Sedation in critically ill patients
Chapter 5

Comparative evaluation of sedation guidelines and clinical practice in long-term sedated critically ill patients

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submitted
Abstract

Background: Sedation protocols in the intensive care have been shown to reduce the duration of mechanical ventilation and length of stay. In this study a sedation protocol for long-term sedated patients is implemented and evaluated by comparing target levels to observed levels of sedation.

Methods: Propofol administration was titrated by the nurses to a physician determined Ramsay score, using a protocol driven approach. Twenty-six critically ill patients were included, who were expected to require mechanical ventilation and sedation > 2 days. The BIS was recorded concurrently.

Results: 541 Ramsay observations were obtained with a median of 16 observations per patient. Target Ramsay scores were achieved in only 28% of the assessments (difference \(d\) between observed and target equals 0), while 35% were within clinical acceptable differences \(d = -1\) or \(d = +1\) and 33% were recorded as oversedated \(d > 1\). The mean difference \(d\) was +0.93 (SD 1.3) and represented the consistent significantly \((P < 0.001)\) deeper level of sedation titrated by the nurses than target by the physicians. When target scores were achieved, a dose reduction was attempted 15% of the time. At oversedation \(d > 1\) the infusion rate was mostly maintained (63%). Mean BIS values were significantly different between the groups agitation, light and deep sedation \((P < 0.001)\). The Ramsay score and the BIS were moderately \((r = -0.570, P < 0.01)\) correlated.

Conclusion: We found that in clinical practice, critically ill patients tend to be oversedated. Repeated feedback may be necessary in order to benefit from claimed advantages of a sedation protocol.

Introduction

Mechanically ventilated patients require an appropriate level of sedation and should not have excessive levels to reduce the risk of prolonged mechanical ventilation, related complications and length of stay in the intensive care unit (ICU). A nurse-driven sedation protocol\(^1\) and daily interruption of sedation\(^2\) can decrease these risks, which resulted in recommendation of the Society of Critical Care Medicine\(^3\) to use sedation guidelines. However, there is considerable variability between published evidence and local guidelines with regard to the choice of sedative, sedation scoring systems and the practice of daily interruption.\(^4\) In addition, although most ICUs have developed and stated a (local) sedation protocol, actual clinical practice may (wittingly or unwittingly) differ significantly and this may affect the intended improved health outcome.\(^5\) Specifically, deeper levels of sedation used to be common in most ICUs before the introduction of sedation protocols. Surprisingly, little research is published on the adherence to sedation protocols in the ICU, especially for long term sedated critically ill patients who may benefit the most from the claimed advantages. In this study we implemented a sedation protocol for critically ill patients who were expected
to be mechanically ventilated and sedated for more than 2 days. We evaluated the compliance to the target levels of sedation. Assessment of sedation was performed using the Ramsay score. The Bispectral index (BIS) was recorded concurrently, thereby exploring the BIS as an additional instrument to measure the level of sedation. This enables examination of the relation between the Ramsay and the BIS as a secondary objective, as BIS use is not yet clear in the ICU.\(^6\)

**Materials and Methods**

The study was performed in a 30 bed mixed surgical/medical intensive care unit at the St Antonius Hospital in Nieuwegein, The Netherlands, a tertiary teaching hospital. Patients were eligible for participation in the study if they were between ages of 20-90 years and expected to be mechanically ventilated and sedated for more than 2 days with propofol as the primary sedative choice. Patients with known hypertriglyceridemia, allergic history to propofol or pregnancy were excluded as were patients with a known history of drug abuse. The study was approved by the Ethics Committee of the St Antonius Hospital, Nieuwegein, The Netherlands. Written informed consent was obtained from the next of kin.

**Development of guideline**

Two anesthesiologist-intensivists, two hospital pharmacists and seven ICU nurses developed the sedation guideline for propofol. Propofol was chosen as the drug of choice for long-term sedation, because of the high level of experience with propofol in our clinic, the short duration of action which enables rapid awakening and the local availability of Propofol 6% preventing high fat loads upon prolonged use. Before this study, the nursing staff was familiar with the Ramsay score, but levels of sedation were not systematically scored and recorded.\(^7\) At the time of the investigation, the BIS had not been introduced to monitor sedation in the ICU, despite its routine use in anaesthesia. One ICU nurse tested the feasibility of daily wake up and assessment of the sedation level by the nurses in a pilot study during a period of 1.5 months. Eventually, the final guideline (Figure 1) was presented to and discussed with the physicians and nurses and distributed to the physicians by internal post. At inclusion of each patient, the guideline and disadvantages of inappropriately deep sedation were again discussed with the nurses in the morning and in the afternoon, reaching 2 of the 3 shifts of the primary care nurses daily. Nurses were asked to list reasons for dose adjustments and comment on the patients’ sedation state on the Case Report Form. The nursing staff was instructed to titrate on the Ramsay as shown in the guideline and warned not to use BIS values because of lack of validation. They were told that the BIS decreases with level of consciousness during anaesthesia, but that the role and target values of the BIS in the intensive care patients (without muscle relaxants) are not clear.
Figure 1 Schematic representation of the sedation protocol. The Bispectral index was monitored continuously.

*Sedative and analgesic regimen*

Propofol sedation (Propofol 6%, or Propofol 1% (AstraZeneca, Zoetermeer, The Netherlands) was guided by a sedation protocol (Figure 1), in which the attending physician determined twice daily the target Ramsay score, the need of interruption of propofol or the definitive discontinuation of the sedative. The Ramsay score is a six point scale: 1) patient anxious, agitated, restless, 2) cooperative, orientated and tranquil, 3) drowsy or asleep, easily responding to commands, 4) patient asleep, brisk response to a light glabellar tap, 5) patient asleep, sluggish response to a light glabellar tap and 6) patient asleep, no response to a light glabellar tap. The primary care nurse adjusted the infusion rates according to the target Ramsay score and assessed in standard manner 4 times daily the level of sedation and 30 and 60 minutes after dose adjustment. If the target Ramsay score was achieved, a decrease in dose rate of approximately 10% was attempted. If patients were agitated, the Numeric Rating Scale (a 0-10 point scale) was used as pain instrument to determine whether analgesia was well controlled (NRS ≤ 4) before the propofol infusion rate was increased. Higher requirements than a maximum propofol infusion rate of 6 mg·kg⁻¹·h⁻¹ for a maximum of 6 h were considered therapeutic failures.

The BIS was recorded continuous concurrently as an objective marker for the depth of sedatives (BIS®, XP, A 2000 revision 3.22, Aspect Medical Systems) using the quarto BIS® XP sensor electrodes. The values of the BIS ranges from 100 (awake) to 0 (isoelectric electroencephalogram).
Measurements
The Acute Physiology and Chronic Health Evaluation (APACHE II) score was determined on the first 24 h at admission to the ICU. The severity of illness was measured by the Sequential Organ Failure Assessment (SOFA) score. For safety purposes serum triglycerides were monitored.

Statistical analysis
Statistical analysis was performed using SPSS (version 12.01 for windows; SPSS, Chicago, IL, USA). Measurement of agreement between the target Ramsay score and the observed Ramsay score was performed using a Bland Altman plot. The Wilcoxon signed ranks test for paired data was used to test the null hypothesis that the observed Ramsay score equalled the target Ramsay score.

To study the relation between the Ramsay and the BIS, four paired observations were randomly obtained per patient. The Spearman’s rho was used to determine the correlation between paired Bispectral index and Ramsay scores. The Kruskal Wallis test was used to determine whether the mean BIS values differed between the Ramsay groups agitation (Ramsay 1), light sedation (Ramsay 2-4) and deep sedation (Ramsay 5-6).

Table 1 Patient characteristics (n=26). Data are numbers and median (minimum-maximum).

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M/F</td>
<td>16 / 10</td>
</tr>
<tr>
<td>Age, years</td>
<td>70 (38-81)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.5 (50-120)</td>
</tr>
<tr>
<td>APACHE score at admission ICU</td>
<td>21 (12-49)</td>
</tr>
<tr>
<td>SOFA score at inclusion</td>
<td>12 (5-21)</td>
</tr>
<tr>
<td>Diagnostic group</td>
<td>26</td>
</tr>
<tr>
<td>Cardiac (surgical/medical)</td>
<td>4 / 3</td>
</tr>
<tr>
<td>(ruptured) (thoraco) abdominal aortic aneurysm</td>
<td>5</td>
</tr>
<tr>
<td>sepsis</td>
<td>6</td>
</tr>
<tr>
<td>pneumonia</td>
<td>4</td>
</tr>
<tr>
<td>miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Propofol infusion duration at inclusion, days</td>
<td>1.5 (0-12)</td>
</tr>
<tr>
<td>Studied propofol infusion duration, days</td>
<td>1.9 (0.7-9.7)</td>
</tr>
<tr>
<td>Propofol infusion rate, mg/h</td>
<td>147 (51-398)</td>
</tr>
<tr>
<td>Propofol infusion rate, mg·kg·h⁻¹</td>
<td>2.0 (0.4-5.3)</td>
</tr>
<tr>
<td>Number of infusion rate adjustments per patient</td>
<td>increases 1.1 (0-6.1)</td>
</tr>
<tr>
<td>decreases</td>
<td>1.1 (0-7.1)</td>
</tr>
<tr>
<td>Morphine infusion rate, mg/h</td>
<td>0.8 (0-3)</td>
</tr>
</tbody>
</table>

*gastric tube reconstruction, femoropopliteal bypass surgery, hyperthermic intra-peritoneal chemotherapy, necrotizing pancreatitis.
Results

The characteristics of the patients participating in the study are shown in Table 1. The studied population included 12 surgical and 14 medical patients. Patients were studied for 0.7-9.5 days (median 1.9 days).

Evaluation of the stated sedation protocol

A total of 541 Ramsay observations were obtained with a median of 16 observations (4-67) per patient. In 15% of the observations a period of deep sedation (Ramsay 5 and 6) was desired according to the physicians, because of pressure - and volume controlled ventilation, prone position, defibrillation and/or severe critical illness (SOFA > 15). Light sedation (Ramsay 2-4) was desirable in 67%. In 17% (96 missing values), the target Ramsay score was not recorded. As a measure of agreement between the target Ramsay score and the observed Ramsay score, a Bland-Altman plot was constructed (Figure 2). In this plot, the mean difference between the observed and target Ramsay score \( d \) is +0.93 (SD 1.3) and represents a consistently deeper level of sedation titrated by the nurses than target by the physicians. Thirty-five percent of the assessments were within clinical acceptable differences \( d = -1 \) or \( d = 1 \). Thirty-three percent could be recorded as oversedated \( d > 1 \). The observed deeper level of sedation was significantly different \( (P < 0.001) \). As the period of sedation and thus the number of assessments varied, pairs of means were also calculated from the mean of each patient. A comparable mean difference of +0.96 (SD 1.4) Ramsay score was calculated and percentages of clinical acceptability and oversedation were comparable. In fourteen patients the difference between Ramsay observed and target was significantly different \( (P < 0.05) \) (all deeper). Nurses titrated in 62% to a deep sedation level of 5.

Figure 2 Bland-Altman plot of the differences between observed and target Ramsay score. The horizontal solid line represents the mean of the differences between the observed and the target Ramsay score. The horizontal dashed lines represent the limits of agreement at \( \pm 1.96 \text{SD} \).
and 6. Dose titrations occurred at all levels of sedation. At close titration \((d = -1, n=27 \text{ and } +1, n=118)\), the dose was increased and decreased within 3 hours by the nurses in both 19% of the assessments. At failure \(d < -1 (n=14)\) and \(d > 1 (n=128)\) the infusion was increased and decreased in 71% and 28%, respectively. At correct titration \((n=112)\) a dose reduction was attempted in only 15% of all assessments. The assessments during interruption were excluded from this analysis (46 values). As reported in Table 1, infusion rates were adjusted on average 2.2 times per patient per day. Nurses reported the following reasons for lack of downwards titration in patients who were deeper sedated than target: motor agitation, nursing care, change in mechanical ventilation, hemodynamic effects of propofol, severity of illness, lack of time and difficulty in titration. Interruption was desired by the physician in 9 patients (35%), which were all postoperative patients who were at risk for neurological complications while undergoing pressure control ventilation. The median duration of interruption was 32 minutes (15-238, \(n=12\)). After restarting, in 33 percent the infusion rates could be decreased to 50% of the previous rate. In one patient, interruption after 44 hours infusion lead to agitation, manifested as extreme hypertension. In one patient there was no need to restart the sedative after the interruption, resulting in successful extubation. Two patients showed high dose requirements of propofol and cholestasis, being therapeutic failures and sedation was continued with midazolam.

**Exploration of the role of the Bispectral Index:**

A total of 104 paired observations were analyzed. Mean BIS values were significantly different between the groups agitation, light sedation and deep sedation \((P < 0.001)\) (Table 2). BIS values less than 60, usually associated with deep sedation\(^{14}\) were recorded in 78% of the oversedated patients \((d \geq 2\) Ramsay scores). There was a moderate, but statistically significant correlation between Ramsay and BIS (Spearman’s rho = -0.570, \(P < 0.01\)). One critically ill patient showed during 3.7 days continuously a high BIS and electromyographic activity (EMG), while the level of sedation was clinically assessed at Ramsay 4-6. After administration of muscle relaxant (bolus dose of 50 mg rocuronium) for facilitation of endotracheal tube exchange, the BIS and EMG markedly decreased from 94 ± 3.6 to a minimum of 29 and 53 ± 3.2 dB to 26 dB, respectively.

**Table 2** Mean Bispectral Index values for the grouped Ramsay sedation scores.

<table>
<thead>
<tr>
<th>Ramsay</th>
<th>BIS mean</th>
<th>(N)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (agitation)</td>
<td>93</td>
<td>4</td>
<td>2.20</td>
</tr>
<tr>
<td>2-4 (light sedation)</td>
<td>75</td>
<td>37</td>
<td>22.0</td>
</tr>
<tr>
<td>5-6 (deep sedation)</td>
<td>55</td>
<td>63</td>
<td>20.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>104</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discussion

In this study we show that actual clinical sedation practice often differs from sedation guidelines, evidenced by differences between the target and actually observed levels of sedation in long-term sedated critically ill patients. The intention of sedation guidelines to improve the patients’ outcome by reduction of the duration of the mechanical ventilation, ICU and hospital length of stay\(^1\text{,}^2\) may therefore be not fully identified in current practice.

According to the advice of the Committee of the Society of Critical Care Medicine\(^3\) and the Netherlands Society of Intensive Care, doses of the sedative were adjusted to the Ramsay scale using a protocol-driven approach, a situation similar to most ICUs. However, we found that patients were often sedated to a deeper level \((P < 0.001)\) than was defined by the attending physician (Figure 2). Specifically, the differences between the observed and target Ramsay score \((d)\) was \(+0.93\) (SD 1.3) Ramsay score. Deep levels of sedation Ramsay 5 and 6 were scored by the nurses in 62% in total, whereas deep sedation was defined as ideal by the physician in only 15% of the cases.

The defined deep sedation by the physicians seems judged to the mode of mechanical ventilation, although definitions of ideal sedation in critically ill patients may be disputable. Previous publications have stated different Ramsay scores as ideal varying from Ramsay 3-4\(^15\), 5-6\(^16\), 2-3 to deep sedation for patients nursed with unconventional ventilator strategies (prone positioning, pressure controlled ventilation and low tidal volumes).\(^17\) According to the nurses’ opinion in our ICU, some patients required deeper sedation because of severe illness, motor agitation, facilitation of caring practices and variation of mode of ventilation during the day. The rate of infusion was often increased at undersedation, however, oversedation was not reliably followed by a decrease in infusion rate, which suggest that ICU nurses are particularly focused on reducing patient distress. Reported barriers to titrate correctly were lack of time, difficulty to titrate and concern on the hypotensive effects of propofol. However, the low median numbers of propofol adjustments per day indicate a tendency to keep the same infusion rate constant. Interestingly, Cabana et al.\(^18\) offered reasons why physicians do not follow practice guidelines. For physicians, lack of familiarity and awareness affecting knowledge, lack of agreement affecting attitude and finally external barriers as lack of time affecting attitude were the most often reported reasons for limiting adherence. The present study suggests that for ICU nurses, lack of familiarity or awareness are not the exclusive reasons for low adherence and inappropriately deep sedation, as the nurses were instructed and special emphasis was put on the negative effects of oversedation. Similar results were shown in a previous study.\(^2\) Unfortunately, comments on non-compliance were not extensively reported by the nurses in this study. Further studies are therefore needed to find the exact reasons of the nurses for not following guidelines in practice. In our view, potential quality improvement of guideline adherence may include frequent redefinition of the target levels in critically ill patients, since their condition may change rapidly during the day. Moreover, daily reevaluation of the achieved sedation level in the multidisciplinary meeting to allow for feedback from the primary care nurse.

Although patients were sedated to a deeper level than target, knowledge of the effects of
oversedation may have already resulted in our ICU in a less aggressive sedation level. In a previous study from our group in 1999/2000, we noted a tendency to aggressively sedate critically ill patients during the whole ICU period, assessing 60-80% of the sedation levels at Ramsay 6 without sedation protocol, judged as adequate by the nurses, while in the current study 34% of the assessments were in Ramsay 6 at comparable severity of illness.

In contrast to the defined daily interruption in the studied protocol, interruption for neurological assessment was only standard practice in patients who were at risk for neurological complications following vascular surgery. Daily interruption was not primarily used to optimize the dosage or decrease the tendency to keep the same infusion rate, using lower infusion rates at restarting. However, if sedatives are well titrated a wake-up period will not be required theoretically and the benefit for sedatives with low risk of accumulation may be less pronounced.

To evaluate the BIS as an objective endpoint of a patient’s level of sedation, the BIS was monitored continuously in addition to the Ramsay score. Although the Ramsay score is the most widely used titration endpoint, it is well known that the Ramsay score is not ideal as a sedation instrument. Due to the subjective nature of the score, it is for example difficult to discriminate between 3, 4 and 5, while Ramsay 6 seems to be a mixture of different levels of unconsciousness. In our study, BIS values were found to be significantly different between agitation, light sedation and deep sedation with values of 93, 75 and 55, respectively. Between the scales, a moderately significant correlation \( r = -0.570 \) was found. In the oversedated patients \( (d \geq 2 \text{ Ramsay score}) \) low BIS values less than 60, associated with deep sedation were recorded in 78% of the critical ill patients. Apart from the shortcomings of the BIS, such as EMG interference, the BIS in our view might be helpful to differentiate in level of sedation in deeply sedated patients and might stimulate nurses to decrease the infusion rate if low values of the BIS are recorded, which should be evaluated in further studies.

In conclusion, in order to benefit from claimed advantages of a sedation protocol in the ICU, its implementation should be accompanied with repeated feedback, since in clinical practice in 33% of the cases, patients were sedated to a deeper level by the nurses than was defined by the attending physician.

Acknowledgements

The authors wish to thank the medical and nursing staff in particular Enny Noordzij, Roelie Deuten and Annette de Bruijn of the Intensive Care Unit and the staff of the department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, The Netherlands for their help and cooperation. Furthermore, we would like to thank Ellen Tromp, methodologist, Ph.D., St Antonius Hospital, Nieuwegein, The Netherlands for statistical support. We thank also Martijn Pruissen, M.D., Department of Neurology for his advice and Douglas Eleveld, M.D. Ph.D., Departments of Anesthesiology, University Medical Center Groningen, Groningen, The Netherlands for critically reading the manuscript.
References


Chapter 5


