L’analgo-sédation en réanimation : *Peu c’est trop!*

M Boussarsar

Réanimation Médicale - Sousse
“... But what I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise.”

Thomas L. Petty, 2012

“... But what I saw several years ago when arriving in Sousse, were agitated patients, bathing in their sweats, with tachycardia, and attached by four plus a chest strap and fighting the ventilator!”

Mohamed Boussarsar, 2004
Ere 1: Modern intensive care therapy

Section of Epidemiology

President—A. Bradford

The Epidemic of Poliomyelitis

By H. C. A.
Professor of Epidemiology, Chief Physician Blegdam Hos,

Proceedings of the Royal Society of

Fig. 1 A young patient with poliomyelitis being manually ventilated by a medical student during the poliomyelitis epidemic in Copenhagen, 1953 [Source: Medical History Museum in Copenhagen]
Ere 2: From anesthesia to ICU care

L'Engström 150 (1954), (l’équipe du Dr. Carl Gunnar Engström) ventilateur à fréquence fixe, a été en Europe l'appareil qui contribua le plus au développement de la ventilation mécanique et à l'essor de la réanimation.
The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation.

Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G.

Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA.
Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation.


Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, MO, USA
Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial.


Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN 37232-8300, USA. timothy.girard@vanderbilt.edu

Time to wake up the patients in the ICU: a crazy idea or common sense?

Strøm T, Toft P.

Department of Anesthesia and Intensive Care Medicine, Odense University Hospital, University of Southern Denmark, Odense C, Denmark. t.s@dadlnet.dk
Analgo-sédation : késako?

Analgo-sédation : recommandations?

Analgo-sédation : écarts?
- **Analgo-sédation :** *késako?*

- **Analgo-sédation :** *recommandations?*

- **Analgo-sédation :** *écarts?*
Analgo-sedation: objectifs

- Diminution douleur, anxiété
- Adaptation patient-machine
- Diminution du travail respiratoire
- Diminution de la réponse neuroendocrine au stress (↓VO2)
- Prévenir les extubations accidentelles
- Réduire l’apparition de délirium
- Réduire l’incidence du PTSD
Analgo-sedation: *balance*

- Under Sedation:
  - Pain
  - Self Extubation
  - Misery
  - Awake
  - Aware

- Over Sedation:
  - VAP
  - Long-term decrease in cognitive function
  - Hemodynamic instability
  - Increased LOS and cost
  - PTSD

- Titration
  - Pain
  - Sedation
  - Delirium

- Reduced pain
- Decreased anxiety
- Managed delirium
- Amnesia
- Recovery
Analgo-sedation: Souvenirs!

- 66% des patients se souviennent de leur séjour
- Le séjour est très inconfortable :
  - ne pas pouvoir communiquer (65%)
  - avoir soif (62%)
  - se sentir tendu (46%)
  - perdre la maîtrise de soi (46%)
  - avoir des difficultés à déglutir (44%)
- L’IT est très inconfortable :
  - ne pas pouvoir parler (68%)
  - douloureuse (56%), avec VAS 4-8 mm
  - angoissante (59%)
- L’IT est associée à :
  - troubles du sommeil (insomnie, réveil brusque, cauchemars)
  - périodes de terreur, panique
  - peur de la solitude

Rotondi, Crit Care Med, 2002
Analgo-sedation: Moyens

Moyens non pharmacologiques:

- La communication (information du patient, visites) et le maintien du rythme nycthéméral et de l'orientation temporo-spatiale des patients (présence de fenêtres, horloges).

- Les techniques d'approche psychologique (approche cognitive, hypnose, musique) ou la stimulation électrique ne sont au mieux que des adjuvants de la sédation.

- Chez l'enfant, la participation des parents est mieux intégrée dans les soins que la présence de la famille chez l'adulte.
Analgo-sedation: Moyens

Table 6: Agents for Sedation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical IV Bolus Dose</th>
<th>Typical Infusion Rate</th>
<th>Onset to Peak</th>
<th>Duration</th>
<th>Average Price/Day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fastest onset and shortest</td>
</tr>
<tr>
<td>Fentanyl (Diprivan)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NSAIDs (Parenteral)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (Caldolor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketorolac (Toradol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Agents for Delirium

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antipsychotic Agent</th>
<th>Dosage Form</th>
<th>Metabolism</th>
<th>Metabolizing Enzyme</th>
<th>Equine Doses (approx)</th>
<th>Max Dose (mg/day)</th>
<th>QTc Prolongation</th>
<th>Potential Dose Related Effects</th>
<th>Sedation</th>
<th>Dopaminergic Receptor Affinity/ Extrapyramidal Symptoms</th>
<th>Anticholinergic Effects</th>
<th>Orthostatic Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haloperidol</strong></td>
<td>Haloperidol (Haldol)</td>
<td>Tab, IV injection</td>
<td>T1/2, 21 hrs Hepatic</td>
<td>CYP3A4, 2D6</td>
<td>2</td>
<td>35</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>LORazepam</strong></td>
<td>LORazepam (Ativan)</td>
<td>Tab, ODT tab, solution (1 mg/ml)</td>
<td>T1/2, 3 hrs Hepatic</td>
<td>CYP2D6, 3A4</td>
<td>1</td>
<td>4</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Aripiprazole</strong></td>
<td>Aripiprazole (Abilify)</td>
<td>Tab, solution (5mg/ml), IM injection</td>
<td>T1/2, 75 hrs Hepatic</td>
<td>CYP2D6, 3A4</td>
<td>5</td>
<td>30</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Black Box Warning: Increased mortality seen when used in elderly patients with dementia-related psychosis due to cardiovascular or infectious complications.

The use of these agents for delirium in ICU patients has not been tested in large, randomized, placebo-controlled trials.

* Use heightened caution and be aware that there is a dose related QT interval prolongation and torsades de pointes (Tdp) risk when using in excess of >20 mg per day.

The following agents are NOT recommended for ICU use.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Capsule</th>
<th>T1/2, 7 hrs Hepatic</th>
<th>CYP3A4, 1A2</th>
<th>40</th>
<th>160</th>
<th>High</th>
<th>High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Moderate</th>
</tr>
</thead>
</table>

Notes:
- Equivalent prices and doses
- Doses higher than recommended (Fentanyl 0.1-0.5 mcg/kg/min)
- Midazolam and LORazepam in high bolus doses and resultant sedation
- Based on clinical experience

References:

* Tdp: Torsades de pointes
* Uses: Increased with IV formulation
* Contraindications: Bone marrow suppression, blood dyscrasias
* Secondary to high risk for QT prolongation
* Secondary to high risk for metabolic syndrome
Analgo-sedation: Outils

**Figure 6: 10 Point Non-Verbal Pain Scale**

Directions: Observe patient per category and, based on your first impression, place mark on the scale corresponding to the patient's non-verbal expression of pain.

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No pain</td>
<td>No pain</td>
</tr>
<tr>
<td>1</td>
<td>Alert</td>
<td>Alert</td>
</tr>
<tr>
<td>2</td>
<td>Smiling</td>
<td>Smiling</td>
</tr>
</tbody>
</table>

**Table 1:**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score</th>
<th>Label</th>
</tr>
</thead>
</table>
|          | 0     | No
treatment     |
|          | 1     | Occasional
wring        |
|          | 2     | Frequent
wring         |

**Table 2: Riker Sedation-Agitation Scale (SAS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No agitation</td>
<td>Patient is at rest or sleeping</td>
</tr>
<tr>
<td>1</td>
<td>Drowsy</td>
<td>Patient is sleepy but easily aroused by verbal or tactile stimuli</td>
</tr>
<tr>
<td>2</td>
<td>Very Drowsy</td>
<td>Patient is sleepy and requires frequent verbal or tactile stimulations</td>
</tr>
<tr>
<td>3</td>
<td>Agitated</td>
<td>Patient is restless and agitated, requiring sedation</td>
</tr>
</tbody>
</table>
| 4     | Calm and
Cooperative | Patient is calm and cooperative, easily aroused by verbal or tactile stimuli                  |
| 5     | Sedated       | Patient is considerably impaired, requiring sedation to wake or maintain alertness              |
| 6     | Very Agitated | Patient is agitated, requiring sedation to control or maintain alertness                        |
| 7     | Dangerous
Agitation | Patient is combative, requiring physical restraint to control or maintain alertness             |

**SAS Target Sedation = 3 to 4**

- 3: Sedated
- 4: Very Sedated

Examples:

- **Sedated**: Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again.
- **Very Sedated**: Aroused to physical stimuli but does not communicate or follow commands, may move spontaneously.
- **Dangerous Agitation**: Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side.
- **Very Agitated**: Requiring restraint and frequent verbal reminding of limits, biting ETT.
Analgo-sedation: évaluations
Analgo-sedation: *charte*

**Problem Statement:**
For patients in adult ICUs, there are:
- Inconsistent interpretation of provider orders
- Inconsistent practice in the use of sedation and analgesia
- Lack of an executable plan
- Assessment tools and protocols are shortcoming

**Customer(s) and Requirements:**
Critical care health care professionals need a straightforward protocol that can be consistently executed.

**Deliverables:**
Tool kit for the assessment and management of intubated ICU adult patients who need sedation to include:
1. Guidelines/Protocols and Algorithm
2. Assessment Tools (pain, sedation, and delirium scales)
3. Evidenced-based Order Set

**Project Scope:**
This project includes intubated patients in adult ICUs who require more than 24 hours of ventilatory support. This project *excludes* the following types of patients:
- Extubated patients in adult ICUs
- Pediatrics
- Head trauma and burn injuries
- End of Life care
- Non-Intensive care
- Chemically paralyzed
- Chronic substance abuse

**Goal and Other Potential Benefits of Appropriate Sedation Protocol:**
To develop an evidenced-based tool kit that supports the achievement of the following metrics of appropriate sedation:
- Decrease pain
- Decrease anxiety
- Decrease patient’s ventilator days
- Decrease patient’s ICU length of stay
- Reduce long term cognitive decline
- Avoid heart, lung, liver, and kidney complications
- Reduce the incidence of PTSD
- Reduce occurrences of spontaneous extubation
- Reduce the occurrence of delirium and/or improve the management of delirium
Analgo-sédation : késako?

Analgo-sédation : recommandations?

Analgo-sédation : écarts?
Analgo-sédation : recommandations?
Analgo-sedation: protocols
Analgo-sedation: protocols

Scheduled opioid doses or a continuous infusion is preferred over an “as needed” regimen to ensure consistent analgesia. A PCA device may be utilized to deliver opioids if the patient is able to operate the device. (Grade of recommendation = C)

Fentanyl is preferred for sedation of acutely agitated or in acutely distressed patients. (Grade of recommendation = C)

Fentanyl or hydromorphone with hemodynamic instability (Grade of recommendation = B)

Morphine and hydromorphone with intermittent therapy because of side effects. (Grade of recommendation = B)

Recommendation: Sedation patients should be started on an adequate analgesia and treatment for causes. (Grade of recommendation = B)

Recommendations: Midazolam is recommended for short-term use only, as it produces unpredictable awakening and time to extubation when infusions continue longer than 48–72 hours. (Grade of recommendation = A)

Propofol is the preferred agent when rapid awakening (neurologic assessment or extubation) is important. (Grade of recommendation = B)

The titration of the sedative dose to a defined endpoint is recommended with systematic tapering of the dose or daily interruption with retitration to minimize prolonged sedative effects. (Grade of recommendation = A)

Recommendation: The potential for opioid, benzodiazepine, and propofol withdrawal should be considered after high doses or more than approximately seven days of continuous or tapered systematically. (Grade of recommendation = C)

Recommendations: Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. (Grade of recommendation = C)

Patients should be monitored for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol. (Grade of recommendation = B)

Recommendation: Sleep promotion should include optimization of the environment and nonpharmacologic methods to promote relaxation with adjunctive use of hypnotics. (Grade of recommendation = B)
Analgo-sédation: protocoles

- **Analgo-sédation** Propofol midazolam / Sufentanil remifentanil

- **Echelles** EVA / BPS

- **Evaluations régulières** Ramsay / ATICE

- **Protocoles** Arrêt quotidien / titration
Analgo-sédation : *késako*?

Analgo-sédation : *recommandations*?

Analgo-sédation : *écarts*?
Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult
Crit Care Med 2002

Current Practices in Sedation and Analgesia for Mechanically Ventilated Critically Ill Patients

A Prospective Multicenter Patient-based Study

Jean-Francois Payen, M.D., Ph.D.,* Gérald Chanques, M.D.,† Jean Mantz, M.I. Igor Auriant, M.D.,‖ Jean-Luc Leguillou, M.D.,§ Michèle Binhas, M.D.,** Céline Jean-Luc Bosson, M.D., Ph.D.¶¶ for the DOLOREA Investigators

Perceived versus Actual Sedation Practices in Adult Intensive Care Unit Patients

Kimberly Varney Gill PharmD BCPS, Stacy A Volls PharmD BCPS, Gregory A Chenaud PharmD, Gretchen M Brophy Pha


Analgesedation: a paradigm shift in intensive care unit sedation practice.

Devabhakthuni S, Armahizer MJ, Dasta JF, Kane-Gill SL.

Research

Sedation practice in the intensive care unit: a UK national survey

Henrik Reschreiter¹, Matt Maiden¹ and Atul Kapila²

Table 2. Incidence (%) of Patients Being Assessed and Those Receiving Sedatives and Analgesics during the ICU Stay

<table>
<thead>
<tr>
<th></th>
<th>D2 (1,360 Patients)</th>
<th>D4 (1,256 Patients)</th>
<th>D6 (1,099 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on MV</td>
<td>94</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-recruiter</td>
<td>36</td>
<td>31</td>
<td>49</td>
</tr>
<tr>
<td>Dedicated</td>
<td>39</td>
<td>37</td>
<td>74</td>
</tr>
<tr>
<td>Educated</td>
<td>80</td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>Sedation on D2</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Assessment</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Treatment</td>
<td>21*</td>
<td>22*</td>
<td>36</td>
</tr>
<tr>
<td>Analgesia on D2</td>
<td>39</td>
<td>37</td>
<td>74</td>
</tr>
<tr>
<td>Assessment</td>
<td>39</td>
<td>37</td>
<td>74</td>
</tr>
<tr>
<td>Treatment with</td>
<td>572</td>
<td>447</td>
<td>647</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedural pain</td>
<td>335</td>
<td>143</td>
<td>158</td>
</tr>
<tr>
<td>Assessment</td>
<td>335</td>
<td>143</td>
<td>158</td>
</tr>
<tr>
<td>Treatment</td>
<td>148</td>
<td>158</td>
<td>158</td>
</tr>
<tr>
<td>Non-opioids on</td>
<td>217</td>
<td>230</td>
<td>230</td>
</tr>
<tr>
<td>D2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Impact of the Use of Protocol for Sedation and Analgesia Management among the 44 Participating Sites

<table>
<thead>
<tr>
<th></th>
<th>Use of Protocol (n = 16 Sites)</th>
<th>No Use of Protocol (n = 28 Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University hospital, n</td>
<td>12 (75)</td>
<td>22 (79)</td>
</tr>
<tr>
<td>ICU beds per site, median (range)</td>
<td>13 (8–31)</td>
<td>12 (8–24)</td>
</tr>
<tr>
<td>Caregivers per bed, median (range)</td>
<td>4.1 (2.7–5.6)</td>
<td>4.1 (2.0–7.5)</td>
</tr>
<tr>
<td>Low-recruiter sites, n</td>
<td>5 (31)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Dedicated education, n</td>
<td>12 (75)</td>
<td>11 (39)*</td>
</tr>
<tr>
<td>Patients on MV on D2, n</td>
<td>602 (91)</td>
<td>672 (96)*</td>
</tr>
<tr>
<td>SAPS II, median (range)</td>
<td>41 (8–107)</td>
<td>44 (6–112)*</td>
</tr>
<tr>
<td>Sedation on D2, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment</td>
<td>370 (56)</td>
<td>215 (31)*</td>
</tr>
<tr>
<td>Treatment</td>
<td>451 (68)</td>
<td>530 (76)*</td>
</tr>
<tr>
<td>Analgesia on D2, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment</td>
<td>398 (60)</td>
<td>175 (25)*</td>
</tr>
<tr>
<td>Treatment with opioids</td>
<td>572 (87)</td>
<td>647 (92)*</td>
</tr>
<tr>
<td>Procedural pain on D2, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment</td>
<td>335 (51)</td>
<td>143 (20)*</td>
</tr>
<tr>
<td>Treatment</td>
<td>148 (22)</td>
<td>158 (23)</td>
</tr>
<tr>
<td>Non-opioids on D2, n</td>
<td>217 (33)</td>
<td>230 (33)</td>
</tr>
</tbody>
</table>

Low-recruiter sites were defined as less than 20 patients included per site during the study. The number of patients in the intensive care unit (ICU) on day 2 (D2) was 600 in sites using a protocol and 700 in sites using no protocol.

* P < 0.05 and † P < 0.01 vs. “use of protocol.”

MV = mechanical ventilation; SAPS = Simplified Acute Physiology Score.
Utilisation des échelles de sédation dans les réanimations européennes

Perceived versus Actual Sedation Practices in Adult Intensive Care Unit Patients Receiving Mechanical Ventilation

Kimberly Varney Gill PharmD BCPS, Stacy A Voils PharmD BCPS, Gregory A Chenault PharmD, Gretchen M Brophy PharmD BCPS FCCP FCCM

Conclusions: These data suggest differences in perceived and actual sedation practice in the US, as well as underutilization of evidence-based interventions. Most notable was the limited use of sedation treatment algorithms, daily interruption of sedation, and monitoring for delirium. Individual sedation and delirium protocols should be evaluated and updated based on evidence-based recommendations.
Conclusion: Analgosedation is an efficacious and well-tolerated approach to management of ICU sedation with improved patient outcomes compared to sedative-hypnotic approaches. Additional well-designed trials are warranted to clarify the role of analgosedation in the management of ICU sedation, including trials with nonopioid analgesics.
What constitutes the ideal level of sedation in the ICU is still controversial. In the past, the practice of ICU sedation has focused on the extensive use of sedatives to achieve deep sedation or "detachment" from the environment.

Recent evidence suggests that patient outcomes are significantly influenced by the choice of agent, the presence of over- or undersedation, poor pain control, and delirium.

Thus, there is a trend toward lighter sedation guided by sedation assessment tools.
Conclusions Most UK ICUs use a sedation guideline and sedation scoring tool. The concept of sedation holding has been implemented in the majority of units, and most ICUs have a written sedation guideline.
No sedation: *Is it possible?*


**Comfort without coma: changing sedation practices.**
Fraser GL, Riker RR.

Crit Care Med. 2009 Sep;37(9):2654-5.

**Living on the lighter side of sedation in the intensive care unit: is there a psychological cost?**
Girard TD.
A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial.

Strom T, Martinussen T, Toft P.
**Design overview**

In the main study the primary end point was to prove the effect of a no sedation strategy compared to a standard strategy with sedation and daily interruption of sedative infusions.

**The primary endpoints were the length of mechanical ventilation, length of ICU stay and total hospital length of stay.**

Secondary endpoints were the number of ventilator associated pneumonias (VAP), number of CT or MR scans of the cerebrum and number of accidental extubations.

In the renal posthoc study we defined the renal effects in terms of urine output and RIFLE classification as the primary endpoints.

Secondary endpoints were the mean arterial blood pressure, fluid balance and the use of vasoactive drugs between the two groups.

For the psychological follow up study the primary endpoint was the rate of PTSD between the groups. Other measures such as general health, rate of depression and recalls from the ICU were secondary outcomes.
Strom T, Johansen RR, Prahl JO et al.
Sedation and renal impairment in critically ill patients: a post hoc analysis of a randomized trial.

Strom T, Stylsvig M, Toft P.
Long-term psychological effects of a no-sedation protocol in critically ill patients.
Crit Care 2011;15:R293.
patients, the study period started upon admission to the intensive care unit; no patient was excluded because of the duration for which patients required mechanical ventilation before they were randomized.

The study was approved by the local research ethics committee, and written informed consent was obtained from every patient or their designated legal representatives. Consent was given by the patients regarding the intervention and consent was obtained from the patients' legal representatives.

Randomisation and masking

Within 24 h after intubation, patients were randomly assigned in a 1:1 ratio to the no sedation group or the intravenous analgesics and sedation with daily intensive care nurse-led weaning trials (sedation group). Attending doctors excluded any patients who were considered unsuitable, and started the assignment process. Each allocation was concealed by placing it into a sealed envelope for consent. A total of 140 envelopes were prepared, 70 for each group. Every envelope was labelled with the patient number. The attending doctors and investigators had manually assigned the envelopes to each patient before the start of the study. The investigators analysing data were blind to the interventions or assessing outcomes.
previous dose and titrated to a Ramsay score of 3–4. After 48 h, the sedative was changed to an infusion of midazolam (1 mg/mL) titrated to a Ramsay score of 3–4. Thereafter, daily interruption of sedation, and titration of midazolam to a Ramsay score of 3–4 was continued as for treatment with propofol. Daily interruption of sedation and testing was done by a nurse, and checked by the attending doctor; if the nurse and attending doctor were in doubt of whether the patient could be judged as awake, the investigators assessed the patient.

If possible, both groups of patients were mobilised daily to a chair, despite mechanical ventilation, as per our standard routine; patients from the control group were mainly mobilised during daily interruption of sedation. The standard ventilation method was pressure support. Patients were only put on controlled ventilation in the case of severe prolonged hypoventilation. We decided a priori to stop infusion of sedatives in the control group when ventilator settings reached an FiO2 of 40% and a positive end-expiratory pressure of 5 cm H2O; after this point, patients were not sedated and treatment was identical to that of the intervention group. Sedation was started again if patients in the control group needed increased respiratory support (FiO2 >50% and positive end-expiratory pressure

<table>
<thead>
<tr>
<th></th>
<th>No sedation (n=55)</th>
<th>Sedation (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 (54–74)</td>
<td>65 (54–74)</td>
</tr>
<tr>
<td>Women</td>
<td>13 (24%)</td>
<td>24 (41%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.0 (74.0–92.0)</td>
<td>78.5 (70.0–83.0)</td>
</tr>
<tr>
<td>APACHE II</td>
<td>26 (19–30)</td>
<td>26 (22–31)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>46 (36–56)</td>
<td>50 (43–63)</td>
</tr>
<tr>
<td>SOFA (at day 1)</td>
<td>7.5 (5.0–11.0)</td>
<td>9.0 (5.5–13.5)</td>
</tr>
</tbody>
</table>

Data are in number (%) or median (IQR). APACHE II—acute physiology and health evaluation. SAPS II—simplified acute physiology score. SOFA—sequential organ-failure assessment. *Pneumonia, chronic obstructive pulmonary disease, and asthma.

Table 1: Baseline characteristics on admission to the intensive care unit.
<table>
<thead>
<tr>
<th></th>
<th>Nosedation (n=55)</th>
<th>Sedation (n=58)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days without mechanical ventilation (from intubation to day 28)</td>
<td>13.8 (11.0); 18.0 (0-24.1)</td>
<td>9.6 (10.0); 6.9 (0-20.5)</td>
<td>0.0191†</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>13.1 (5.7---)‡</td>
<td>22.8 (11.7---)§</td>
<td>0.0316§</td>
</tr>
<tr>
<td>Hospital</td>
<td>34 (17-65)</td>
<td>58 (33-85)</td>
<td>0.0039§</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>12 (22%)</td>
<td>22 (38%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospital</td>
<td>20 (36%)</td>
<td>27 (47%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Drug doses (mg/kg)††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol (per h of infusion)**</td>
<td>0 (0-0.515)</td>
<td>0.773 (0.154-1.648)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Midazolam (per h of infusion)</td>
<td>0 (0-0)</td>
<td>0.0034 (0-0.0240)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Morphine (per h of mechanical ventilation)</td>
<td>0.0048 (0.0014-0.0111)</td>
<td>0.0045 (0.0020-0.0064)</td>
<td>0.39</td>
</tr>
<tr>
<td>Haloperidol (per day of mechanical ventilation)</td>
<td>0 (0-0.0145)</td>
<td>0 (0-0)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>16 (29%)</td>
<td>17 (29%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>6 (11%)</td>
<td>7 (12%)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Data are mean (SD), median (IQR), or number (%). ††Data not available because of censoring at day 28. *Corrected for baseline variables: age, sex, weight, acute physiology and chronic health evaluation (APACHE II), simplified acute physiology score (SAPS II), and sequential organ failure assessment (SOFA) at day 1. ‡Calculated from multiple linear regression. †More than 25% of patients remained in the intensive care unit for more than 28 days (figure 2). §Calculated from Cox regression analysis. ¶Calculated for the first 30 days to agree with the proportional hazards assumption. ||Drug dose (mg) as a proportion of bodyweight (kg). **Maximum dose during 48 h of treatment.

Table 2: Outcome data

(HRs), after adjustment for the baseline variables mentioned above. Patient data were right-censored when the patient was transferred to another hospital, discharged, or died. The sample size was stopped within 48 h (figure 1). An extra person was enrolled as a fatal case, namely 14 patients (11 in the sedation group and 3 in the no sedation group) died in 48 h after intubation. The mortality data was then calculated on the number of patients remaining in ICU for 28 days (as described above).
Mean doses of propofol and midazolam are shown in table 2. The protocol was deviated for ten (18%) patients in the intervention group, who received continuous sedation on more than two occasions. In most cases, sedation was needed to permit sufficient oxygenation in severe acute respiratory distress syndrome (e.g., prone ventilation), but one patient was sedated after request from relatives. These ten patients account for most of the sedative drugs used in the intervention group, but use of these sedatives was significantly lower in the intervention group than in the control group. Difference in morphine dose between the two groups was not significant.

Delirium was recorded in 11 (20%) patients in the intervention group and 4 (7%) in the control group (p=0.0400). Haloperidol was used more frequently in the intervention group (n=19) than in the control group (n=8; p=0.0100), but the doses were very low for both groups (table 2).

**Discussion**

Findings from our study show that in critically ill patients receiving mechanical ventilation, a protocol of no sedation significantly increased the number of days without ventilation in a 28-day period compared with daily interruption of sedation. Use of no sedation was also associated with a significant reduction in the length of stay in the intensive care unit and in hospital. No difference in complications such as accidental removal of the endotracheal tube, ventilator-associated pneumonia, or need for CT and MRI brain scans were recorded. Mortality was increased in the group receiving sedation, but the difference compared with the group receiving no sedation did not reach significance. The occurrence of agitated delirium was increased in the group receiving no sedation.

Our study responded to calls in editorials and review...
No sedation price?

- Autoextubation : idem
- Delirium : 20 vs 14%
- Haloperidol : 35 vs 14%
- Extraperson : 20 vs 5%
- Violation/déviation : 18%
Are both sedative and analgesic drugs needed upfront?

Does the patient have one or several pathological disorders that result in drug accumulation?

Could a different ventilator setting help adaption and reduce or eliminate the need for drug treatment?

If treatment with both sedative and analgesic drugs is needed on initial examination, does the patient continue to need both drugs at the same doses?