0.001   |
| > 2                                         | 32 (16.2)          | 47 (37.6)             |          |
| Admission source                            |                    |                       | 0.038    |
| Ward                                        | 52 (26.4)          | 49 (39.2)             |          |
| Emergency room                              | 79 (40.1)          | 46 (36.8)             |          |
| Operation room                              | 66 (33.5)          | 30 (24)               |          |
| Cause of respiratory failure                |                    |                       |          |
| Pneumonia                                   | 66 (33.5)          | 39 (31.2)             | 0.668    |
| Nonpulmonary sepsis                         | 30 (15.2)          | 15 (12)               | 0.415    |
| Asthma/COPD                                 | 23 (11.7)          | 7 (5.6)               | 0.068    |
| Cardiogenic pulmonary edema                 | 11 (5.6)           | 9 (7.2)               | 0.558    |
| Extracranial trauma                         | 11 (5.6)           | 12 (9.6)              | 0.173    |
| Hypovolemic/cardiogenic shock               | 10 (5.1)           | 8 (6.4)               | 0.614    |
| Aspirative syndromes                        | 10 (5.1)           | 3 (2.4)               | 0.234    |
| Pulmonary embolism                          | 4 (2)              | 5 (4)                 | 0.296    |
| Others                                      | 32 (16.2)          | 27 (21.6)             | 0.226    |
| Comorbidities                               |                    |                       |          |
| Hypertension                                | 63 (32)            | 58 (46.4)             | 0.008    |
| Diabetes                                    | 30 (15.2)          | 42 (33.6)             | <0.001   |
| Heart failure                               | 12 (6.1)           | 14 (11.2)             | 0.101    |
| COPD                                        | 12 (6.1)           | 12 (9.6)              | 0.243    |
| Chronic renal failure                       | 11 (5.6)           | 23 (18.4)             | <0.001   |
| Respiratory data                            |                    |                       |          |
| ARDS mild                                   | 29 (14.7)          | 21 (16.8)             | 0.004    |
| ARDS moderate/severe                        | 19 (9.6)           | 30 (24)               |          |
| PO2/FiO2 ratio                              | 287 (220 to 350)   | 252 (184 to 328)      | 0.019    |
| Tracheostomy                                | 54 (27.4)          | 36 (28.8)             | 0.817    |
| Extubation failure                          | 23 (11.7)          | 19 (15.2)             | 0.182    |
| Length of ventilatory support (days)        | 5 (3 to 8)         | 6 (3 to 11)           | 0.260    |
| ICU support                                 |                    |                       |          |
| Renal replacement therapy                   | 27 (13.7)          | 42 (33.6)             | <0.001   |
| Vasopressors                                | 140 (71.1)         | 107 (85.6)            | 0.003    |
| Outcomes                                    |                    |                       |          |
| ICU length of stay (days)                   | 11 (7 to 19)       | 11 (5 to 18.5)        | 0.389    |
| Hospital length of stay (days)              | 23 (14 to 36)      | 14.5 (7.3 to 27)      | <0.001   |
characteristic, observed in 35.1% of patients. Deep sedation was associated with increased disease severity, longer duration of ventilatory support and higher need for tracheostomy. In a multivariate analysis, deep sedation was an independent factor associated with increased hospital mortality (odds ratio = 2.36).

The more frequently used sedative regimens in our study were the association of midazolam and fentanyl or of propofol and fentanyl. When compared by sedation depth, the administration of fentanyl or dexmedetomidine as single drugs was more frequent in lightly sedated patients (15.3% vs. 7.1% for fentanyl, \( P = 0.033 \); 8.6% vs. 0.9%).

Table 1 General characteristics of study patients according to survival status (Continued)

| Sedation depth | All patients (n = 322) | Light sedation (n = 209) | Deep sedation (n = 113) | \( P \) value
|----------------|------------------------|--------------------------|-------------------------|-------------------|
| Light sedation | 136 (69.0)             | 73 (58.4)                | 0.051                   |
| Deep sedation  | 61 (31.0)              | 52 (41.6)                |                         |

Data presented as median (25 to 75% interquartile range) or n (%). ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; PO2/FiO2, arterial partial pressure of oxygen/fraction of inspired oxygen; SAPS3, Simplified Acute Physiology Score 3; SOFA, Sequential Organ Failure Assessment. *\( P \) value of the comparison between survivors and nonsurvivors.

Table 2 General characteristics of study patients according to sedation depth

| Characteristic                  | All patients (n = 322) | Light sedation (n = 209) | Deep sedation (n = 113) | \( P \) value
|-------------------------------|------------------------|--------------------------|-------------------------|-------------------|
| Age (years)                   | 59 (40.8 to 74)        | 61 (44 to 74.5)          | 55 (33.5 to 73)         | 0.068             |
| Male gender                   | 187 (58)               | 108 (52)                 | 79 (70)                 | 0.002             |
| Charlson comorbidity index    |                        |                          |                         |                   |
| 0                             | 136 (42.2)             | 72 (34.4)                | 64 (56.7)               | <0.001            |
| 1 to 2                        | 107 (33.2)             | 75 (35.9)                | 32 (28.3)               |                   |
| > 2                           | 79 (24.5)              | 62 (29.7)                | 17 (15)                 |                   |
| Comorbidities                 |                        |                          |                         |                   |
| Hypertension                  | 121 (37.7)             | 88 (42.1)                | 33 (29.2)               | 0.026             |
| Diabetes                      | 72 (22.4)              | 50 (25.4)                | 22 (17.6)               | 0.381             |
| Heart failure                 | 26 (8.1)               | 21 (10.7)                | 5 (14.7)                | 0.077             |
| COPD                          | 24 (7.5)               | 21 (10)                  | 3 (2.7)                 | 0.016             |
| Chronic renal failure         | 34 (10.6)              | 24 (12.2)                | 10 (8)                  | 0.463             |
| Admission source              |                        |                          |                         | 0.103             |
| Ward                          | 101 (31.4)             | 74 (35.4)                | 27 (23.9)               |                   |
| Emergency room                | 125 (38.8)             | 77 (36.8)                | 48 (42.5)               |                   |
| Operation room                | 96 (29.8)              | 58 (27.8)                | 38 (33.6)               |                   |
| Admission scores (points)     |                        |                          |                         |                   |
| Admission SAPS3               | 61 (50 to 72)          | 59 (48 to 70)            | 65 (54 to 78)           | 0.001             |
| SOFA score day 1              | 8 (6 to 11)            | 8 (5 to 11)              | 9 (7 to 11)             | 0.001             |
| Cause of respiratory failure  |                        |                          |                         |                   |
| Pneumonia                     | 105 (32.6)             | 69 (33)                  | 36 (31.9)               | 0.833             |
| Nonpulmonary sepsis           | 45 (14)                | 30 (14.4)                | 15 (13.3)               | 0.790             |
| Asthma/COPD                   | 30 (9.3)               | 19 (9.1)                 | 11 (9.7)                | 0.850             |
| Cardiogenic pulmonary edema   | 20 (6.2)               | 15 (7.2)                 | 5 (4.4)                 | 0.329             |
| Extracranial trauma           | 23 (7.1)               | 13 (6.2)                 | 10 (8.8)                | 0.382             |
| Hypovolemic/cardiogenic shock | 18 (5.6)               | 12 (5.7)                 | 6 (5.3)                 | 0.872             |
| Aspirative syndromes          | 13 (4)                 | 9 (4.3)                  | 4 (3.5)                 | 0.739             |
| Pulmonary embolism            | 9 (2.8)                | 6 (2.9)                  | 3 (2.7)                 | 0.911             |
| Others                        | 59 (18.3)              | 36 (17.2)                | 23 (20.4)               | 0.488             |

Data presented as median (25 to 75% interquartile range) or n (%). COPD, chronic obstructive pulmonary disease; SAPS3, Simplified Acute Physiology Score 3; SOFA, Sequential Organ Failure Assessment. *\( P \) value of the comparison between light and deep sedation.
These findings may be attributed to a rapid onset and offset of action of these drugs and their easiness to titrate, while benzodiazepines are more likely to accumulate, especially during continuous infusion and when associated with other drugs [26,27]. Recent studies demonstrate that sedation with benzodiazepines aiming at the same target is usually associated with a higher rate of sedation depth beyond the target as compared with dexmedetomidine [28].

Although important studies were published recently, a systematic review published in 2010 showed that clinical trials on sedation are commonly reported as low quality, mainly due to their design (for example, before and after studies), heterogeneous protocols and the relatively small number of patients in a single center or few centers [29]. These factors generate limited evidence to guide sedation drug choice and administration strategies in mechanically ventilated patients. Moreover, most studies – including recent randomized clinical trials – have enrolled patients 24 to 48 hours after the initiation of MV, making the clinical relevance of sedation depth in the early period more difficult to understand. A recent multicenter prospective cohort study by Shehabi and colleagues enrolled 251 patients, aiming to characterize the patterns of early sedation practice in 25 Australia and New Zealand (ANZ) ICUs and to assess its relationship with relevant clinical outcomes. After adjusting for potential confounding, early deep sedation was a predictor of time to extubation and mortality [30]. These results were corroborated by a cohort study in 11 Malaysian hospitals including medical/surgical patients (n = 259) who were sedated and ventilated ≥24 hours [31]. Likewise, in our study we could assess sedation strategies in the first 48 hours of MV and its relevant clinical outcomes in a large number of patients (n = 322), and demonstrated that early deep sedation was an independent predictor of hospital mortality.

Unlike the other variables that were also found to be independently associated with mortality in our study, such as ARDS severity, comorbidities and disease severity, sedation depth is a potentially modifiable risk factor for mortality. Implementing sedation protocols to achieve light sedation has been proven feasible and reproducible [32,33]. This

| Clinical outcomes                      | All patients (n = 322) | Light sedation (n = 209) | Deep sedation (n = 113) | P valuea |
|----------------------------------------|------------------------|-------------------------|-------------------------|----------|
| **Respiratory data**                   |                        |                         |                         |          |
| ARDS mild                              | 50 (15.5)              | 35 (16.7)               | 15 (13.3)               | 0.521    |
| ARDS moderate/severe                   | 49 (15.2)              | 35 (16.7)               | 14 (12.4)               |          |
| PO2/FiO2 ratio                         | 278 (208 to 339)       | 268 (208 to 329)        | 282 (208 to 353)        | 0.486    |
| Tracheostomy                           | 90 (28.3)              | 46 (22)                 | 44 (38.9)               | 0.001    |
| Extubation failure                     | 42 (13.8)              | 32 (15.3)               | 10 (8.8)                | 0.119    |
| Length of ventilatory support (days)   | 5 (3 to 9)             | 5 (3 to 9)              | 7 (4 to 10)             | 0.041    |
| Ventilator-free days                   | 17.5 (0 to 23.3)       | 21 (0 to 25)            | 0 (0 to 21)             | <0.001   |
| **ICU support**                        |                        |                         |                         |          |
| Renal replacement therapy              | 69 (21.7)              | 54 (25.8)               | 15 (13.3)               | 0.008    |
| Vasopressors                           | 247 (77.4)             | 162 (77.5)              | 85 (75.2)               | 0.629    |
| **Outcomes**                           |                        |                         |                         |          |
| ICU length of stay (days)              | 11 (6 to 19)           | 11 (6 to 19)            | 11 (6 to 18)            | 0.633    |
| Hospital length of stay (days)         | 20 (12 to 34)          | 21 (13 to 35.8)         | 19 (10 to 27)           | 0.084    |
| ICU mortality                          | 98 (30.4)              | 56 (26.8)               | 42 (37.2)               | 0.054    |
| Hospital mortality                     | 125 (38.8)             | 73 (34.9)               | 52 (46)                 | 0.051    |

Data presented as median (25 to 75% interquartile range) or n (%). ARDS, acute respiratory distress syndrome; PO2/FiO2, arterial partial pressure of oxygen/fraction of inspired oxygen; aP value of the comparison between light and deep sedation.

Figure 2 Kaplan–Meier analysis depicting the impact of sedation depth on hospital mortality. Blue line, patients with light sedation at day 2; red line, patients with deep sedation at day 2. P = 0.051.
ARDS, acute respiratory distress syndrome; SAPS3, Simplified Acute Physiology Score 3.

### Table 4 Factors associated with hospital mortality in a multivariate analysis

| Parameter                        | Odds ratio | 95% confidence interval | P value |
|----------------------------------|------------|-------------------------|--------|
| Age                              | 1.02       | 1.00 to 1.03            | 0.047  |
| Charlson comorbidity index >2    | 2.06       | 1.44 to 2.94            | <0.001 |
| SAPS3                            | 1.02       | 1.00 to 1.04            | 0.038  |
| Severe ARDS                       | 1.44       | 1.09 to 1.91            | 0.011  |
| Deep sedation                    | 2.36       | 1.31 to 4.25            | 0.004  |

Area under receiver operating curve for predicted mortality (95% confidence interval) = 0.768 (0.718 to 0.813), P < 0.001. Hosmer–Lemeshow $\chi^2 = 6.5670$, P = 0.5840.

ARDS, acute respiratory distress syndrome; SAPS3, Simplified Acute Physiology Score 3.

Evidence is important because deep sedation still seems to be current practice in many ICUs worldwide [5,13] and is present in 35% of the patients enrolled in the present study. Accordingly, Payen and colleagues observed in their survey a large proportion of patients in a deep state of sedation, and in addition no major changes in sedation depth or sedative dosages occurs during the first week of the ICU stay [34].

Finally, our findings provide validation of the concept that early sedation has a major impact on outcomes. Demonstrating this in a middle-income country in South America is an important step to provide generalizability of previous findings because the main previously published results on this issue are from ANZ ICUs. Several ANZ trials are well known for frequently presenting different results compared with similar interventions in other parts of the world, as demonstrated by studies in the last decade in the critical care field [35,36] and even in the sedation area [37]. This discrepancy is attributed to substantial differences due to the high standards in process of care and staffing patterns, and is consequently translated into lower mortality in ANZ ICUs [38,39].

The present study has some limitations that must be considered. First, the sedation level was not assessed using a specific sedation scale. Nonetheless, although originally created to assess the level of consciousness after head injury, it is known that GCS (the chosen scale) <9 denotes a comatose state even in nontraumatic settings, such as cerebral depression by pharmacological cause [40,41]. Moreover, the GCS shows excellent correlation and discrimination with the RASS ($r = 0.91$, $P < 0.001$), as described by Ely and colleagues from 1,360 paired observations among 275 adult patients in medical and coronary ICUs [25]. This strong correlation between the RASS and the GCS was also shown in other sedation scale validation studies [42,43], which allows its applicability as a surrogate for sedation depth in the present study.

Another limitation is the potential influence of previous neurological status on GCS values. Data regarding GCS on day 1 were collected in patients who were already sedated and under MV. A reported low GCS could therefore be influenced by the baseline neurological status and not only by sedation strategies, because it may also reflect acute neurological conditions associated with the current illness presented by the critically ill, such as encephalopathy. However, this is not an exclusive limitation of the GCS because this may also occur with the more specific sedation assessment scales such as the RASS or Sedation-Agitation Scale (SAS). Moreover, it is possible that certain patients may have required larger sedative doses on day 2 of MV for other reasons (ICU procedures, for instance) and we did not collect these data. In order to minimize the impact of other conditions in GCS values, we excluded patients with primary or known acute neurological disorders and included only patients under sedation in the present study. Considering the potential confounders mentioned above, the strong association between deep sedation and mortality must be analyzed regarding our interpretation of GCS values mainly as a surrogate of sedation depth.

Finally, we have not evaluated the presence of delirium. In mechanically ventilated patients, delirium is an independent predictor of hospital and 6-month mortality [6,44]. These outcomes are shown even in light sedated patients, where a dose–effect response was described [45]. Despite this clinical relevance, the incidence of delirium could not be evaluated in our study, since it was not the aim of the primary analysis. Finally, participant ICUs reported the existence of a sedation protocol, but the actual adherence for local recommendations was not assessed in the present study as it was beyond its initial scope.

### Conclusions

Early deep sedation is associated with worse outcomes and constitutes an independent predictor of hospital mortality in a prospective cohort of mechanically ventilated patients. Randomized clinical trials should be designed to address the impact of light versus deep sedation in the early phase (<48 hours) of MV.

### Key messages

- Early deep sedation is associated with longer duration of ventilator support and higher need for tracheostomy in mechanically ventilated patients.
• Early sedation depth is independently associated with increased hospital mortality.

• Sedation depth is a potentially modifiable risk factor for adverse outcomes; future clinical trials of light sedation with early (<24 hours) randomization of patients should therefore be encouraged.

**Additional file**

**Additional file 1:** is a table listing the sites, investigators and institutional review boards that participated in the Epidemiology of Respiratory Insufficiency in Critical Care study.

**Abbreviations**

ANZ: Australia and New Zealand; ARDS: acute respiratory distress syndrome; GCSS: Glasgow Coma Scale; MCISS: Modified Coma Intensity Score; RASS: Richmond Agitation Sedation Scale; SAPS3: Simplified Acute Physiology Score 3; SOFA: Sequential Organ Failure Assessment.

**Competing interests**

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**Authors’ contributions**

LMST participated in study conception, data acquisition, data analysis and interpretation, and drafting of the manuscript. LCPA participated in data acquisition, drafting of the manuscript and revising the manuscript for important intellectual content. FD-P participated in data acquisition and revising the manuscript for important intellectual content. APNJr participated in data acquisition, drafting of the manuscript and revising the manuscript for important intellectual content. MP participated in study conception, data analysis and interpretation, and drafting of the manuscript. MP participated in study conception, data analysis and interpretation, and drafting of the manuscript. FRM participated in study conception, data acquisition, data analysis and interpretation, and drafting of the manuscript. FPG participated in data acquisition and revising the manuscript for important intellectual content. AR-N participated in data acquisition and revising the manuscript for important intellectual content. LT participated in data acquisition and revising the manuscript for important intellectual content. AT participated in data acquisition and revising the manuscript for important intellectual content. VCDS-D participated in data acquisition and revising the manuscript for important intellectual content. TL participated in data acquisition and revising the manuscript for important intellectual content. CP participated in data acquisition and revising the manuscript for important intellectual content. FBC participated in data acquisition and revising the manuscript for important intellectual content. MDOM participated in data acquisition and revising the manuscript for important intellectual content. APNh participated in data acquisition, drafting of the manuscript and revising the manuscript for important intellectual content. APNh participated in data acquisition, drafting of the manuscript and revising the manuscript for important intellectual content. FPGMPT participated in data acquisition and revising the manuscript for important intellectual content. MS participated in study conception, data analysis and interpretation, and drafting of the manuscript. JIFS participated in study conception, data analysis and interpretation, and drafting of the manuscript. All authors approved the final copy of the manuscript.

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