Analgesia and sedation in critically ill patients

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Summary

In critically ill patients, adequate analgesia and sedation increase comfort, reduce stress response and facilitate diagnostic and therapeutic procedures. Analgesia and sedation may also have a beneficial impact on morbidity, particularly by reducing pulmonary complications such as atelectasis and pneumonia, and delirium or agitation with subsequent accidental extubation. The method and depth of analgesia and sedation should be adapted to the needs of the individual patient. While evaluation of analgesia and sedation is important, technical tools for assessment are generally unreliable. Accordingly, management of these patients is best guided by simple clinical scores, though there is no consensus on how frequently pain and sedation should be evaluated. While there is some degree of consensus on what constitutes an acceptable level of pain relief, the same is not true of sedation, with the attendant risk of over-sedation. Analgesia and sedation are performed chiefly by pharmacological means. The first step includes adequate analgesia, usually with opioids. There is no evidence of a difference in efficacy between opioids as far as clinically relevant outcomes are concerned. However, there is some evidence that more sophisticated methods of opioid administration, such as patient-controlled analgesia, may improve pulmonary outcomes. In Europe, midazolam and propofol are most frequently used for sedation of the critically ill. Regular evaluation of the effect of these drugs and subsequent adaptation of dosage are more important than the choice of specific analgesics and hypnotics. Implementation of guidelines for rational analgesia and sedation would help to reduce patients' length of stay in the intensive care unit.

Key words: propofol; midazolam; hypnotic; anxiety; agitation; delirium; neuroprotection; sleep; morphine; opioids; pain

Introduction

In critically ill patients there are three rationales for adequate analgesia and sedation. Firstly, analgesia and sedation ensure an optimal level of comfort; the patient should have no more than moderate pain and should be calm and alert. Secondly, analgesia and sedation are thought to reduce the "stress response" that is related to inflammation and trauma. Thirdly, analgesia and sedation facilitate diagnostic and therapeutic procedures, as well as nursing care.

Analgesia is the act of blunting pain, chiefly through administration of drugs which exert an effect on the peripheral or central nervous system, but also through positioning of the patient, stabilising fractures and minimising harmful physical stimulation [1]. 45–82% of critically ill patients suffer from pain depending on their degree of activity [2]. They are exposed to numerous noxious stimuli, e.g. the average pain produced by endotracheal suctioning is 4.9 and by chest tube removal 6.6 on a 0–10 point pain rating scale (ranging from 0 = no pain to 10 = worst pain imaginable) [3].

Sedation in critical care is the act of calming, especially through administration of centrally acting drugs, but also through reassurance, information, and music [4]. 71% of critically ill patients have been shown to suffer from anxiety, confusion and agitation [5].

In a trial of 50 patients in an intensive care unit (ICU), stressors and their intensity (minimum 1, not stressful, maximum 4, very stressful) were evaluated by a validated questionnaire during the first week of ICU stay [6]. Being in pain (average intensity: 3.4), being unable to sleep (3.4) and having tubes in nose and/or mouth (3.3) were the major stressors. It is generally accepted that these patients require some degree of analgesia and sedation to minimise perception of and stress response to pain and anxiety, and to reduce sleeplessness [7].

The impact of discomfort in the ICU and of ICU stressors on the long-term outcome of critically ill patients has rarely been investigated. Health-related quality of life was evaluated retrospectively in 80 patients after acute respiratory distress syndrome [8]. Those who reported multiple

stressors (19 of 80) during their ICU stay had the lowest general health quality and the highest degree of physical pain, suggesting an association between traumatic events during an ICU stay and poor outcome at long term. In these patients a posttraumatic stress disorder was postulated.

Why are analgesia and sedation important in critically ill patients?

There is evidence that analgesia and sedation may enhance the dignity and comfort of patients and may improve health-related quality of life. Analgesia and sedation may also decrease morbidity, at any rate in the postoperative setting.

Reduction of pulmonary and airway complications

In a meta-analysis of randomised, controlled trials, the relative efficacy of postoperative analgesia with respect to pulmonary outcome was reviewed [9]. There were differences in the incidence of atelectasis and pulmonary infections favouring epidural pain treatment (with opioids or local anaesthetics) compared with systemic opioid administration (Table 1). A limitation of this meta-analysis was that pain relief was not assessed; thus, the beneficial contribution of sympathetic block caused by an epidural local anaesthetic could not be separated from that of analgesia. In a recent randomised controlled trial including data from 915 patients, epidural analgesia had a more beneficial effect on pulmonary outcomes than systemic analgesia [10]. Patients receiving epidural analgesia also had significantly better pain relief. Patient-controlled analgesia (PCA) with opioids was also shown to reduce pulmonary complications compared with conventional opioid analgesia [11] (Table 1). A reduction in pulmonary complications is of particular interest since they may considerably prolong hospital stay [12] and increase health care costs.

Inadequate analgesia and sedation may aggravate the risk of accidental self-extubation, with subsequent acute respiratory insufficiency due to upper airway collapse. In two large prospective studies with data on more than 700 patients, 11–14% of accidental extubations were the result of inadequate management of analgesia and sedation [13, 14]. When accidental extubation occurred 60% of patients were agitated. One death occurred as a direct consequence of an unplanned extubation [14]. Using multivariate analysis, four risk factors contributing to unplanned extubation were identified: chronic respiratory failure, orotracheal intubation, fixation of the endotracheal tube with thin adhesive tape only, and lack of intravenous sedation [14].

Reduction of cardiac complications

Intensified analgesia in patients after major surgery may reduce the risk of myocardial infarction. In a meta-analysis including data from 501 patients, thoracic epidural analgesia with a duration of at least 24 hours significantly reduced the incidence of postoperative myocardial infarction compared with non-epidural analgesia (2.6% versus 5.5%) [15]. This result was confirmed in a large randomised controlled trial comparing epidural with systemic analgesia in patients undergoing abdominal aortic surgery [16]. In the group with epidural analgesia pain relief was improved, the rate of myocardial infarction was reduced, the time of intubation was 13 hours shorter, and the length of stay in the ICU was shortened by 3.5 hours. A limitation of this trial was the long delay until extubation, though this may not have had an impact on cardiac events. In a randomised controlled trial comparing PCA with hydromorphine with conventional nurse-controlled analgesia in patients undergoing coronary artery bypass grafting, a statistically significant reduction in the incidence of myocardial ischaemia on day 3 was observed in the PCA group [17].

Control of agitation and delirium

Anxiety, confusion, agitation and delirium are frequent in ICU patients. They may be related to a large variety of pathologies such as pain, depression, disturbed sleep pattern, metabolic encephalopathy (hypoxaemia, hypoglycaemia, arterial hypotension, inflammation, brain injury), fever, sepsis, renal failure, medication, adverse drug reactions, or withdrawal from alcohol or other drugs [1, 5]. Although the importance of appropriate analgesia and sedation appears to be obvious in these patients, there is little scientific evidence to link successful control of agitation or delirium with improved outcome [18]. In a prospective cohort study including 130 ICU pa-

Table 1
Type of analgesia and pulmonary complications.

Comparison	First Author	Type of design	Number of patients	Atelectasis	Pneumonia	Pulmonary complication
Epidural opioids vs. systemic opioids	Ballantayne 1998 [9]	sysRev	769 (11 trials)	RR 0.53 (0.33–0.85)	RR 0.53 (0.18–1.53)	
Epidural local anesthetic vs. systemic opioids	Ballantayne 1998 [9]	sysRev	215 (5 trials)	RR 0.74 0.50–1.11)	RR 0.36 (0.21–0.65)	
PCA with opioids vs. systemic opioids	Walder 2001 [11]	sysRev	152 (2 trials)			OR 0.12 (0.02–0.74)

tients, at least one episode of agitation occurred in 71%, and was severe (i.e. potentially self-destroying) in 41% [5]. Agitated patients are more likely to remove devices; as a result, important therapy (e.g. inotropes) may be discontinued, bleeding at the site of insertion may occur, and the devices need to be replaced. In agitated patients the length of stay in the ICU has been shown to be prolonged compared with non-agitated patients (11 vs 5 days) [19].

Reduction of wound infection

There is indirect evidence that optimisation of analgesia may reduce wound infection, one of the most important postoperative complications. Poor analgesia reduces subcutaneous oxygen tension [20]. Reduced wound tissue oxygenation has been associated with an increase in surgical wound infection [21].

Interaction between analgesia and sedation and mechanical ventilation in critically ill patients

Many patients in the ICU are mechanically ventilated and the mode of ventilation may influence the need for analgesia and sedation. In a prospective study of patients following cardiac surgery, less sensitive modes of ventilation (assist/controlled and synchronised intermittent mandatory ventilation, 677 patients) were compared with a more sensitive mode of ventilation allowing unrestricted spontaneous breathing in all phases of the respiratory cycle (biphasic positive airway pressure ventilation, 42 patients) [22]. The mean total amount of midazolam and the consumption of pethidine and piritramide was reduced under biphasic positive airway pressure ventilation. Pa-

tients who were ventilated with biphasic positive airway pressure had a shorter mean duration of intubation (10 hours) than patients treated by less sensitive modes of ventilation (13–15 hours). Similar results were observed in a randomised controlled trial which included patients with severe trauma [23]; those ventilated by a spontaneous breathing mode needed significantly less midazolam and sufentanil compared with those on controlled mechanical ventilation. Patients with spontaneous breathing also had a significantly shorter mean duration of ventilation (15 vs 21 days) and of ICU stay (23 vs 30 days).

How to treat pain in critically ill patients

Evaluation of pain and monitoring of analgesia

There is no neurobiological parameter for the evaluation of pain and no objective quantification of pain intensity or relief is possible. Nurses have been shown to underestimate the intensity of pain compared with the patients' own rating [24, 25].

The visual analogue scale (VAS), a frequently used tool for the assessment of pain intensity and relief, is a horizontal, non-graded 100 mm line [26]. The ends of the line are described as "absence of any pain" (= 0 mm) and "worst pain imaginable" (= 100 mm). The patient indicates his pain on the line between these extremes. Pain can also be estimated on a numerical rating scale; the patient indicates orally or in writing her assessment of pain using a number between 0 = "no pain" and 10 = "worst pain imaginable" [27]. Numerical rating seems to be easier to use (2% non-responders) than the VAS (11% non-responders) [27], and thus may be preferred in geriatric populations with an increased incidence of neurological alterations and lowered visual acuity [28, 29], in patients with neurological diseases, and in young children. In the acute pain setting, a VAS for pain intensity >30 mm has been defined as more than moderate pain [30]. This degree of pain intensity is now

often used as an arbitrary cut-off for worthwhile pain treatment.

Both VAS and numerical scores are unidimensional; they are limited in the validity of their content, and they may be influenced by other sensations. For instance, patients who were severely depressed or anxious reported higher levels of pain than non-depressed and non-anxious patients [27]. Critically ill patients may be unable to indicate their pain intensity due to the underlying disease or sedation. In a prospective investigation, 70% of postoperative cardiac patients were unable to use the VAS on the day of surgery, and 10–14% were unable to do so thereafter [31]. In patients who are unable to complete a unidimensional evaluation, a behavioural pain scale may be indicated. A new scale with the items "facial expression", "upper limb behaviour", and "compliance with ventilation" has recently been developed and validated in 30 critically ill patients [32]. However, this score only differentiated accurately between non-noxious and noxious stimuli.

Analgesia with opioids

In critically ill patients opioids are most often used for acute pain treatment. However, opioids may not necessarily be effective for particular pain

such as aching due to prolonged immobility. Non-steroidal anti-inflammatory drugs, are highly effective, but the increased risk of potentially serious adverse effects (gastrointestinal, renal) limit their usefulness in critically ill patients. Paracetamol is a weak analgesic and may be used as an adjunct to opioid analgesia, although its opioid-sparing effect has never been shown to improve outcome.

Efficacy of opioids

A large variety of opioids are used in daily clinical practice: morphine, codeine, pethidine (meperidine), synthetic morphine analogues (fentanyl, sufentanil, alfentanil, remifentanil, piritramide), agonist-antagonist opioids (nalbuphine), and atypical opioids (tramadol). Few opioids have been tested against morphine as a standard in critically ill patients. The utility of pharmacological data on opioids, in particular elimination data, is limited in view of the widely varying clinical effects in critically ill patients irrespective of the opioid used [33–35]. The observed variability in efficacy and adverse effects with similar regimens may be related to differences in perception of pain, underlying diseases (particularly hepatic and renal dysfunction), differences in the co-administration of other medication, and in the duration of opioid treatment.

In patients following cardiac surgery intermittent morphine administration (average dose 2.2 ± 2.1 mg/h) induced greater ST changes compared with continuous sufentanil administration (1 mcg/kg/h) [36]. However, there was no difference in the rates of myocardial infarction (3/54 with morphine vs 3/52 with sufentanil). Since there was no pain assessment in this study, no comparison of analgesia was possible and it thus remained unclear whether equianalgesic doses had been used. In contrast to current trends in the treatment of post-operative cardiac patients, this study population was sedated for a very long period and extubation was late (24 ± 8 hours vs 27 ± 11 hours after admission; mean ± S.D.). In a similar randomised trial, PCA with morphine (n = 60) was compared with a target-controlled alfentanil infusion (n = 60). Patients receiving morphine presented slightly higher median pain intensity scores (VAS 3.0 vs 2.3) [37]. This difference was not clinically relevant. No differences were found for haemodynamic instability, myocardial ischaemia or hypoxaemia.

In head-injured patients it is debatable whether opioids increase intracranial pressure, decrease cerebral perfusion pressure, and induce cerebral ischaemia. Differences between opioids have been evaluated in small randomised controlled trials only. Titrating fentanyl (3.0 ± 1.7 μg/kg; n = 5), sufentanil (0.4 ± 0.1 μg/kg; n = 5) or morphine (0.07 ± 0.03 μg/kg; n = 5) to a maximal decrease of 10% in mean arterial pressure did not increase intracranial pressure with any of these opioids [38]. In contrast, fentanyl (3 or 10 μg/kg), sufentanil (0.6 or 1 μg/kg), and alfentanil (100 μg/kg) transiently increased intracranial pressure and decreased cerebral perfusion pressure by about 30 mm Hg [39, 40]. On the basis of these preliminary results we may conclude that differences in intracranial pressure and cerebral perfusion pressure as between regimens are due to dosages rather than the opioids themselves.

The development of PCA pumps with opioids is a major breakthrough in intravenous pain treatment. These devices allow the patients to administer the analgesic independently of the care provider. The technique has found widespread use in most acute pain services, and has been applied successfully in critically ill patients [11]. Four randomised controlled trials in patients after cardiac surgery compared morphine PCA with standard morphine administration (on demand, given intravenously by a nurse) [41–44], and two trials compared piritramide PCA with standard piritramide administration [45, 46]. All studies included 30–40 patients per group. Three of the four morphine trials reported on morphine consumption. All three observed an increase in morphine administration in the PCA group, the difference being statistically significant in one trial [44]. Unfortunately, the trials did not report on pain intensity, length of stay in the ICU or respiratory and cardiac complications. Also, data on patient satisfaction were inconsistent. The clinical relevance of these results for ICU patients therefore remains unclear.

Adverse effects of opioids

Problems relating to tolerance, withdrawal, nausea and vomiting, pruritus, urinary retention, intestinal hypomobility and respiratory depression have been described with all opioids [47]. In hypovolaemic patients opioids may induce arterial hypotension [48]. Opioid-induced adverse effects may aggravate the patient's illness and prolong the clinical course [49].

Few human studies have addressed the issue of opioid tolerance. One prospective study reported on 466 critically ill patients who received sufentanil and midazolam continuously to facilitate ventilatory support. The dose of sufentanil and adverse effects were recorded at 24-h intervals. 72 hours after the start of analgesia and sedation, the average dose of sufentanil increased significantly compared with the first 24 hours [50]. It was suggested that this increase in the dose of sufentanil might be due to tolerance.

In an observational study on 23 children aged 1 week to 22 months (mean 6 months), who received a continuous fentanyl infusion for >24 hours, withdrawal with agitation or delirium was observed in 13 infants (57%). The average cumulative fentanyl dose was significantly larger (3.0 ± 4.1 vs 0.5 ± 0.4 mg/kg) and the length of the fentanyl infusion was significantly longer (13.1 ± 11.3 vs 3.8 ± 1.5 days, p <.0001) in infants with narcotic withdrawal than in those without. A cumulative fentanyl dose >2.5 mg/kg or a duration of infusion

>9 days was 100% predictive for withdrawal [51]. Withdrawal phenomena after opioid use in critically ill adult patients have been reported in rare cases only. Addiction in adult patients receiving opioids also seems to be unusual; in a large series of 11 882 patients treated with various opioids, four were reported to have become addicted [52].

Nausea and vomiting are among the most frequent adverse effects in postoperative patients; the average incidence without antiemetic prophylaxis is approx. 30% [53]. Nausea and vomiting may endanger therapeutic goals such as early enteral nutrition [54] or mobilisation. Thus, antiemetic prophylaxis may be indicated in particular in patients requiring prolonged opioid administration, since opioids increase the risk of adverse emetic events. A well-established drug for the prevention of opioid-induced nausea and vomiting is the butyrophenon droperidol. In a randomised dose-finding study including more than 80 patients per group, the cumulative incidence of nausea (and vomiting) over 24 hours was 48.8% (24.4%) without droperidol, 42.7% (23.2%) with 5 µg droperidol / mg morphine, 32.9% (22.0%) with 15 µg, and 21.7% (12%) with 50 µg [55]. The incidence of sedation without droperidol was 2.4%, with 5 µg droperidol per mg morphine 8.5%, with 15 µg 6.1%, and with 50 µg 18.1%. The optimal antiemetic dose of droperidol is thus between 15 and 50 µg/mg morphine. In our institution, we prophylactically add 2.5 mg droperidol to 100 mg morphine in the PCA pump.

For rare opioid-related adverse reactions such as respiratory depression, only few prospective data are available. A retrospective assessment based on data from a patient data management system was used to estimate the incidence of respiratory depression due to sufentanil in 395 surgical and trauma patients with an ICU stay of more than 48 hours, who were spontaneously breathing with assisted mechanical ventilation. Continuous sedation with sufentanil alone, or a combination of sufentanil, midazolam and clonidine was used to achieve a Ramsay sedation score (minimum score = 1 [agitation], maximum = 6 [coma]) between 2 and 4. Mean arterial PCO_2 of spontaneously breathing patients without continuous sedation (control group) was 39.5 ± 7.3 mm Hg compared with 42.7 ± 6.8 mm Hg in those on sufentanil alone, and was 39.8 ± 5.6 mm Hg in those who received the combination [56]. The difference in PCO_2 values between sufentanil and control was statistically significant. However, the increase in PCO_2 in patients receiving sufentanil alone is unlikely to be of clinical relevance. Doses and adverse effects of the most frequently used opioids in the ICU are summarised in Table 2.

How to sedate critically ill patients

Evaluation and monitoring of sedation

Scores to evaluate sedation are used with widely varying frequency between institutions and within countries, ranging from 16% in Danish ICUs to 67% in British ICUs [47, 57]. In 1999, a formal sedation policy was implemented in only

Table 2
Doses and adverse effects of the most frequently used opioids in critically ill patients.

Doses	
Morphine	
	1. Initial titration period: 1 to 4 mg as an IV bolus every 10 to 15 minutes
	2. Continuous administration: 1 to 4 mg/h IV (contra-indication: renal insufficiency)
	3. PCA: Bolus 1 to 2 mg, lock-out 5 to 8 minutes, maximum dose at 4 hours 40 mg, no background infusion
Fentanyl	
	1. Initial titration period: 25 µg to 75 µg as an IV bolus every 5 to 10 minutes
	2. Continuous administration: 50 to 300 µg/h IV
	3. PCA: Bolus 10 to 30 mg, lock-out 5 minutes, maximum dose at 4 hours 300 to 400 mcg, no background infusion

Doses need to be adapted based on regular evaluation with VAS/NRS data or with a sedation scale in patients without non-verbal communication.

Adverse effects	
Addiction:	Few data available, probably extremely rare (about 1 : 2500 patients)
Withdrawal:	In children with fentanyl, cumulative doses >2500 µg/kg or duration >9 days
Nausea, vomiting:	Add droperidol 2.5 mg to 100 mg morphine (25 µg droperidol per mg morphine)
Respiratory depression:	Only rarely clinically relevant. Check blood gas analysis: If pH <7.30 and $paCO_2$ >50 mm Hg consider IV naloxone
Arterial hypotension:	May be relevant in hypovolaemic patients
Tolerance:	Cannot be excluded, but few data available
Urinary retention:	No clinical problem since most ICU patients have urinary catheter
Intestinal hypomobility:	Few data available, may interact with enteral nutrition

Table 3

The Richmond agitation-sedation scale (RASS).

Score	Term	Description
+4	Combative	Overtly combative, violant, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to *voice* (*>10 seconds*)
–2	Light sedation	Briefly awakens with eye opening to *voice* (*>10 seconds*)
–3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)
–4	Deep sedation	No response to voice, but movement or eye opening to *physical stimulation*
–5	Unarousable	No response to voice or *physical stimulation*

With permission from Sessler CN, Richmond, Virginia, USA

43% of British ICUs, and the opinions of caregivers regarding the "ideal" level of sedation for a critically ill patient varied widely [57].

Regular assessment of the depth of sedation is important, particularly if continuous intravenous sedation is used. It is likely that regular assessment reduces over-sedation and possibly the number of unnecessary cranial CT scans to exclude other reasons for a non-responsive state. Regular assessment (e.g. half-hourly) and a clear cut-off for treatment (e.g. Ramsay ≤4) has been shown to reduce the use of sedatives [58]. With these simple guidelines, and if analgesia is adequate, one third of patients after coronary bypass grafting needed no sedatives at all.

However, there is no consensus about the best tool to evaluate sedation and how frequently it should be used. There is a plethora of clinical evaluation methods. A systematic review reported on 25 instruments for the assessment of sedation [59]. For most instruments, the validation process was shown to be incomplete or to be based on a limited amount of data only [60]. None of the scales has been tested for responsiveness to changes of sedation strategy. One of the oldest and most frequently used sedation scores in the ICU is the six-item Ramsay score [61]. However, this score does not properly discriminate deeper sedation levels and there is non-detailed discrimination of states of agitation. Today, the best validated tool for the evaluation of sedation and agitation is the recently published 10-point Richmond Agitation-Sedation Scale [62, 63] (Table 3).

The number of nurses staffing an ICU is likely to be important for successful and appropriate evaluation of sedation. It has been speculated that units with understaffing tend to under-use sedation scores and to over-treat patients with sedative drugs [64, 65].

To overcome the problem of subjectivity, interindividual rating variability, and lack of continuity of measurements, on-line heart rate variability, lower-oesophageal contractility, auditory and somato-sensory evoked potentials and processed electroencephalography (EEG) using automated monitoring systems have been suggested for the assessment of sedation. These tools are still experimental, none having been sufficiently validated and most having limited accuracy in daily clinical use [66–68].

Sedation with midazolam or propofol

There is a large body of scientific literature on pharmacological sedation in critically ill patients, comprising reports on benzodiazepines (midazolam, lorazepam, diazepam, flunitrazepam), propofol, ketamine, isoflurane, chloral derivates, barbiturates, centrally acting alpha-2 sympathomimetics (clonidine, dexmedetomidine), clomethizole, neuroleptics (droperidol, haloperidol), and combinations of these. However, only a few agents have been evaluated in more than two randomised controlled trials [69].

This section will focus on the role of midazolam and propofol, perhaps the most frequently used sedative drugs in this setting in recent years [47, 57].

Midazolam is a benzodiazepine. Midazolam is sedative but also induces amnesia and anxiolysis, which is potentially beneficial in critically ill patients [70]. This hypnotic has a rapid onset and a short duration of action with single bolus doses. In critically ill patients, the elimination half-life is 5.4 hours [71]. Midazolam may accumulate when the pharmacodynamic and pharmacokinetic profiles are altered by organ dysfunction, for instance, in patients with cardiac [72], renal [73, 74] or hepatic [75] disease. Accumulation has also been described in obese patients [76], in the elderly [77] and in patients with a low plasma albumin level [78]. Significant interaction of the metabolism of midazolam through inhibition of the cytochrome P450 isoenzyme 3A4 has been reported with diltiazem [79], with macrolide antibiotics [80], with antimycotics [81], and with cimetidine and ranitidine [82].

Propofol (2,6-di-isopropylphenol), an intravenous sedative drug that is widely used for induction and maintenance of general anaesthesia, has

Figure 1a

Figure 1b

also become popular as a hypnotic in critically ill patients [83]. However, only limited data are available on long-term use of propofol in the ICU setting. The advantages of this sedative drug are a short duration of action, related to a redistribution half-life of 13.4 min only [84], a lack of prolonged sedation despite a long elimination half-life of 7.8 hours [84], and a metabolic profile that appears to be independent of hepatic function [85]. No change in kinetic parameters has been reported in patients with renal and hepatic dysfunction. Thus, this drug is easily titratable even in patients with renal or hepatic diseases. The emergence time from sedation with propofol varies with the depth and duration of sedation and the patient's bodyweight. The deeper the sedation (i.e. the lower the sedation score), the longer the wake-up time (34 minutes for a Ramsay score 3 vs 59 hours for a Ramsay score 5); the longer the period of sedation, the longer the wake-up time (25 hours for a 1-day sedation vs 74 hours for 14 days' sedation); and the more obese the patient, the longer the wake-up time [86].

In a quantitative systematic review of randomised controlled trials comparing midazolam and propofol for sedation in mechanically ventilated, critically ill patients, data from 27 trials (1624 adults) were analysed [87]. The average du-

ration of sedation varied between 4 and 339 hours. In 10 trials the duration of adequate sedation was longer with propofol (weighted mean difference about 3 hours) (figure 1). In 13 trials (chiefly postoperative), sedation lasted 4 to 35 hours; in 9 of these, average weaning time from mechanical ventilation with propofol was 0.8–4.3 hours and with midazolam 1.5–7.2 hours (weighted mean difference about 2 hours) (figure 2). In 8 trials, sedation lasted 54–339 h; there was no difference in weaning times between the two drugs. The efficacy of these two sedative drugs is thus very similar.
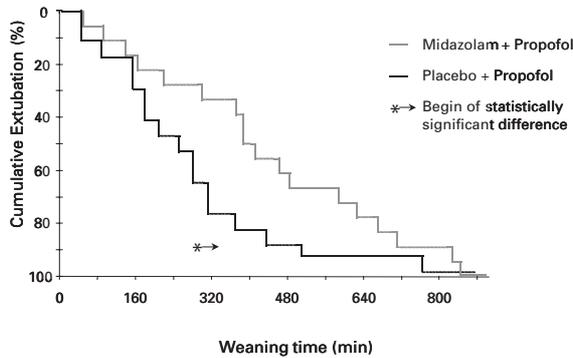
Midazolam, propofol and other sedatives may be administered continuously or intermittently. The potential risk of continuous sedation in patients who were mechanically ventilated for prolonged periods was investigated in an observational comparison of two sedation regimens. In patients from a medical ICU the average duration of mechanical ventilation was 148 hours for those who received continuous sedation, compared with 79 hours for those who received intermittent sedation [88]. In a further observational study in 250 medical and surgical patients, continuous sedation without assessment of the depth of sedation was a significant and independent predictive factor for the development of pneumonia within 48 hours of intubation [89]. In this study, 24% of patients on continuous sedation had pneumonia, compared with 10% of patients without continuous sedation. This observation was confirmed in a randomised controlled trial where in the experimental group, analgesia and sedation (with propofol or midazolam) were interrupted for neurological evaluation on a daily basis [90]. Patients were assessed during an "awake test", and, if necessary, analgesia and sedation were re-introduced thereafter at half of the previous dose with adjustments as needed. The duration of mechanical ventilation in the experimental group was significantly reduced (median approx. 5 days compared with more than 7 days). Length of ICU stay was also reduced (6 days vs 10 days). Last but not least, significantly fewer CT scans were needed in patients of the experimental group [90].

Figure 3

Cumulative extubation curve from the end of the consious sedation period to end of the study period. The percent of patients extubated between the two groups was significantly greater in the group placebo + propofol.

It has been proposed that a combination of propofol and midazolam may be advantageous for long-term sedation compared with either drug alone; theoretically, propofol-related adverse effects (e.g. arterial hypotension) may be prevented while preserving the potential benefits of propofol (e.g. rapid extubation) [91]. We tested this hypothesis in a randomised, double-blind, controlled trial in patients following coronary artery bypass grafting [58]. The aim was to compare the efficacy and adverse effects of propofol combined with continuous low-dose midazolam vs propofol alone. 60 male patients were enrolled; postoperatively, patients who had a Ramsay score ≥4 were randomised to receive either a continuous intravenous infusion of midazolam 1 mg/h or placebo. Target Ramsay score was 3–5, corresponding to conscious sedation. To reach this target score, supplementary propofol was added if necessary. Efficacy of sedation was statistically significantly increased under the combined regimen compared with propofol alone. There was no difference in the administration of supplementary propofol between the groups. Average weaning time from mechanical ventilation was longer in the propofol-midazolam group, and irrespective of whether or not the patients required supplemental propofol (fig. 3). Four hours after the end of sedation the cumulative number of patients remaining intubated was significantly higher in the propofol-midazolam group. In conclusion, a combination of these two drugs does not appear to offer any advantage after cardiac surgery.

Administration of sedative drugs should only be considered after pain has been excluded. Analgesia must be the first step in all analgesia and sedation protocols. Even in critically ill non-surgical patients there are many sources of pain, ranging from backache due to prolonged supine position to invasive monitoring catheters penetrating the integument [92]. Inadequate pain control is a common reason for agitation and a significant cause of anxiety. Inclusion of analgesics as part of any critical care treatment is therefore essential [93]. Sedatives combined with opioids may cause changes in efficacy and adverse effects for both drug classes, related to altered actions of the drugs on the effect site (i.e. in the brain) or to interactions with the drugs' metabolism (e.g. at the cytochrome P450 enzyme system). These interactions may influence the quality of both analgesia [94–96] and sedation

[95, 97–99]. Sedative drugs also seem to have an antiemetic effect when used in combination with opioids [94, 95]. However, few data on interactions between sedatives and opioids are available for critically ill patients. In a randomised controlled trial testing the efficacy and harm of propofol and midazolam, patients in the propofol group received more morphine, and with wider variability, than the group with midazolam [100]. This finding could be interpreted as suggesting that midazolam may enhance analgesic effects of opiates.

Adverse effects of midazolam and propofol

Drug tolerance may be related to long-term sedation (>2 days). Acute midazolam tolerance or hypo-reactivity is a well known phenomenon, although it has been rarely described in the scientific literature. In an observational study on 50 patients, average doses of midazolam nearly doubled over one week of continuous administration to maintain the same degree of sedation [101]. Tolerance to benzodiazepines may occur within hours to several days of therapy. Predictive factors are unknown [102].

Withdrawal from benzodiazepines with delirium, agitation or anxiety even after a short course has most often been described in children. In two retrospective data collections on children who received sedation with midazolam for mechanical ventilation, 7.5% and 35% respectively had withdrawal symptoms [103, 104]. The onset of abnormal behaviour followed within 12 hours of discontinuation of midazolam. The duration of abnormal behaviour ranged from 3 hours to 1 week. A total cumulative dose of midazolam of >60 mg/kg during the sedation period was significantly associated with the occurrence of withdrawal [103, 104]. Similar data from adults, based on retrospective data collection, support the hypothesis that high doses of midazolam may be followed by withdrawal [105]. Data on addiction to hypnotics are rare. Benzodiazepines, for instance, almost never induce behaviour that satisfies any reasonable definition of addiction in patients without a history of substance abuse, and who are prescribed benzodiazepines under medical supervision [106].

In randomised comparisons of propofol and midazolam, arterial hypotension occurred more often with propofol (relative risk 2.5; number-needed-to-treat, 12) [87]. With propofol, negative chronotropic effects including bradycardia and cardiac arrest have been described [107]. The "propofol infusion syndrome" (i.e. progressive myocardial failure, cardiac dysrhythmia, rhabdomyolysis, metabolic acidosis, and hyperkalaemia) has been observed when higher doses of propofol (>5 mg/kg/h) were used over days; all patients who developed these symptoms died [108]. Impaired fatty acid oxidation with failure of the mitochondrial respiratory chain at complex 11 mimicking mitochondrial myopathies has been proposed as the origin of this syndrome [109].

Inappropriate aseptic technique while using

Table 4

Doses and adverse effects of the most frequently used sedatives – midazolam and propofol – in critically ill patients.

Doses	
Midazolam	
1. In agitated patients: 1 to 3 mg as IV bolus	
2. Continuous administration: 1 to 4 mg/h IV	
Propofol	
1. In agitated patients: 20 to 40 mg as IV bolus	
2. Continuous administration: 2 to 6 mg/kg/h IV	
Doses need to be adapted based on regular evaluation using a sedation scale.	

Adverse effects	
Both drugs	
Accumulation:	Obesity and long-term sedation
Pneumonia:	Long-term sedation in intubated patients (up to 24% of intubated patients)
Midazolam	
Accumulation:	Cardiac, renal and hepatic diseases, older patients, low plasma albumin concentration
Interactions:	Diltiazem, macrolide antibiotics, antimycotics, cimetidine, ranitidine
Tolerance:	Sedation >2 days
Withdrawal:	In children with cumulative doses >60 mg/kg
Propofol	
Arterial hypotension:	More frequent compared with midazolam (relative risk 2.5)
Bradycardia:	Few data available in ICU patients, most data are from anaesthetised patients
Propofol syndrome:	Rare, long-term sedation with doses >5 mg/kg/h
Bacteremia:	If inappropriate aseptic technique is used
Hypertriglyceridaemia:	In susceptible patients
Seizure-like phenomena:	Rare, most often during induction and of emergence from sedation

propofol may lead to nosocomial infection [110, 111]. More recent solutions of propofol contain edetic acid, which may reduce the risk of bacteraemia [112].

Propofol 1% is an emulsion in a phospholipid vehicle which provides 1.1 kcal/ml fat. Thus, similar to parenteral nutrition, intravenous administration of propofol may interact with lipid metabolism. Systematic review of randomised trials confirms that the administration of propofol for 12–339 hours may result in hypertriglyceridaemia in critically ill patients [87]. More recent solutions contain 2% (instead of 1%) propofol, and since the amount of phospholipids is halved, the risk of hypertriglyceridaemia may be reduced.

Seizure-like phenomena in association with propofol have been observed during sedation and during anaesthesia [113]. In patients without epilepsy, these phenomena occur most often during induction and during emergence of sedation or anaesthesia, and less during maintenance. Different seizure-like phenomena have been described in association with propofol: generalised tonic-clonic seizures, focal motor seizures, events presented as increased tonus with twitching and rhythmic movements not perceived as generalised tonic-clonic seizures, opisthotonus and involuntary movements. Among those, generalised seizures and twitching and rhythmic movements appear to be the most frequent. In contrast, patients with epilepsy present seizure-like phenomena most often during emergence from sedation or anaesthesia, and these were usually generalised tonic-clonic seizures [113]. The time of occurrence of seizure-like phenomena suggests that a change in cerebral concentration of propofol may be causal.

Doses and adverse effects of hypnotics that are most frequently used in the ICU are summarised in Table 4.

Agenda for future research

Evaluation of analgesia and sedation

The plethora of evaluation methods for analgesia and sedation is highly unsatisfactory. It would be desirable to create an international task force to study these different instruments and to suggest what instruments should be used for clinical needs and future research. This would ensure adequate comparison between studies and institutions. Evaluation tools should also be assessed for their impact on quality of care and length of stay of patients in the ICU. Research on simple technical monitoring should be encouraged.
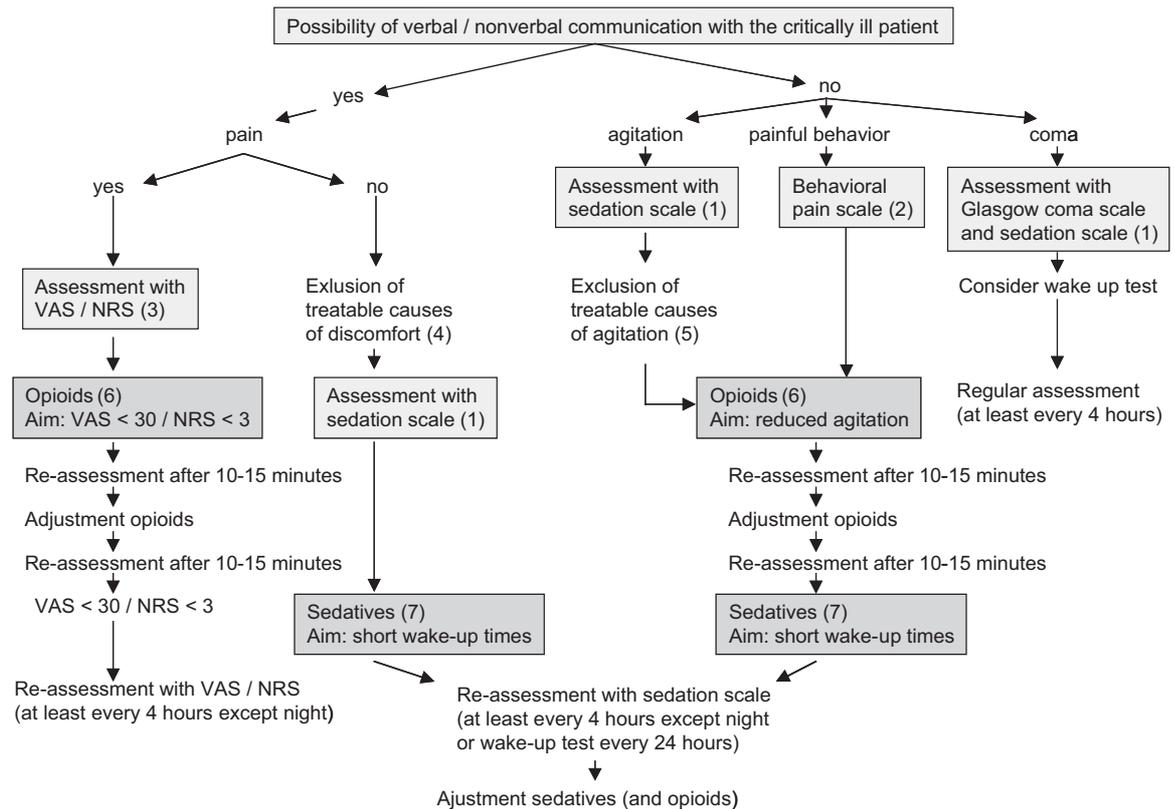
Table 5

Effect of a systematic, standardized analgesia and sedation protocol on outcome [114].

Outcome	Proctocol-directed analgo-sedation (n = 162)	Non-protocol-directed analgo-sedation (n = 159)	P
Duration of mechanical ventillation (hours)	89 ± 134	124 ± 154	0.003
Length of ICU stay (days)	5.7 ± 5.9	7.5 ± 6.5	0.013
Length of hospital stay (days)	14.0 ± 17.3	19.9 ± 24.2	<0.001
Mortality (n, %)	49 (30)	57 (36)	0.342
Reintubation (n, %)	14 (9)	21 (13)	0.213
Tracheostomy (n, %)	10 (6)	21 (13)	0.038
Continuous analgo-sedation infusion (n, %)	66 (41)	66 (42)	0.889

Figure 4

Decision tree for analgesia and sedation in critically ill patients.

1. For instance, Richmond Agitation-Sedation Scale (table 3).
2. Includes the criteria facial expression, upper limbs behavior and compliance with ventilation.
3. No pain = 0; worst imaginable pain = 10 (numeric rating scale) or 100 (visual analog scale).
4. Wet bed, urinary catheter occlusion, patients positioning, inadequate ventilator mode.
5. Hypoxia, hypoglycemia, fever, adverse drug reaction (for instance, ketamine; paradoxal reaction of midazolam), drug withdrawal, alcohol withdrawal.
6. Most frequent used opioids: morphine and fentanyl (table 2).
7. Most frequent used sedatives: midazolam and propofol (table 4).

Guidelines and their implementation

Adequate analgesia and sedation may result in a significantly improved outcome if a systematic and standardised approach, based on interdisciplinary cooperation, is adopted [114] (Table 5). However, in a Danish survey protocols for sedation were followed in only 16% of ICUs, many referring to specific situations such as patients with renal failure [47]. For every critically ill patient, a specific regimen for analgesia and sedation with clear cut-offs for treatment should be formulated. A proposal for a rational decision tree for analgesia and sedation is summarised in figure 4. Guide-

lines should include information on estimated durations of analgesia and sedation, levels of analgesia and sedation during therapeutic and diagnostic interventions (e.g. tracheal aspiration or removal of a thoracic drain), and during mobilisation. Guidelines should also consider adverse drug reactions, identify periods of uninterrupted sleep with decreased levels of noise and light, facilitate regular temporal orientation of patients using large clocks and calendars, define daytime activities with space orientation (with vision and hearing aids, if needed), and ensure cognitive stimulation. Guidelines for analgesia and sedation should

be in agreement with guidelines on mechanical ventilation and on weaning from ventilation support [115]. Randomised trials investigating weaning of critically ill patients from ventilatory support or analgesia and sedation should systematically include all these factors.

Analgesia and sedation in brain injury

Traumatic brain injury is a silent epidemic related to road accidents, falls, and assaults. About 15 patients with severe brain injury per 100 000 residents are admitted to ICUs per year [116–118]. Although the number of patients with severe brain injury is high worldwide, data on the efficacy of analgesia and sedation in these patients are limited. Considering the rate of traumatic brain injury and the relatively young age of this population, there is a need for rational algorithms for analgesia and sedation. These should be based on randomised controlled trials and prospective observational studies with relevant end points and health-related long-term quality of life.

Pain and outcome

Randomised controlled trials are needed to confirm the hypothesis of an interaction between pain and wound infection in critically ill patients. More evidence is necessary to confirm the potentially protective effect of PCA with opioids on pulmonary complications [11].

Cost-effectiveness

There is no evidence of a major difference between sedation with midazolam and propofol in terms of efficacy and risk. In this situation cost may become an important issue for clinical decision-making. Studies should include endpoints that are relevant to costs, such as duration of ventilation, ventilation-related complications (ventilation-induced lung injury, ventilation-associated pneumonia), complications related to inadequate management of pain and sedation (agitation, self-extubation, catheter removal), length of stay in the ICU and in hospital.

Conclusions

Analgesia and sedation have become integral parts of the multimodal management of ICU patients. Adequate analgesia and sedation facilitate patient care, increase comfort, and are likely to improve outcome. The risks of pulmonary complications, unplanned extubation, and agitation and delirium are reduced. Thus, analgesia and sedation should not simply be regarded as a possible adjunct to patient management but as a true need.

Many factors delay successful implementation of evidence-based guidelines for efficacious and safe analgesia and sedation in ICU patients. Technical tools for the assessment of analgesia and sedation cannot be recommended. However, pragmatic and simple clinical assessment must be regarded as the only reliable way to evaluate the depth and quality of analgesia and sedation. This assessment is more important than the choice of the specific analgesics and hypnotics.

The mode of administration of analgesia (for instance, through a PCA device), and discontinuous sedation (as compared with continuous sedation), have been shown to reduce pulmonary complications at least in some critically ill patients. As a rule, minimum effective doses should be given and for a minimum of time. Exclusion of unacceptable pain before a hypnotic is added to a regimen is essential to avoid over-sedation with subsequent weaning failures and prolonged length of stay in the ICU.

In ICU patients, analgesia and sedation should be systematic and standardised, and supported by interdisciplinary cooperation. Clinical assessment should be simple, the intervals for evaluation should be regular, and cut-offs for worthwhile treatment need to be defined. With this approach we can look forward to an improved outcome in critically ill patients.

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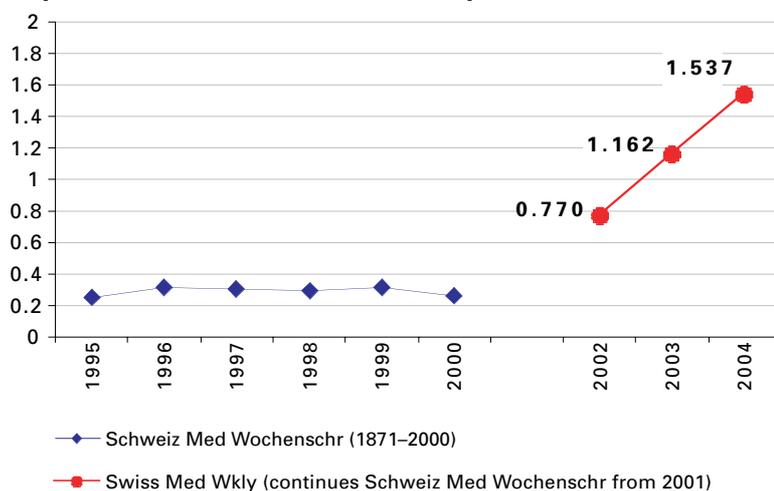- No page charges and attractive colour offprints at no extra cost

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