The implementation of an analgesia-based
sedation protocol reduced deep sedation and
proved to be safe and feasible in patients on
mechanical ventilation

Implantação de protocolo de redução de sedação profunda
baseado em analgesia comprovadamente seguro e factível em
pacientes submetidos à ventilação mecânica

INTRODUCTION

Sedation and analgesia are essential for the majority of patients who
require mechanical ventilation in the intensive care unit (ICU). Sedation
reduces the stress response, provides anxiolysis, and improves tolerance for
ventilatory support. However, sedative drugs have been associated with
adverse effects, which result in prolonged ventilatory support and lengthy
hospital stays. Different studies have shown that the use of protocols, sedation scoring
systems, and daily interruption of sedative agents may reduce the duration of mechanical ventilation and the length of the ICU stay. However, there
is reportedly a wide variation of sedation schemes and practices used in ICUs worldwide, and 32-57% of the patients are deeply sedated or are sedated at deeper levels than required. \(^{(1,2,4,5)}\) Analgesia has been suggested to be the first step toward improving comfort in mechanically ventilated patients. \(^{(12,13)}\) Recent data have suggested that an analgesia-based sedation protocol reduces the use of hypnotics and may improve the practice of sedation in patients who require mechanical ventilation. \(^{(14-16)}\)

In the present study, we evaluate the clinical practice of analgesia and sedation in critically ill patients who require mechanical ventilation for more than 48 hours. Based on these findings, we designed and implemented an analgesia based, goal-directed, nurse-driven sedation protocol and evaluated its impact on the duration of mechanical ventilation, the deepness of sedation and the prevalence of post-traumatic stress disorder symptoms one year after mechanical ventilation.

**METHODS**

**Study design**

This prospective, two-phase (before-after), non-randomized multicenter study focuses on critically ill patients who required mechanical ventilation for more than 48 hours and involved 13 ICUs in Chile (e-supplement). An observational period lasted 10 weeks from April to June 2006. \(^{(17)}\) This observational phase was followed by data analysis and a workshop in which an analgesia-based, goal-directed, nurse-driven sedation protocol was designed. After nurse and medical training for its application, the interventional phase was applied for 12 weeks from late October 2006 until January 2007. All of the institutions and their corresponding Institutional Review Boards approved the protocol. Written consent from a patient-authorized surrogate was obtained for the interventional period.

**Patients**

The study population included patients older than 18 years old with an anticipated requirement of mechanical ventilation for longer than 48 hours. The 13 ICUs comprised a heterogeneous group that included university centers, a private health system and public hospitals. Trained nurses from the research team screened the patients daily for eligibility.

Exclusion criteria included the following: patients with neurologic diseases as the primary admission diagnosis (head trauma, stroke, etc), previous end-stage liver and renal failure, a second period of mechanical ventilation during hospitalization, mechanical ventilation for more than 24 hours before ICU admission, drug abuse, and short-term expected mortality.

**Observational group**

During the observational period, nurses in each ICU were trained to use the sedation-agitation scale (SAS), \(^{(18)}\) which was performed twice a day. Only two centers had a sedation protocol by the time, and no other sedation protocol was introduced during this phase. The data obtained were not made available to the ICU staff physician.

**Intervention group**

In August 2006, a one-day workshop was performed with the participation of at least one nurse and one physician from every ICU to define the prospective sedation protocol. The data from the observational period were presented and discussed. A key finding was the high proportion of patients in deep sedation. \(^{(17)}\) Based on this finding, an analgesia-based, goal-directed, nurse-driven sedation protocol was designed for the research team. This proposal was discussed in group sessions, and it was finally approved by all of the participants.

This protocol can be summarized in the following steps. The attending physician defined a daily goal of sedation, usually SAS 3-4. A deep level of sedation (SAS 1-2) was allowed in the presence of severe respiratory failure (\(\text{PaO}_2/\text{FiO}_2\) ratio <150 with PEEP \(\geq\)10cm H\(_2\)O, significant patient-ventilator asynchrony, non-conventional modes of mechanical ventilation, or high-minute ventilation) or severe-cardiovascular failure (high doses of vasoactive drugs, cardiac index \(<2.0\text{L/min/m}^2\) or arterial lactate >4mmol/L). Fentanyl (from 0.6µg/kg/h to 3.6µg/kg/h) and midazolam (from 0.015mg/kg/h to 0.09mg/kg/h) by continuous i.v. infusions were titrated according to a prescribed table, generating 12 different levels of drugs (Table 1). To avoid deep sedation and to manage pain control, fentanyl was applied in the first three levels before starting midazolam. \(^{(12)}\) This table was designed based on the observed doses of fentanyl and midazolam during the observational phase. \(^{(17)}\) At any time, i.v.
boluses were allowed before increasing the infusion rates of the sedatives. If the patient was agitated despite the administration of maximal doses (fentanyl 3.6µg/kg/h and midazolam 0.09mg/kg/h), an increase in midazolam doses or a third drug was allowed according to the directions of the staff physician. Haloperidol was recommended for agitation and delirium. In the present trial, we did not implement a systematic evaluation for the diagnosis of delirium. Neuromuscular blockade (NMB) was not routinely used. However, it was allowed in patients with severe respiratory failure and asynchrony, and its requirement was assessed daily. Deep sedation was assured before starting NMB.

The nurse/bed ratio in Chile is typically 1:3-4. Once the patient was intubated, fentanyl was started at 1.8µg/kg/h (level 3), and drug infusions were titrated to ensure that the patient remained calm and cooperative or mildly sedated (SAS 3 or 4). If the daily goal was SAS 1 or 2, drug infusions were increased. At least 4 daily SAS evaluations were recommended.

Once the protocol was designed, an educational program with onsite training was provided for all of the nurses and physicians working in each ICU. During these sessions, the data from the observational phase were disclosed, as well as the newly designed protocol. Daily sedation goals and SAS evaluations were reinforced. Recruitment of patients for the intervention period started in late October 2006 and ended in January 2007.

**Data acquisition and analysis**

One or two nurses for each center were trained for data acquisition. The primary demographic data, admission diagnosis and the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scores were recorded. Hemodynamic data, ventilator parameters, and arterial blood gases were monitored and recorded daily for the first week.

The type of analgesics and sedatives administered, their dosage, and administration method (i.v. boluses or infusion) were recorded for the first week and weekly thereafter. SAS analyses considered only two evaluations from the interventional period to compare with the observational phase. Deep sedation was defined as SAS level 1-2, and agitation was defined as SAS level 5-7.

**Outcome measures**

The primary outcome was to achieve ventilator-free days on day 28 (defined as “zero” for nonsurvivors). The secondary outcomes were decreased hospital and ICU length of stay as well as a reduced proportion of patients in deep sedation. Safety issues included self-extubations and central catheter and nasogastric tube displacements.

Survivors at one year were screened via telephone interview for memories of traumatic experiences during their ICU stay (nightmares, panic, pain, and suffocation) and post-traumatic stress disorder (PTSD) symptoms by means of the Post-Traumatic Stress Syndrome-10 (PTSS-10) scale. A PTSS-10 score >35 was defined as PTSD.

**Statistical analysis**

The descriptive data are presented as percentages, means (SD) for normally distributed variables and medians (IQR) for non-normally continuous variables. To compare the differences between the groups, Fisher’s exact test was used for categorical variables, two-sample Student’s t-test was used for parametric continuous variables and two-sample Mann-Whitney-Wilcoxon was used test for non-parametric variables. Based on previous data, the present study had planned to include 280 patients to detect a 20% difference in ventilator-free days at day 28, with 80% of power and a 0.05 type I error.

All of the statistical tests were two-tailed and were considered to be statistically significant at 0.05. Statistical Package for the Social Sciences (SPSS) for Windows version 13.0 was used for all of the analyses.

**Table 1 - Continuous infusion rates for both fentanyl and midazolam, which started at level 3 (fentanyl 1.8µg/kg/min and no midazolam)**

| Infusion level | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---------------|---|---|---|---|---|---|---|---|---|----|----|----|
| Fentanyl (µg/kg/h) | 0.6 | 1.2 | 1.8 | 1.8 | 2.4 | 2.4 | 3 | 3 | 3.6 | 3.6 | 3.6 | 3.6 |
| Midazolam (mg/kg/h) | 0 | 0 | 0 | 0.015 | 0.015 | 0.03 | 0.03 | 0.045 | 0.045 | 0.06 | 0.075 | 0.09 |
RESULTS

During the observational and interventional periods, we reviewed 634 and 598 patients who required mechanical ventilation, respectively. After we reviewed the exclusion criteria, we enrolled 155 (24.4%) patients in the observational group and 132 (22.1%) patients in the interventional group (e-supplement). Both groups were comparable in admission diagnosis, severity of illness and co-morbidities (Table 2).

Table 2 - Baseline demographics of patients

| Variables                     | Observational group (N=155) | Intervention group (N=132) | p value |
|-------------------------------|-------------------------------|----------------------------|---------|
| Male                          | 88 (57)                       | 66 (50)                    | 0.251   |
| Age (years)                  | 60±18                         | 59±19                      | 0.578   |
| APACHE II                    | 18±15-22                      | 17 (12-22)                 | 0.839   |
| SOFA                         | 7 (6-10)                      | 8 (5-10)                   | 0.762   |
| Admission diagnosis          |                               |                            |         |
| Medical condition            | 82 (53)                       | 83 (63)                    | 0.088   |
| Sepsis                       | 98 (63)                       | 90 (68)                    | 0.379   |
| ALI/ARDS                     | 73 (47)                       | 58 (44)                    | 0.495   |
| COPD                         | 30 (19)                       | 21 (16)                    | 0.447   |
| Heart failure                | 27 (17)                       | 17 (13)                    | 0.287   |
| Acute myocardial infarction  | 6 (4)                         | 6 (5)                      | 0.776   |
| Immunosuppression            | 10 (7)                        | 7 (6)                      | 0.709   |
| Trauma                       | 14 (9)                        | 12 (9)                     | 0.986   |
| Reason for mechanical ventilation |               |                             |         |
| Acute respiratory failure    | 86 (56)                       | 82 (62)                    |         |
| Hypercapnic respiratory failure | 21 (14)                     | 19 (14)                    |         |
| Circulatory failure          | 48 (31)                       | 31 (24)                    | 0.364   |
| Ventilatory parameters       |                               |                            |         |
| Tidal volume (ml/kg)         | 9.2±2.0                       | 9.3±2.1                    | 0.745   |
| PEEP (cmH\textsubscript{2}O) | 7.7±3.1                       | 8.2±2.8                    | 0.181   |
| Plateau pressure (cm H\textsubscript{2}O) | 22.9±4.9                  | 23.4±6.3                   | 0.541   |
| PaO\textsubscript{2}/FiO\textsubscript{2} ratio | 225±97                      | 241±115                    | 0.209   |
| PaO\textsubscript{2}/FiO\textsubscript{2} ratio <200 | 42.5                        | 44.7                       | 0.720   |

Extended data relative to the observational group have been previously published. Midazolam and fentanyl were the most frequently used drugs for sedation and analgesia during mechanical ventilation. They were used in 133 (85.8%) patients and 126 (81.3%) patients, respectively. Propofol, morphine and lorazepam were used in only 17 (10.9%) patients, 26 (16.8%) patients and 6 (3.9%) patients, respectively.

During the interventional phase, the application of the protocol increased the dose of fentanyl and decreased that of midazolam (Table 3). Twenty-five percent of the patients in the interventional group did not require midazolam infusions. Neuromuscular blocker use was not significantly reduced in the interventional group (Table 3).

Table 3 - Midazolam and fentanyl doses from days 1 to 7 and use of haloperidol and muscle relaxants

| Variables                        | Observational group (N=155) | Intervention group (N=132) | p value |
|----------------------------------|-------------------------------|----------------------------|---------|
| Midazolam                        |                               |                            |         |
| Total dose (mg)                  | 287 (24-731)                  | 86 (0-404)                 | <0.001  |
| Average rate (µg/kg/h)           | 0.03 (0.01-0.06)              | 0.01 (0-0.03)              | <0.001  |
| Fentanyl                         |                               |                            |         |
| Total dose (mg)                  | 5.2 (0.36-15.8)               | 14.1 (4.5-27.3)            | <0.001  |
| Average rate (µg/kg/h)           | 0.6 (0.1-1.4)                 | 1.5 (0.8-2.4)              | <0.001  |
| Use of haloperidol               | 15 (9.7)                      | 16 (12.1)                  |         |
| Average daily dose (mg)          | 2.4±3.2                       | 2.8±2.9                    |         |
| Use of neuromuscular blockade    |                               |                            |         |
| Infusions and i.v. boluses       | 47 (30.3)                     | 29 (22)                    | 0.110   |
| Infusions > 24 hours             | 25 (16.1)                     | 13 (9.8)                   | 0.118   |

The results are expressed as the number (percentage), the mean±standard deviation or the median (interquartile range).

There were 1,640 SAS evaluations in the observational group and 1,350 SAS evaluations in the interventional group. The proportion of SAS scores 3-4 increased from 37.1% to 48.7% in the interventional group, whereas SAS scores 1-2 decreased from 55.2% to 44.0% (p=0.001) (Figure 1). Agitation did not change between the periods and remained at approximately 7%.

The time on mechanical ventilation, the number of ventilator-free days, the length of the ICU and hospital stay and 28-day mortality were similar in both groups (Table 4). Safety issues related to the interventional protocol did not differ from the observational period (Table 4). Two patients in the interventional group were retired from the protocol because of adverse effects, which were likely related to high doses of fentanyl (both patients had ileus and intra-abdominal hypertension).

The one-year mortality for the entire population was 49% (142/287), and 52% of the survivors (75/149) answered the PTSS-10 questionnaire (42 could not
Table 5 - Traumatic memories and post-traumatic stress syndrome-10 (PTSS-10) scale at one year

| Variables                  | Observational group (N=40) | Intervention group (N=35) | p value |
|----------------------------|----------------------------|---------------------------|---------|
| Nightmares                 | 22 (55)                    | 15 (43)                   | 0.294   |
| Severe anxiety or panic    | 16 (40)                    | 12 (34)                   | 0.610   |
| Severe pain                | 12 (30)                    | 13 (37)                   | 0.513   |
| Suffocation                | 18 (45)                    | 18 (51)                   | 0.578   |
| PTSS-10                    | 28 (19-3)                  | 26 (17-38)                | 0.840   |
| PTSS-10 >35                | 11 (27.5)                  | 9 (25.7)                  | 0.980   |

PTSS - post-traumatic stress disorder; PTSS-10 - post-traumatic stress syndrome-10. The results are expressed as the number (percentage) or the median (interquartile range).

DISCUSSION

In the present two-phase, multicenter, single nation-wide study, the design and application of an analgesia-based, goal-directed, nurse-driven sedation protocol did not show significant differences in major outcomes. However, the present protocol was shown to be safe and feasible in our population and demonstrated decreased time in deep sedation. Additionally, post-traumatic stress disorder symptoms in survivors one year after mechanical ventilation were comparable between the groups.

Analgesia-based sedation, which has been used primarily in the surgical field(21) and more recently in the general mixed population,(15,16,22) is a relatively new term in the ICU. Analgesia is not usually measured and is sometimes ignored during mechanical ventilation. (14) Although sedation guidelines recommend that sedation be started only after providing adequate analgesia,(12,13) a significant proportion of the patients in recent trials did not receive opioids or pain management as needed.(23,24) Moreover, in a large Italian sample of postoperative patients who underwent elective or emergency surgery, 49% did not receive any opioids. (25) When we designed the protocol during the workshop, we wanted to ensure adequate analgesia before administering hypnotics.

During the observational phase, we found that a large proportion (approximately 50%) of the patients were in deep states of sedation, similar to the study of Payen et al.(2) Midazolam and, in a lesser proportion, propofol were mostly used in our patients. When we applied our protocol, we strongly reduced the use of midazolam and observed a 10% reduction in the number of patients in deep sedation, which was a persistent finding during the first week of mechanical ventilation. However, we could not determine if the positive impact on the level of sedation observed in the interventional group could have been achieved because of the systematic use of a sedation scale, because of the decrease in the midazolam requirement, or both. (11)
Hypnotics are associated with recognized side effects, such as deeper levels of sedation, hemodynamic depression, longer times on mechanical ventilation, and more recently, delirium and chronic cognitive dysfunction. Hypnotics have long been recognized as hypnotic-sparing drugs, which could lighten the level of sedation, facilitate patient evaluation, hasten awakening and decrease the time on mechanical ventilation. The hypnotic-sparing effect we obtained with our protocol compares closely to the findings in the study of Park et al., who found that 37% of patients in a mixed medical-surgical population did not require hypnotics during ventilatory support when an analgesia-based sedation regimen was instituted.

One controversial finding of the present study was that the application of an analgesia-based sedation protocol decreased the incidence of deep sedation but failed to decrease the duration of mechanical ventilation. The study was designed to detect a 20% difference in ventilator-free days, which seems to be a very obtainable effect, based on the literature. The use of continuous infusions, which may prolong the duration of mechanical ventilation, may explain this lack of benefit. However, cultural barriers are hard to challenge because of the low nurse/bed ratio in our country. By introducing a nurse-driven, goal-directed protocol, we may have established a first step in a patient-safety initiative for sedating patients who require mechanical ventilation in our country.

The use of drugs with relatively long elimination half-times, such as midazolam and fentanyl, could also explain this lack of benefit. However, cultural barriers are hard to challenge because of the low nurse/bed ratio in our country. By introducing a nurse-driven, goal-directed protocol, we may have established a first step in a patient-safety initiative for sedating patients who require mechanical ventilation in our country.

Several other reasons can explain this negative trial, such as the lack of a protocol for weaning from mechanical ventilation, which may have a major impact on the time required for mechanical ventilation. This fact also reflects the heterogeneity in the care in the involved ICU (e-supplement). Moreover, the intensity of activities in our protocol was low, compared to recent trials. More frequent evaluations of the sedation level and interventions may have shown a major clinical impact. However, we observed that the present protocol was safe and feasible.

Finally, by decreasing the depth of sedation, we expected a lower incidence of PTSD symptoms. However, no differences were found between drug exposure or level of sedation and the development of PTSD. The high rate of missed data, mostly from patients from rural zones, may preclude us from generating additional conclusions in this regard.

Limitations of the study

The longitudinal nature of the study, in opposition to a randomized one, could influence the type of patients and their management. This method was preferred for several reasons. First, most units involved in the study did not have a sedation protocol for patients who required mechanical ventilation. By first knowing what we were doing and which drugs were preferred, we were able to gain more acceptance for the proposed protocol.

Although we designed an analgesia-based sedation scheme, we did not routinely assess pain levels in our patients. Chanques et al. have suggested that systematic pain evaluation can reduce the time required for mechanical ventilation. However, we designed the interventional protocol after the observational data had already been collected; thus, we did not have baseline data with which to compare. Moreover, because of the nature of the analgesia-based protocol, we did not expect pain to be a major problem.

For the same reason, we should have measured the adverse effects of opioids, such as adynamic ileus or delirium. However, recent studies on analgesia-based sedation have not shown differences in the incidence of ileus compared to standard hypnotic-based sedation. Finally, delirium is a complication of sedative drugs. By the time of the present study, delirium was not usually measured in the units involved in the study; however, since the completion of this study, we have a validated instrument for delirium diagnosis in ICU patients. Agitation, unplanned self-extubations and the use of haloperidol were not increased despite increased awareness.

CONCLUSIONS

We designed and implemented an analgesia-based, goal-directed, nurse-driven sedation protocol in a multicenter, single nation-wide study. Despite the fact
that there was no improvement in major outcomes, we observed that the present protocol was demonstrated to be safe and feasible and that it showed decreased periods in deep sedation without increased agitation. This may be a first step in a patient-safety initiative for sedating mechanically ventilated patients in Chile.

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Authors’ contributions

G Bugedo and E Tobar conceived the study, participated in its design and coordination, performed the statistical analysis and helped to draft the manuscript.

MT Lira participated in the design and coordination of the study.

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All of the authors read and approved the final manuscript.

RESUMO

Introdução: A sedação profunda em pacientes gravemente enfermos se associa a uma maior duração da ventilação mecânica e à permanência mais longa na unidade de terapia intensiva. Diversos protocolos foram utilizados para melhorar esses desfechos. Implantamos e avaliamos um protocolo de sedação baseado em analgesia, direcionado por objetivos e cuidado por enfermeiros, em pacientes gravemente enfermos submetidos à ventilação mecânica.

Métodos: Realizamos um estudo multicêntrico prospectivo em duas fases (antes e depois), que envolveu 13 unidades de terapia intensiva localizadas no Chile. Após uma fase observacional (grupo observacional, N=155), delineamos, implantamos e avaliamos um protocolo de sedação cuidado por enfermeiros, direcionado por objetivos (grupo de intervenção, N=132) para tratar pacientes que necessitaram de ventilação mecânica por mais do que 48 horas. O parâmetro primário de avaliação foi a obtenção de dias livres de ventilador até o dia 28.

Resultados: No grupo de intervenção, a proporção de pacientes com sedação profunda ou coma diminuiu de 55,2 para 44,0%. A incidência de agitação não se alterou entre os períodos, permanecendo em cerca de 7%. Dias livres de ventilador até o dia 28, permanência na unidade de terapia intensiva e mortalidade foram similares em ambos os grupos. Após 1 ano, a presença de sintomas de desordem de estresse pós-traumático nos sobreviventes foi similar entre os grupos.

Conclusões: Delineamos e implantamos no Chile um protocolo de sedação baseado em analgesia, direcionado por objetivos e cuidado por enfermeiros. Embora não se tenha observado melhora nos principais desfechos, observamos que o presente protocolo foi seguro e factível, e que resultou em períodos mais curtos de sedação profunda, sem aumento da agitação.

Descritores: Analgesia; Sedação profunda; Segurança do paciente; Respiração artificial; Protocolos clínicos; Unidades de terapia intensiva
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