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Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-Ventilation): a randomised, parallel-group clinical trial

Gerald Chanques, Matthieu Conseil, Claire Roger, Jean-Michel Constantin, Albert Prades, Julie Carr, Laurent Muller, Boris Jung, Fouad Belafia, Moussa Cissé, Jean-Marc Delay, Audrey de Jong, Jean-Yves Lefrant, Emmanuel Futier, Grégoire Mercier, Nicolas Molinari, Samir Jaber, on behalf of the SOS-Ventilation study investigators *

Summary

Background Avoidance of excessive sedation and subsequent prolonged mechanical ventilation in intensive care units (ICUs) is recommended, but no data are available for critically ill postoperative patients. We hypothesised that in such patients stopping sedation immediately after admission to the ICU could reduce unnecessary sedation and improve patient outcomes.

Methods We did a randomised, parallel-group, clinical trial at three ICUs in France. Stratified randomisation with minimisation (1:1 via a restricted web platform) was used to assign eligible patients (aged ≥18 years, admitted to an ICU after abdominal surgery, and expected to require at least 12 h of mechanical ventilation because of a critical illness defined by a Sequential Organ Failure Assessment score >1 for any organ, but without severe acute respiratory distress syndrome or brain injury) to usual sedation care provided according to recommended practices (control group) or to immediate interruption of sedation (intervention group). The primary outcome was the time to successful extubation (defined as the time from randomisation to the time of extubation or tracheotomy mask) for at least 48 h. All patients who underwent randomisation (except for those who were excluded after randomisation) were included in the intention-to-treat analysis. This study is registered with ClinicalTrials.gov, number NCT01486121.

Findings Between Dec 2, 2011, and Feb 27, 2014, 137 patients were randomly assigned to the control (n=68) or intervention groups (n=69). In the intention-to-treat analysis, time to successful extubation was significantly lower in the intervention group than in the control group (median 8 h [IQR 4–36] vs 50 h [29–93], group difference –33·6 h [95% CI –44·9 to –22·4]; p<0·0001). The adjusted hazard ratio was 5·2 (95% CI 3·1–8·8, p<0·0001).

Interpretation Immediate interruption of sedation in critically ill postoperative patients with organ dysfunction who were admitted to the ICU after abdominal surgery improved outcomes compared with usual sedation care. These findings support interruption of sedation in these patients following transfer from the operating room.

Articles

Research in context

Evidence before this study
We searched MEDLINE and ClinicalTrials.gov from their inception to March 21, 2017. The search term equation was: ((ICU) or (critical care)) and ((sedation) or (sedatives) or (analgesia) or (analgesics) or (pain) or (agitation) or (delirium) or (mechanical ventilation)). Studies were included if they evaluated an intervention concerning sedation practices aimed at decreasing sedation in intensity (ie, level of sedation) or duration, or both, in adult patients aged 18 years or older and admitted to an intensive care unit (ICU). We found one randomised controlled trial assessing the effect of early interruption of sedation in a mixed medical and surgical population of ICU patients within 24 h after intubation. The no-sedation group had a significant increase in days without ventilation and a decrease in days in the ICU and hospital compared with the control group. After completion of our trial, a meta-analysis of six randomised controlled trials of protocolised sedation in medical or mixed medical and surgical ICU patients reported a significant association between protocolised sedation and a reduction in overall mortality and length of stay in ICU and hospital compared with usual care. The quality of the evidence was moderate for all six trials. However, none of these trials exclusively enrolled postoperative surgical ICU patients; also, enrolment occurred after a 24–48 h period of mechanical ventilation. Thus, we identified a need for an interventional study on sedation practices during the early period of mechanical ventilation.

Added value of this study
In this study, sedation was decreased in postoperative, critically ill ICU patients much sooner than in previous studies. Sedation was interrupted as soon as possible after admission to the ICU from the operating theatre. Patients in the intervention group had a median time of less than 2 h of sedation. Unnecessary deep and prolonged sedation in the control group (where median sedation time was 33 h) was also avoided to prevent iatrogeny. The effect of this immediate interruption of sedation was a significantly shorter median time to successful extubation in the intervention group than in the control group (8 h vs 50 h). Moreover, this study is, to our knowledge, the first randomised controlled trial evaluating a sedation intervention that showed a positive effect on delirium. The findings of our study reinforce the rationale for interrupting sedation as early as possible in ICU patients.

Implications of all the available evidence
Given the clinical and economic burden of critical illness, postoperative morbidity, and the substantial number of patients who could benefit from this strategy, sedation should be immediately interrupted in postoperative patients admitted to an ICU. Further studies should be done to investigate whether such an immediate cessation of sedation would have similar effects in medical ICU and postoperative ICU patients with a more severe acute respiratory failure at time of admission or patients undergoing surgery other than abdominal surgery.

Methods

Study design
The SOS-Ventilation study was an investigator-initiated, multicentre, stratified, parallel-group clinical trial with a computer-generated allocation sequence and centralised randomisation. In accordance with French law, the study protocol and statistical analysis plan were approved for all centres by the local ethics committee (Comité de Protection des Personnes Sud-Méditerranée IV, Montpellier, France). The full protocol is provided in the appendix. The trial was done in accordance with the Declaration of Helsinki and was registered on Nov 10, 2011 (ClinicalTrials.gov, number NCT01486121). Three ICU centres participated in the study, with a patient to nurse ratio of 2·5 to 1 and a patient to assistant nurse ratio of 4 to 1 (patient to bedside caregiver ratio of 1·5 to 1). Unlike the randomised trial by Strøm and colleagues,7 no extra individuals (such as an assistant nurse or a family member) were required to reassure the non-sedated patients specifically for the purpose of the present trial.

Patients
Patients with national health-care insurance, who were older than 18 years, intubated and mechanically ventilated in volume assist-control mode in ICUs less than 24 h after a surgery, for an expected 12 h mechanical ventilation, with at least one organ dysfunction defined by a Sequential Organ Failure Assessment (SOFA) score5 greater than 1 for any organ, were eligible for participation as soon as they were postoperatively normothermic (body temperature >36°C) without any residual paralysis induced by neuromuscular blocking

ventilation and a decrease in days spent in the ICU and hospital, but also with an increased incidence of delirium and antipsychotic requirements. The effect of early interruption of sedatives in postoperative patients remains unknown. Although pain might necessitate high analgesia and sedation requirements, anaesthesia could worsen overall clinical status.

We hypothesise that certain critically ill patients admitted to an ICU following surgery might not actually require sedation and ventilation at all, and that avoidance of continuous sedation as soon as possible would be a feasible strategy associated with improved outcomes. Because of the substantial number of postoperative patients sedated for mechanical ventilation in the ICU in whom avoidance of continuous sedation could be a feasible intervention, we did the Strategy of Optimized Sedation-Ventilation (SOS-Ventilation) study to evaluate whether immediate cessation of sedation could improve postoperative outcomes compared with usual sedation care.

Articles

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agents potentially used for anaesthesia, as clinically assessed by the head lift test or with a monitoring device according to local practices.

Patients who had been admitted to the hospital ICU for more than 7 days before surgery, had brain injury, had severe acute respiratory distress syndrome (ARDS, as previously defined in the ACURASYS trial by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 150), had a history of drug abuse, had withdrawal of care, were under guardianship, were pregnant, were enrolled in another trial evaluating sedation or ventilation, or had a surgical contraindication to discontinuing sedation (ie, uncontrolled bleeding, surgical re-intervention planned within 24 h, or open abdominal wall) were excluded. The trial was interrupted if patients or their proxies declined participation or if brain injury occurred after enrolment.

Taking into account the fact that patients would be sedated following ICU admission, and that certain admissions would occur after an unplanned surgery under emergency conditions, complete adherence to patient consent procedures was deemed impossible before surgery or following ICU admission. In accordance with French law and with the approval of the ethics committee in favour of the research objective, a consent dispensation for emergency situations was enabled to minimise the time between ICU admission and randomisation as much as possible. Written consent to continue the research and analyse the data was obtained from the patient or their proxies as soon as possible.

Randomisation

Patients were screened and underwent randomisation between Dec 2, 2011, and Feb 27, 2014. Patients were randomly assigned (1:1 ratio) by stratified randomisation with minimisation via a restricted web platform. Randomisation was stratified according to centre, the SAPS II20 (SAPS II score <38 or ≥38). These cutoffs were assessed by the Simplified Acute Physiological Score (SAPS) II20 (SAPS II score <38 or ≥38). These cutoffs were determined on the basis of the mean scores observed in our ICU population. The SAPS II score used for stratification randomisation took into account the worst value available up to the previous 24 h from randomisation.

Procedures

Patients were assigned to receive either continuous sedation for tolerance of assist-control ventilation according to recommended guidelines (control group) or an immediate interruption of sedation (intervention group). In the intervention group, when anxiety, agitation, pain, discomfort, polypnoea, or patient-ventilator asynchrony persisted after management optimisation according to established protocols (appendix pp 5–9), continuous sedation was used for 6 h. If more than two periods of sedation were required within 24 h, continuous sedation was prolonged until the next day.

In both groups, sedation was standardised according to recommended guidelines to minimise the risk of oversedation. A previously published sedation analgesia protocol was used by bedside nurses every 4 h and sedation levels and pain intensity were assessed with the Richmond Agitation Sedation Scale (RASS) and the Behavioral Pain Scale (BPS). Sedation was primarily targeted at a light or moderate level (RASS between –1 and –3). Sedatives were interrupted daily every morning according to criteria selected by French intensive care societies (see the protocol in the appendix p 5). After interruption of sedation, agitation was again assessed every 4–8 h until discharge from the ICU by the RASS in all patients (sedated and non-sedated, intubated and non-intubated). Pain was assessed either by the BPS in patients unable to communicate or by the visually enlarged 0–10 Numeric Rating Scale (NRS) in those able to communicate. Diagnosis and therapeutic management of pain and agitation were standardised according to published protocols. Major opioid infusions (ie, sufentanil or remifentanil) were stopped at the same time as sedatives. Postoperative analgesia was provided by use of a multimodal strategy with paracetamol, nefopam, and tramadol (appendix p 9). Major opioids were reintroduced if multimodal analgesia was insufficient for treatment of basal pain, or for prevention and treatment of procedural pain. When severe ARDS occurred after randomisation, deep sedation was reintroduced at the same time as a neuromuscular blocking agent (cisatracurium) for a maximum of 48 h, according to the ACURASYS sedation protocol. Patients who developed severe ARDS were not excluded from the trial or the analysis.

Ventilators were set according to a lung protective ventilation strategy in both groups. Pressure support ventilation, a mode allowing for spontaneous breathing and less asynchrony, was used after interruption of sedation. Sedation interruption was coupled with a spontaneous breathing trial on at least a daily basis. Exubation was implemented in accordance with standardised criteria, as recommended (appendix p 5).

Outcomes

The primary outcome measure was time to successful extubation, defined as the time from randomisation to the time of extubation (or tracheotomy mask) for at least 48 h, as previously defined (the time of extubation corresponds to the beginning of a 48 h tube-free period). This outcome was centrally assessed. Secondary outcomes calculated on day 28 were the number of ventilator-free days (ie, days alive and without invasive mechanical ventilation between day 1 and day 28), the duration of ICU and hospital stays, and mortality. Secondary outcome reporting included the following health-care-related complications during the ICU stay: coma as defined by a RASS of –4 or –5; delirium as defined by the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU); pain as defined by a BPS score of more than 3 (or a self-reported 0–10 NRS >3 in
Articles

1614 patients were assessed for eligibility

1428 ineligible
1 aged ≤18 years
328 had no organ dysfunction
1090 were not admitted from operating room

186 screened

46 excluded
3 for technical reasons
43 because of exclusion criteria
4 under guardianship
5 had a brain injury
7 had severe ARDS
12 had an ICU stay >7 days before surgery
14 had a withdrawal of care decision

140 randomised

3 excluded after randomisation
2 patients’ proxies declined to participate
1 was enrolled in another study

68 assigned to control group
69 assigned to intervention group

68 (100%) included in 28-day analysis
69 (100%) included in 28-day analysis

Figure 1: Trial profile
Technical reasons preventing enrolment were related to a high workload in the intensive care unit (ICU). ARDS=acute respiratory distress syndrome.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
From Dec 2, 2011, to Feb 27, 2014, 1614 ICU patients were assessed for eligibility. Among the 186 eligible patients, 137 were included in the intention-to-treat analysis and were followed up for 28 days (figure I). Data for the primary outcome measure were available for all patients. Of the 137 patients, 68 were randomly assigned to the control group and 69 to the intervention group. Following inclusion, baseline characteristics were similar in both groups (table I; appendix pp 11–15). All patients were admitted to ICU after abdominal surgery, primarily for septic shock.

Statistical analysis
We calculated that a sample size of 140 patients would provide a power of 80% to detect an absolute between-group difference of 72 h with an SD of 140 h in the primary outcome at a two-sided alpha level of 0·05.

All analyses were done on data from the modified intention-to-treat population, which included all patients who underwent randomisation except for those who were excluded after randomisation. Group medians for the primary outcome were compared by use of the Mann-Whitney U test (the day of extubation was considered as the day of death for patients who died while still intubated). Hazard ratios (HRs) with 95% CIs were calculated by use of multivariate Cox regression to take into account the censored primary outcome for deceased patients. Stepwise selection was used to determine the final Cox regression model (p<0·10 to enter the model, p<0·05 to remain in the final model, in addition to randomisation stratification parameters). A competing risk model for the competing risk of death was used as a sensitivity analysis. A secondary analysis of the primary outcome measure involving a bootstrapped t test (frailtypack in R) was also done to support the findings of our original analysis.

For secondary outcomes, continuous variables were compared with the unpaired t test or the Mann-Whitney U test; categorical variables were compared with the χ² test or Fisher’s exact test, as appropriate (univariate analysis).

For the time-to-extubation analysis, the event occurred when a patient was extubated within 28 days from randomisation and remained extubated for more than 48 h. Patients who died before extubation were censored at death. The time-to-event curves were calculated for hospital discharge by use of the same method. All analyses were done with R statistical software, version 3.0.1, and SAS, version 9.3. A two-sided p value of less than 0·05 was considered to indicate statistical significance.

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There were significantly more delirium or delirium compared with the control group (table 2). The log-rank test for between-group differences applied to the Kaplan-Meier estimates for the primary outcome yielded a p value of less than 0·0001 in favour of the intervention group (appendix p 27).

Fewer patients in the intervention group had a coma or delirium compared with the control group (table 2). There were significantly more delirium-free days in the intervention group than in the control group (median 4 (2–6) vs 2 (1–6); p<0·0001; table 2).

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26 days [IQR 24–27] vs median 28 days [26–28], p=0.002).

There were no significant differences between groups for the other complications observed in the ICU (pain, self-removal of medical devices, ileus, pressure ulcers, health-care-associated infections, and surgical re-interventions).

The use of prophylactic or curative postoperative non-invasive ventilation did not differ significantly between groups [33 [48%] of 69 in the intervention group vs 36 [53%] of 68 in the control group; absolute difference −5%, p=0.55).

Other health-care resource utilisation was significantly reduced in the intervention group, with an increased number of ventilator-free days, fewer days on high-dose vasopressors (norepinephrine), and a higher probability of being discharged at day 28 (table 2; figure 3). Day 28 mortality did not differ significantly between the two groups (table 2). No significant difference between the two groups was observed for mortality, post-traumatic stress disorder, anxiety, depression, and quality of life at 3 months and 12 months (appendix pp 25, 26).

After randomisation, continuous sedation was stopped according to the protocol after a median time of 15 min in the intervention group and 33 h in the control group (table 3). Sedation was resumed in less than 30% of patients in both groups, mainly due to patient–ventilator asynchrony (62%) or surgical re-intervention (26%), without any significant difference between groups. Seven patients in the control group had a protocol deviation with an immediate interruption of sedation, and one patient in the intervention group had a longer duration of sedation than expected. The appendix (pp 20, 21) describes the drugs used for sedation–analgesia after randomisation in both groups. As expected, according to the research protocol, sedatives and major opioids were used significantly more often in the control group than in the intervention group, whereas minor opioids (eg, tramadol) were used significantly more often in the intervention group. There were no significant differences between groups in the use of other drugs (eg, neuromuscular-blocking agents, anxiolytics, and antagonists).

**Discussion**

In this multicentre, randomised controlled trial of critically ill postoperative ICU patients after abdominal surgery, immediate interruption of sedation and early use of spontaneous ventilation decreased the time to extubation compared with usual sedation care. Immediate interruption of sedation also led to significant decreases in coma, delirium, and high-dose vasopressor use. Patients who received the intervention had a significantly higher number of ventilator-free days and a higher probability of being discharged at day 28 than did patients who received usual care.

Times to extubation reported in both groups in our study are much lower than those reported in previous randomised controlled trials evaluating sedation practices.4,6,36 There are two main reasons that might help explain these differences: the duration of sedation before enrolment was over 48 h in most previous studies, whereas in our study enrolment occurred immediately after ICU admission (following a surgical

### Table 2: Resource utilisation in ICU and hospital

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Control group (n=68)</th>
<th>Intervention group (n=69)</th>
<th>Group difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between randomisation and successful extubation, h</td>
<td>50 (29–93)</td>
<td>8 (4–36)</td>
<td>−33 6 (−44 9 to −22 4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI) for competing risk of death (95% CI)</td>
<td>.. ..</td>
<td>5.2 (3.1–8.8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Bootstrap t test (95% CI)</td>
<td>.. ..</td>
<td>6.0 (3.3–13.0)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

### Secondary outcome measures at day 28

<table>
<thead>
<tr>
<th>Neurological complications and pain in the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma†</td>
</tr>
<tr>
<td>Days with coma</td>
</tr>
<tr>
<td>Delirium‡</td>
</tr>
<tr>
<td>Days with delirium</td>
</tr>
<tr>
<td>Severe pain§</td>
</tr>
<tr>
<td>Days with severe pain</td>
</tr>
<tr>
<td>Moderate pain§</td>
</tr>
<tr>
<td>Days with moderate pain</td>
</tr>
</tbody>
</table>

### Other complications in ICU

| Coma† | 34 (50%) | 15 (22%) | −28 (−45 to −11) | 0.0006 |
| Days with coma | 1 (0–2) | 0 (0–0) | −0.5 (−1.0 to 0.0) | 0.0008 |
| Delirium‡ | 48 (72%) | 28 (43%) | −29 (−50 to −14) | 0.0004 |
| Days with delirium | 2 (0–4) | 0 (0–2) | −0.5 (−1.0 to 0.0) | 0.003 |
| Severe pain§ | 14 (21%) | 14 (20%) | −0.6 (−1.0 to 1.0) | 0.93 |
| Days with severe pain | 0 (0–0) | 0 (0–0) | 0 (−1.0 to 1.0) | 0.95 |
| Moderate pain§ | 41 (61%) | 38 (55%) | −6 (−24 to 12) | 0.47 |
| Days with moderate pain | 1 (0–2) | 1 (0–1) | 0 (0.0 to 0.0) | 0.62 |

### Health-care associated infections in ICU and hospital

| At least one health-care-associated infection | 9 (13%) | 7 (10%) | −2 (−10 to 4) | 0.57 |
| Pneumonia | 2 (3%) | 1 (1%) | NA | NA |
| Bacteraemia | 6 (9%) | 5 (7%) | NA | NA |
| Urinary tract infection | 1 (1%) | 1 (1%) | NA | NA |
| Central venous catheter colonisation | 1 (1%) | 0 (0%) | NA | NA |

### Resource utilisation

<table>
<thead>
<tr>
<th>Resource utilisation</th>
<th>Control group (n=68)</th>
<th>Intervention group (n=69)</th>
<th>Group difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free days</td>
<td>25 (13–27)</td>
<td>27 (10–28)</td>
<td>1.4 (0.0 to 2.1)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Ventilator-free days with decreased accounting for 0</td>
<td>25 (0–27)</td>
<td>27 (4–28)</td>
<td>1.1 (0.0 to 1.8)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Extubation</td>
<td>58 (85%)</td>
<td>63 (91%)</td>
<td>6 (−6 to 18)</td>
<td>0.27</td>
</tr>
<tr>
<td>Re-intubation</td>
<td>12/58 (21%)</td>
<td>18/63 (29%)</td>
<td>8 (−8 to 19)</td>
<td>0.32</td>
</tr>
<tr>
<td>Tracheotomy</td>
<td>1 (1%)</td>
<td>3 (4%)</td>
<td>3 (−4 to 10)</td>
<td>0.62</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>36 (53%)</td>
<td>33 (48%)</td>
<td>−5 (−23 to 13)</td>
<td>0.55</td>
</tr>
<tr>
<td>Days of non-invasive ventilation</td>
<td>0 (2–6)</td>
<td>4 (2–5)</td>
<td>−0.5 (−2.0 to 1.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Use of norepinephrine</td>
<td>50 (74%)</td>
<td>50 (73%)</td>
<td>−1 (−18 to 14)</td>
<td>0.77</td>
</tr>
<tr>
<td>Days with norepinephrine dose &gt;0.1 µg/kg per min</td>
<td>2 (2–4)</td>
<td>1 (0–3)</td>
<td>−0.5 (−1.0 to 0.0)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

(Table 2 continues on next page)
procedure); and the population in this study differed from those of previous studies (mainly medical in the other studies and exclusively surgical in our study). However, illness severity as evaluated by the SAPS II and SOFA scores was similar between our study and previous studies. Additionally, time to extubation is dependent on sedation practices, as shown in this study, and sedation practices can differ between surgical and medical ICU patients. However, there is a paucity of data about sedation in postoperative ICU patients. The study by Schaller and colleagues7 evaluating an early mobilisation programme for postoperative ICU patients reported a duration of sedation of 4–5 days within 28 days. In our study, both groups had much lower durations of sedation (1–2 days). This decrease is explained by careful decision making in sedation management, including daily interruptions in accordance with the study objectives and design.

Most patients in our study were admitted directly to the ICU for septic shock after abdominal surgery. Intra-abdominal infection is the second leading cause of ICU admission (after complicated pneumonia), accounting for almost 10% of all ICU patients,36,37 and almost 20% of all patients with infections.38 It is the most common cause of infection (70%) in septic patients admitted to a surgical ICU.40 In patients with septic shock, sedation is often required to manage invasive treatments and to enable tolerance to mechanical ventilation, improve gas exchange, control agitation and pain, and therefore improve tissue oxygenation.41 A fundamental reason for our trial was to ascertain whether the sustained use of sedatives during recovery after surgery might be unnecessary and lead to increased iatrogenic morbidity and increased resource utilisation. Our hypothesis was that in this specific population of critically ill patients in the postoperative period of abdominal surgery, haemodynamic instability could be, in part, the consequence of the vasodilator side-effects of anaesthesia drugs. After transfer to the ICU, anaesthesia is continued to some extent by intravenous sedatives (continuous sedation), until the patient recovers from hypothermia and neuromuscular blockade. After this point, the benefits of sedation are unclear. The vasodilator effects of sedation, especially propofol, might interfere with the course of disease itself (sepsis), thus artificially worsening the clinical condition.42–44 In support of this hypothesis, we observed a significant reduction in the duration of high-dose vasopressor use in the intervention group, although illness severity (as assessed by SAPS II and SOFA scores) and serum lactate did not differ significantly between the groups at enrolment (appendix p 13). This study showed that, to test related effects on the overall clinical picture for a given patient, sedation should be stopped as soon as possible, immediately after the patient’s transfer from the operating room. We showed that resumption of sedation was unnecessary in more than 70% of these patients. The 2012 International Guidelines for Management of Severe Sepsis and Septic Shock (Surviving Sepsis Campaign)45 recommended minimisation of sedation through appropriate protocols, lighter sedation targets, or daily interruption of sedatives.

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<table>
<thead>
<tr>
<th>Study group</th>
<th>Control group (n=68)</th>
<th>Intervention group (n=69)</th>
<th>Group difference* (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days in ICU</td>
<td>6 (3–11)</td>
<td>5 (3–9)</td>
<td>−0.9 (−2.5 to 0.6)</td>
<td>0.87†</td>
</tr>
<tr>
<td>Days in ICU (survivors only)</td>
<td>7 (4–10)</td>
<td>4 (3–8)</td>
<td>−1.2 (−2.9 to 0.5)</td>
<td>0.28‡</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>25 (21–28)</td>
<td>17 (10–27)</td>
<td>−2.2 (−4.5 to 0.1)</td>
<td>0.04§</td>
</tr>
<tr>
<td>Days in hospital (survivors only)</td>
<td>27 (17–28)</td>
<td>23 (14–27)</td>
<td>−2.0 (−3.9 to −0.1)</td>
<td>0.01¶</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU mortality</td>
<td>14 (21%)</td>
<td>13 (19%)</td>
<td>−2 (−17 to 13)</td>
<td>0.97</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>17 (25%)</td>
<td>17 (25%)</td>
<td>−0 (−16 to 16)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

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Data are n (%) or median (IQR), unless otherwise stated. ICU=intensive care unit. NA=not applicable. *Group difference refers to the intervention group value minus control group value: absolute difference (%); †Hodges-Lehmann median difference. ‡Coma was defined by a Richmond Agitation Sedation Scale (RASS) of −4 or −5, assessed by the research team every morning. §Delirium was defined by a positive score on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), assessed by the research team every morning. ¶Missing data on delirium assessment correspond to one patient in the control group and four in the intervention group. The research team assessed pain intensity every morning at rest by use of the Behavioral Pain Scale (BPS) in patients unable to communicate, or by use of a visually enlarged 0–10 Numeric Rating Scale (NRS) in patients able to communicate. Severe pain was defined by a BPS greater than 5 or an NRS score greater than 6. Moderate pain was defined by a BPS of 4–5 or an NRS of 4–6, according to usual definitions. ‡Missing data on pain assessment correspond to one patient in the control group. ¶Comparisons between groups were made by use of the log-rank test, with the variable being truncated at day 28.

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Figure 2: Primary outcome measure, according to study group
Median time between randomisation and successful extubation (the primary outcome) was significantly lower in the intervention group than in the control group: 8 h (IQR 4–36) versus 50 h (29–93); mean times were 50 h (SD 13) versus 89 h (14); W=966.5 (Mann-Whitney’s test), p<0.0001. For the box and whisker plots, the horizontal double bar indicates the median, the upper and lower limits of the boxes the IQR, and the ends of the whiskers the 95% CI. The diamonds indicate the means with their bars indicating the standard error.

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Table 2: Primary and secondary outcomes according to study group

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Our study in postoperative patients with septic shock suggests that sedation should in fact be completely stopped as soon as possible after ICU admission.

In this population of surgical ICU patients, resumption of sedation was often determined by the need for surgical re-intervention (30%), but the main reason was patient-ventilator asynchrony. Sedation is intertwined with mechanical ventilation, as has been previously shown for the development of ventilator-induced diaphragmatic dysfunction: for greater control of mechanical ventilation, more sedatives are required and the risk of ventilator-induced diaphragmatic dysfunction is increased.16–20 Consequently, while attempting to reduce the use of sedatives in critically ill patients, it also seems paramount that mechanical ventilation be carefully adapted.21,22 Another feature of the present study is the protocolisation of pain, agitation, and delirium management in both groups. This protocol is now recommended as the so-called ABCDEF approach.49 Our study represents a step forward by showing that an approach involving reduced use of sedatives and major opioids (which are frequently associated with side-effects such as decreased respiratory drive, delayed ventilator weaning, and increased risk of coma and delirium) should be integrated into a comprehensive strategy for the systematic assessment and management of pain, agitation, and delirium (which should be further associated with early mobilisation).

Strengths of this trial include the methods used to minimise bias (centralised randomisation, complete follow-up, and intention-to-treat analyses). The trial protocol was pragmatic, with recommended practices applied by intensive care staff, including nurses and physicians, by use of validated and reliable instruments for sedation, pain, and delirium assessment, thus making it easy to replicate this study. We measured the time between randomisation and the first interruption of sedatives precisely in both groups. The first no-sedation trial by Strom and colleagues7 interrupted sedation within 24 h after intubation but the time between enrolment and interruption of sedation was not clearly reported.50 Patients were enrolled in our study a few hours after admission to the ICU, compared with 2 days after admission in most previous studies that have investigated the effect of different sedation strategies,8,19,31,38,39 These previous studies were done mostly in medical ICU patients. However, our trial, together with the trial by Strom and colleagues, raises the question of whether or not sedation could have been stopped earlier, and whether starting an intervention aimed at minimising sedation within 2 days of admission to the ICU would improve outcomes or not. Although sedation was suspected to be associated with delirium in previous observational studies,5,6,50,51 our study is the first interventional study that shows a positive effect of a no-sedation strategy in decreasing the incidence of delirium, contrary to the findings of Strøm and colleagues.47 This effect might be explained by the different methods used to measure delirium or the different protocols for management of pain and agitation. For example, in our trial we prioritised multimodal analgesia, restricting the use of morphine, whereas in the trial by Strøm and colleagues boluses of 2·5–5·0 mg were used “as needed”.

A limitation of our study is that the durations of mechanical ventilation were shorter than expected compared with previous historical observational data on
which our hypothesis was based, leading to possible underpowering with a difference in time to extubation between groups of much less than the expected 72 h. This difference could be explained by a positive effect generated by the research protocols and the fact that clinicians were aware that their practices were being monitored (ie, the Hawthorne effect, where a positive psychological effect in team management can be observed in both groups under investigation, with workers being motivated to improve their skills and efficiency). Sedation was thus probably reduced in both groups because of stricter application of recommended practices. Daily interruption of the sedatives in both groups was based on criteria selected by French intensive care societies (see the protocol in the appendix). These criteria were more restrictive than those of previous studies investigating daily interruption of sedation. Another limitation of our study is that masking was not possible. Possible biases inherent to such trials investigating sedation strategies aimed at decreasing the duration of mechanical ventilation included possible delays in interruption of sedation or extubation of patients in the control group. However, crossover practices appeared to occur in the reverse direction after randomisation, from the intervention group to the control group: sedation was interrupted immediately in 10% of patients in the control group. To minimise iatrogeny in the control group, we also paid strict attention to the sedation protocol. The RASS level was targeted between −1 and −3 to avoid deep sedation in the control group. The duration of ventilation was much lower in the control group than in previous studies on sedation protocols, as well as in Strom and colleagues' study. This difference suggests that the control group received a high standard of care. However, this difference could also be explained by the characteristics of our study population, which was restricted to postoperative patients, mostly with septic shock but without severe acute respiratory failure at baseline. This description accounts for 75% (140 of 186) of postoperative adult patients admitted to our ICUs with organ dysfunction. In these patients, sedation could be interrupted earlier than in other ICU populations. Further studies are needed to measure the feasibility of our strategy in medical ICU patients and in patients with more severe acute respiratory failure, as well as in patients undergoing surgery other than abdominal surgery. Further studies are also needed in a large number of ICUs with different patient-to-nurse ratios and different organisational cultures and skillsets regarding the management of sedation-ventilation and anaesthesia practices, including monitoring of neuromuscular blockade to avoid any residual paralysis. However, a patient to caregiver ratio of 1:1 should probably be recommended for an intubated patient at the early phase of the postoperative period, to assure careful management of pain, agitation, patient–ventilator asynchrony, monitoring of neuromuscular blockade, body temperature, and shivering (supported by specific protocols), as well as regular education and training. All these practices were implemented in our ICUs, but monitoring for residual neuromuscular blockade could have been improved in some patients, which is another limitation of this study. Finally, our trial was not powered to assess secondary outcomes since the study population was small. Additionally, in a small population of selected patients we could not rule out possible safety issues, particularly rare safety events.

In summary, our trial provides evidence that a strategy of avoiding continuous sedation as early as possible, in the absence of residual neuromuscular blockade and hypothermia, compared with usual sedation care, resulted in improvements in several important clinical outcomes in critically ill postoperative patients. Given the clinical and economic burden of critical illness, postoperative morbidity, and the substantial number of patients who could benefit from this strategy, increased attention should be given to prevention of postoperative iatrogenic injury potentially induced by unnecessary sedation and mechanical ventilation. Future studies should investigate whether immediate interruption of sedation has similar effects in other populations, such as medical ICU patients and patients with more severe acute respiratory failure. This approach would avoid the unnecessary 1–2 days of sedation (a high risk period for oversedation) observed before enrolment in previous studies done in this setting.

Contributors GC and SJ were on the trial management committee. GC, SJ, J-YL, J-MC, and GM were on the scientific committee. AP was the Trial Monitoring and Research Coordinator. NM was responsible for statistical and data coordination. GC, SJ, and BJ were on the writing committee. The following investigators at participating sites were responsible for screening of eligible patients and obtaining patients' and families' consent to participate, as well as inclusion, randomisation, and implementation of the research protocol: MCo, JC, BJ, AdJ, FB, MCI, J-MD, GC, and SJ at Saint Eloi Hospital (Montpellier, France); CR, IM, and J-YL at Caremeau Hospital (Nîmes, France); and J-MC and EF at Estaing Hospital (Clermont-Ferrand, France).

Declaration of interests J-MC reports grants, personal fees, and non-financial support from Baxter, during the conduct of the study. LM reports personal fees from Philips Echo, General Electric Echo, Fresenius Kabi, and Fresenius Medical Care, outside of the submitted work. EF reports personal fees from Baxter, Fresenius Kabi, and General Electric Healthcare; personal fees and non-financial support from Edwards, non-financial support from Drager, and travel reimbursement from Fisher & Paykel, outside of the submitted work. SJ reports personal fees from Drager, Fisher & Paykel, Hamilton, Xenios, and Baxter, outside of the submitted work. All other authors declare no competing interests.

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References


