REVIEW

Analgesia and sedation in the intensive care: a review and the results of a Dutch survey

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Introduction
In critically ill patients discomfort can be alleviated with analgesia with or without the use of sedatives. However, continuous infusion of sedatives and analgesics is associated with prolonged mechanical ventilation [1]. On the other hand, inadequate sedation or analgesia results in unnecessary pain, sleep disturbance and mechanical ventilation [1]. Therefore the ultimate challenge is to provide and maintain patient comfort, without needless days on mechanical ventilation or a redundant stay in the intensive care. Various types of drugs can be used for sedation or analgesia, of which most have a context-sensitive half-life that increases with duration of administration. Therefore short-acting analgesics or sedatives are preferred.

It is recommended that required levels of sedation and analgesia be titrated, based on regular evaluation of the patient’s comfort. In most situations, deep sedation is not necessary and a shift to light sedation is advisable. Daily interruption of sedative administration reduces the duration of mechanical ventilation and length of intensive care stay [4-8], however, maintaining the patient at a comfortable and arousable level throughout the mechanical ventilation period might be equally effective.

The lack of an ideal sedative and analgesic results in different approaches to sedation and analgesia both between intensive care units as well as within intensive care units [9,10]. Several reviews have been written which address different strategies: the implementation of structured assessment tools for pain and depth of sedation, coupled with strategies to guide drug administration and withdrawal, to reduce the likelihood of excessive or prolonged sedation [11,12]. The quality of care can be improved by reducing the variability found in clinical practice through the use of protocols such as the Dutch guidelines on sedation and analgesia (Table 1), but also by implementing new developments such as new drugs. Drugs that tend to accumulate less (e.g. remifentanil, dexmedetomidine), may find a place if evidence of improvements in patient outcomes is demonstrated [13]. In this article we will discuss the various types of analgesia and sedation and the ways to assess and titrate their effect in the intensive care patient. Additionally, we will present the results of a Dutch survey to assess the current practice of sedation and analgesia in 20 Dutch intensive care units, and to determine adherence to the guidelines as proposed by the Dutch Society of Intensive Care. The ultimate goal is to improve current clinical practice.

Analgesia
The majority of patients do not need additional sedation to accept mechanical ventilation providing analgesia is adequate. The ideal analgesic agent should provide an adequate level of analgesia, should be easy to titrate and rapidly adjustable to achieve the desired effect, and once it is discontinued its effects and side-effects should disappear rapidly. All currently available sedatives for use in the intensive care have limitations. Analgesics can be administered by the enteral, transcutaneous and parenteral routes. In critically ill patients, parenteral administration is preferred in order to avoid problems with delayed gastric emptying, continuous gastric drainage, decreased gut function, uncertain first-pass effect, general oedema and use of vasopressors that may limit subcutaneous absorption. In addition, epidural infusions of local anaesthetics (often combined with opioids) can give effective analgesia, for instance following thoracic or abdominal surgery or trauma.

Epidural analgesia is used frequently in current anaesthetic practice. In a meta-analysis of more than 5000 surgical patients evaluating the use of epidural analgesia after surgery under general anaesthesia, postoperative epidural analgesia was shown to reduce the time to extubation, the time spent in the intensive care, the incidence of renal failure, and opiate use during the first 24 hours [14]. In addition, it reduced the maximal serum glucose and cortisol levels and improved the forced vital capacity [14]. Epidural analgesia is also proven to be safe and effective in patients with acute pancreatitis [15], and following cardiac surgery and thoracic trauma [16,17]. However, the use of epidural analgesia may be limited in patients with coagulation abnormalities.

The opioid agonists are the most important analgesic agents in intensive care. They act selectively on central and peripheral neurons that transmit and modulate nociception, without affecting other sensory perceptions or motor function. In normovolaemic patients, the haemodynamic effects are usually minimal; their major side effect is dose-dependent respiratory depression, which is enhanced by benzodiazepines, and reduced gastrointestinal motility. Following prolonged administration, dependence and withdrawal effects can be seen.
Morphine is still the most frequently used analgesic agent in European intensive care practise [18]. It is the most hydrophilic compound of the opioid agonists, which favours its use in obese patients. The effective dose depends on patient characteristics. Morphine is metabolized in the liver to 80% morphine-3-glucuronide (an inactive metabolite) and 20% morphine-6-glucuronide. Because the kidney clears morphine-6-glucuronide, the effect of morphine can be prolonged in patients with renal failure.

The opioids fentanyl, alfentanil, sufentanil and remifentanil are more lipophilic than morphine and therefore have a faster onset of action. However, increased fat solubility also increases their accumulation in fat and muscle tissue. As a result, prolonged infusion leads (especially for fentanyl) to increased context-sensitive half-times (i.e. the time needed for the drug’s plasma concentration to decrease by 50% after cessation of infusion) (Figure 1). The effect of continuous infusion of alfentanil is unpredictable and it should therefore not be used in the intensive care. The exception to this is remifentanil, which is metabolized by aspecific plasma and tissue esterases whereas the other opioids depend on hepatic degradation and renal excretion. Thus, the context-sensitive half time of remifentanil is consistently short (3-5 minutes), even after prolonged infusion or in renal or hepatic dysfunction [19-21]. Because of this unique property, analgesia-based sedation with remifentanil has been introduced as an alternative to sedation-based regimens. In critically ill patients requiring prolonged mechanical ventilation, it was shown that a remifentanil-based regimen could significantly reduce the duration of ventilation by more than two days compared with a midazolam-based regimen [22]. A similar effect was found in a recently published randomized study comparing remifentanil-based analgo-sedation to a traditional regimen [23-25]. In addition, the use of remifentanil in patients with brain injury facilitates rapid neurological assessments [26]. Opioid administration is associated with the development of paradoxical, pathological pain that presents as opioid-induced hyperalgesia (OIH) or tolerance. Hyperalgesia and tolerance seem to occur more frequently and predictably with the administration of remifentanil. A cellular mechanism involving the rapid and prolonged up-regulation of N-methyl-d-aspartate (NMDA) receptor function by remifentanil may contribute to the clinical development of remifentanil hyperalgesia and tolerance [27-33]. The enhancement of NMDA receptor function in DH neurons through μ receptor activation may underlie increased pain states in chronic pain and OIH [34-37]. Remifentanil-induced hyperalgesia however is mostly observed in perioperative patients and healthy volunteers. The clinical consequences of remifentanil-induced hyperalgesia in the intensive care should be evaluated.

Sedation
The term “sedative-hypnotics” refers to a heterogeneous class of drugs that includes benzodiazepines, barbiturates, and various other hypnotics such as etomidate, clonidine and ketamine.

Benzodiazepines
Benzodiazepines exert their principal pharmacodynamic effect via central nervous system GABA receptors. GABA receptors are membrane-bound proteins divided into three subtypes, GABAA, GABAB, and GABAC receptors. The GABAA receptors primarily mediate neuronal excitation (seizures), rapid mood changes, clinical anxiety, and sleep. GABAB receptors mediate memory, mood, and analgesia. Binding affinity for the GABA receptor determines drug potency. It has been suggested that benzodiazepine receptor occupancy of 20% provides anxiolysis, while 30-50% is associated with sedation, and 60% is required for hypnosis [38]. Benzodiazepines produce dose-dependent respiratory depression in patients with chronic respiratory disease and in combination with opioids.

The most commonly used benzodiazepines in European intensive care units are lorazepam and midazolam [18]. Lorazepam is a long acting benzodiazepine (T1/2 13 hours), metabolized by hepatic glucuronidation to inactive metabolites that are cleared by the kidney. Because hepatic dysfunction has more impact on oxidative processes, this does not affect the elimination of lorazepam. Midazolam is a shorter-acting agent (half-life 1-4 hours), which is oxidized in the hepatic cytochrome P-450 enzyme system to water-soluble compounds that are excreted in the urine. The primary metabolite (1 hydroxyethylmidazolam) has a sedative effect as well, which can lead to prolonged sedation in patients with renal dysfunction. Prolonged action of midazolam can occur in hepatic dysfunction but also following inhibition of oxidative processes.

Table 1. Guidelines for the use of sedation and analgesia as proposed by the Dutch Society of Intensive Care

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<th>NETH J CRIT CARE - VOLUME 13 - NO 3 - JUNE 2009</th>
<th>133</th>
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<tbody>
<tr>
<td>1 Treatment of pain, fear, and agitation should be an integral part of quality and treatment</td>
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<td>2 Morphine sulphate is recommended as a first choice analgesic in the intensive care</td>
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<td>3 Fentanyl is recommended in critically ill patients with haemodynamic instability, signs of histamine release after the use morphine sulphate and/or morphine sulphate allergy</td>
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<td>4 Sedatives should be titrated until the patient is comfortable, until intensive therapy can be provided and until a good level of amnesia is reached. Assessing adequacy of sedation on a regular basis (e.g. by using the Ramsay score), followed by applying dose adjustments of sedative medication and daily evaluation of the indication to sedate the patient.</td>
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<td>5 Midazolam and propofol are recommended for short-term (&lt;24 h) sedation</td>
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<td>6 Lorazepam is recommended for long-term sedation</td>
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<td>7 Haloperidol is the preferred agent for the treatment of delirium in critically ill patients</td>
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of the P-450 enzyme by for instance erythromycin or calcium antagonists.

Compared with midazolam, lorazepam has a greater potency but also a slower onset of action (5-20 minutes vs. 1-5 minutes for midazolam). Furthermore, lorazepam is an independent risk factor for the development of delirium [39]. In postoperative surgical intensive care patients it was found that patients receiving lorazepam were optimally sedated (SAS score 3-4) only 49 % of the time versus 69 % in patients receiving midazolam [40]. Nevertheless, patients with lorazepam were more often deeply sedated (SAS score 5-6), needed more time to recover from sedation and were extubated at a later time than patients with midazolam [40].

Propofol
Propofol is a fast and short-acting sedative agent. Similar to the benzodiazepines, it acts on the GABA receptor although at a different site. Because propofol is hydrophobic it is dissolved in an oil-in-water emulsion and crosses the blood-brain barrier easily. Metabolism occurs mainly through hepatic conjugation to inactive metabolites, which are excreted in the urine. Hepatic or renal disease hardly affects the pharmacokinetics of propofol. Besides pain on injection, an important side effect is vasodilatation-induced hypotension, which can be especially pronounced in hypovolaemic patients. Other rare side effects include hypertriglyceridaemia, which is associated with high infusion rates and simultaneous intravenous lipid nutrition, and the so-called ‘propofol infusion syndrome’. The latter is characterized by metabolic acidosis, hyperkalaemia, rhabdomyolysis, dysrhythmias and heart failure. It is a rare complication, which appears has been described only at doses of more than 5mg/kg/hr [41].

Figure 1. Context-sensitive half-times of remifentanil and the other 4-anilido-piperidine opioids. Figure adapted with permission from Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, Shafer SL: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 1993;79:881–892.

Figure 2. Main pathology of the patients as specified by the respondents.
vasodilatation. Adverse events may include hypotension, nausea, bradycardia, and atrial fibrillation. Both drugs have mainly been investigated in postoperative patients. Dexmedetomidine was found to be suitable for short-term postsurgical sedation and to reduce the need for analgesia [45]. Data from small uncontrolled studies suggest that dexmedetomidine may be safe and effective for long-term sedation as well [46,47]. In a small uncontrolled series, dexmedetomidine infused continuously for up to 7 days was an effective sedative and analgesic-sparing drug [46]. Sedation with dexmedetomidine was associated with an increased number of days alive without delirium or coma in mechanically-ventilated ICU patients [48]. However, little is known about the use of these drugs in critically ill, mechanically-ventilated patients. Neither the Dutch guidelines nor the American guidelines recommend alpha-2 agonists.

Ketamine and etomidate
Ketamine and etomidate have not been widely studied in ICU patients and therefore are not used for sedation in the intensive care.

Assessment of analgesia and sedation
In general, deep sedation is only indicated in patients with severe head injury and patients requiring complex mechanical ventilation strategies. In every patient, the sedation level should be individually titrated and regularly assessed. The lack of a standardized protocol for analgesia, sedation, and absence of monitoring of the depth of analgesia and sedation results in over sedation with more days on mechanical ventilation, a longer stay in intensive care and increased complications such as ventilator associated pneumonia [49]. Daily sedative drug interruption can prevent drug accumulation and will reduce the time to extubation with subsequently lower ventilator associated complications [49]. However, if the patient is comfortable, cooperative and arousable, there is no need for a daily sedative interruption.

In order to assess the level of sedation, several different subjective and objective sedation scales have been developed. The most commonly used sedation score is the Ramsay score, even though its reliability is limited [50], and it has been criticized for its lack of clear discrimination and specific descriptors to differentiate between the various levels [51,52].

The Riker Sedation Agitation Scale (SAS) [51,53,54], the Motor Activity Assessment Scale (MAAS) [55], the Richmond Agitation-Sedation Scale (RASS)) [56,57] the Vancouver Interaction and Calmness Scale (VICS) [58], and the Minnesota Sedation Assessment Tool (MSAT) [59] have been proven to be reliable and validated tools to assess sedation depth in patients who are mechanically ventilated. Several other scoring systems are available but further studies are required to choose the best sedation assessment tool [60]. It is important to note that the Glasgow Coma Scale was neither developed nor is suitable for measuring levels of sedation.

A more objective way to assess the depth of sedation might be the Bispectral Index Score (BIS). Bispectral Index Monitoring uses Fourier transform analysis of an electroencephalogram signal to estimate the depth of sedation. It is expressed as a score between 0 (isoelectric) and 100 (fully awake) and is based on a large EEG database recorded in healthy volunteers and patients who were given anaesthetic drugs. The BIS score is correlated with observational sedation scales and is especially useful in deeply sedated or paralyzed patients [61]. The BIS seems a promising tool to objectively assess the level of sedation but it still has its limitations and it is therefore not useful in the intensive care.

Assessing the level of pain is not easy as intensive care patients are often unable to communicate. The Visual Analogue Scale and the Verbal Rating Score are the most frequently used pain-scoring systems but they can only be used in communicative patients. Therefore, the Critical-Care Pain Observation Tool (CPOT) was developed which is based on physiological parameters and behavioural aspects (i.e. facial expression, body movements,
muscle tension and compliance with the ventilator). The CPOT was found to be a reliable and valid tool for the assessment of pain in patients who cannot communicate [62].

In conclusion, regular assessment of the patient's comfort and depth of sedation is necessary with the emphasis on goal-directed delivery of sedative and analgesic administration. Other than suggested by the guidelines of the Dutch Society of Intensive Care, i.e. to use the Ramsay score, validated sedation assessment tools such as the SAS, RASS, VICS, MSAT or the MAAS score should be used in the intensive care.

**Clinical practice**

In 2004, 27 Dutch hospitals were invited to participate in a survey on sedation and analgesia practice in mechanically-ventilated patients. To assess which drugs were prescribed for sedation and analgesia, which sedation and pain assessment tools were used and to determine adherence to the guidelines proposed by the Dutch Society of Intensive Care. These hospitals were well distributed throughout the Netherlands and included peripheral as well as academic hospitals. Each participating intensive care included a minimum of 10 to a maximum of 30 patients, who were ventilated at some point during their stay in intensive care. Questionnaire items were: patient and disease characteristics, drugs used for analgesia and sedation, sedation scores (Ramsay score, Glasgow Coma Scale and the Sedation Agitation Scale), analgesia scores (Verbal Rating Scale VRS and the Visual Analogue Scale) and patient and nurse satisfaction with current practice. Written informed consent was obtained from every patient or their representative.

Twenty intensive care units at 18 hospitals (of which one academic hospital) actually responded. This resulted in complete datasets for 401 patients. As shown in Figure 2, the pathology of these patients was very heterogeneous. Average time on mechanical ventilation was 8.0 ± 11.2 days (mean ± SD) with a median time of 4 days. For sedation, the majority of patients received midazolam, followed by propofol (Figure 3). The mean of the minimum of dose range for midazolam (the lowest dose the patient received during a day during the period the patient was given the drug) was 89.5 mg/day (SD 58.2 mg/day) and a maximum of 148.4 mg/day (SD 162.3 mg/day). The mean of minimum of dose range was 1822 mg/day for propofol (SD 1459.5 mg/day) and the mean of the maximum was 3262.8 mg/day (SD 2143.9 mg/day). Midazolam and propofol were mainly used for longer than 24 hours, with a mean duration of 6.4 days (SD 8.6) and 4.1 days (SD 4.7) respectively. This is in contradiction with the Dutch guidelines. A small group was sedated with a combination of these two drugs, whereas less than 10 percent of the patients received another drug. Switching to lorazepam for long-term sedation as is recommended in the Dutch protocol, is not carried out in clinical practice. The level of sedation was assessed in only 60% of the patients. This is slightly more than in a recent observational study conducted in 44 ICUs in France, in which only about 40% received sedation or analgesia assessments [63]. This was mainly done with the Ramsay sedation scale (82%), in 9% with another sedation scale and in 9% with the Glasgow coma scale (not validated to assess sedation levels). If sedation levels were scored, this was performed at least once per shift in 75% of the patients (Figure 4). In less than 10% of the patients were sedation levels scored every hour. Remarkably, sedative drug interruptions were performed in only 29% of the patients - and then in only a minority of these patients (18%) was this done on a daily basis.

In 88% of the patients analgesics were administered; in 69% of the cases morphine was used for this purpose. The minimum and maximum of dose range per day of morphine was 28.8 mg/ day (SD 15.7) and 42.4 mg/day (SD 14.1) respectively. Morphine was administered over a mean of 6.2 days (SD 7.2). Of the other opioid agonists, fentanyl and sufentanil were used in about 29% whereas remifentanil was hardly used (Figure 5). In 65% of the patients paracetamol was administered. Other NSAIDs, including COX-2-inhibitors, were used very rarely (<2%). Assessment of the presence of pain or adequacy of analgesia occurred in only 8% of the patients. In about a third of these patients the level of analgesia was scored at least once per shift. When sedation and analgesia were scored, in more than 80% of cases both patients and nurses indicated that they were satisfied with the sedation regimen. In more than 90% of cases the analgesia regimen was to the satisfaction of nurses and patients.

Surprisingly, current sedation and analgesia practice in a sample of Dutch ICUs does not reflect the guidelines proposed by the Dutch Society of Intensive Care. There is a remarkable uniformity in the choice for traditional drugs (midazolam and morphine), as recommended by the Dutch Society of Intensive Care. The Dutch guidelines recommend the use of midazolam as well as propofol only for short-term sedation, whereas in daily practice it is also used for long-term use. Lorazepam and fentanyl, recommended as second choice by the Dutch Society, and other drugs such as short-acting opioids or alpha-2-agonists, are not used at all. Regular evaluation of the depth of sedation as advised in the Dutch guidelines, is not effectuated in clinical practice.

**Future developments**

Agents that offer a predictable onset and offset of action, with
little chance of accumulation are the future drugs of choice. Changing from hypnotic-based sedation to analgo-based sedation will reduce the risk of accumulation. Remifentanil-based analgo-sedation seems to be an option for the future. Because remifentanil was only licensed in 2000, more evidence on its efficacy, safety and tolerability must be gathered. Is hyperalgesia relevant in the intensive care setting? Is the use of remifentanil cost-effective? So far only two multicentre studies comparing remifentanil-based analgo-sedation with conventional hypnotic-based sedation have been conducted and one centre randomized study comparing remifentanil-propofol analgo-sedation with a conventional regime [20,21]. More multicentre trials are needed to confirm that remifentanil reduces the length of mechanical ventilation, intensive care and hospital stay. Not until the use of remifentanil meets all these demands, can remifentanil and analgo-sedation be implemented in the Dutch guidelines. Agents such as dexmedetomidine and clonidine may also play a role in the intensive care when used concomitantly with sedatives and analgesics, but here again more evidence is warranted.

Conclusion

Based on these results, we conclude that the analgesia and sedation practice in many intensive care units can be improved. This could be done by choosing alternative drugs but also by protocol-driven sedation. Current sedation and analgesia clinical practice is not in accordance with the recommendations in the Dutch guidelines, although we realize that a treatment protocol is a guide to therapy and cannot address every clinical situation. Routine regular assessment and titration of the required level of sedation with the use of validated sedation assessment tools should be part of daily clinical practice. Also analgo-based sedation in combination with alpha-2-agonists, might make up part of a future Dutch protocol.

Conflict of interest statement

All authors declare that they have no conflict of interest.

References


52. Riker RR, Fraser GL, Simmons LE et al. Validating the sedation-agitation scale with the bispectral index and visual analogue scale in adult ICU patients after cardiac surgery. Intensive Care Med 2001;27(5):853-858.


