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Current Strategies for Sedation in the Critical Care Unit and Perioperative Setting: Dexmedetomidine, A New Approach.

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Summary

Sedation therapy is an essential requirement for nearly every patient in the Intensive Care Unit (ICU). It includes the effective management of pain, anxiety and sleep (hypnosis). The precise and safe control of the depth of sedation still remains challenging. Patient comfort can be obtained by the close control of sedation. This may lead to a faster recovery, shorter time on mechanical ventilator support, reduced length of stay, and improved outcome.

Poorly controlled sedation techniques can lead to dangerous agitation, with resulting injury, undersedation with hemodynamic and psychological consequences, or to oversedation with prolonged recovery and the risk of unrecognized cerebral insult. The result of an inadequate control of sedation can be adverse outcomes and increased cost of care. The average patient in the ICU is sleep deprived and this promotes exhaustion and the development of an ICU psychosis.

Current approaches to sedation require a multimodal regimen, utilizing a combination of analgesics, anxiolytics and sedatives. Each group of drugs has additional unwanted effects. The opiates are the mainstay of analgesic therapy, and while they provide very effective pain relief, their use is associated with respiratory depression, ileus or narcotized bowel syndrome, pruritus, and nausea and vomiting. The sedative agents are also associated with respiratory and cardiovascular depression. Most of the commonly used agents also have active metabolites that rapidly can lead to accumulation in the critically ill patient with impaired clearance. This can result in prolonged and uncontrolled effects. The long-term effects of profound oversedation on cognitive function may be significant.

The routine use of sedation scales in the critical care unit results in an objective assessment and close control of the level of sedation. The precise control of sedation and analgesia can reduce the need for muscle relaxants and the potential complications associated with their administration. Sedation agents should be administered to a defined clinical end-point, as opposed to a set dosage regimen. This allows for continual reassessment of the patient, continuity of care, cost effective use of drugs, and the defining of an optimal target level for the titration of medication. In this manner, critical care can be enhanced, patient safety improved and post discharge complications such as posttraumatic stress disorder reduced.

Protocol controlled sedation infusions may lead to fewer adverse events, shorter stays in the ICU and substantial economic savings.

The introduction of α_2-adrenergic agonists for sedation management has added a new perspective to this critical care pathway.

The challenge of sedation in the ICU

Since the Ramsay Sedation Scale (RSS) was first used to describe the level of sedation in patients receiving alphaxalone-alphadolone (1), the management of critical care patients has witnessed a number of technical and conceptual advances that have resulted in considerably improved patient management, prognosis and long-term outcome. Despite these advances, there remains considerable room for improvement. The effects of oversedation are still commonly seen; generally resulting in prolongation of time on mechanical ventilation and stay in the critical care unit (2).

Sedation of patients is common practice in the intensive care units in order to relieve anxiety and facilitate treatment procedures, particularly in mechanically ventilated patients. The management approach also aims to minimize the acute physiological and psychological responses to the stress and disorientation of the intensive care setting (3,4). In practice, sedation often encompasses a number of elements essential for adequate patient management, such as analgesia and anxiolysis in addition to pure sedation. Therefore, the management regimen should be considered to be one that aims to achieve patient comfort through a combination of hypnosis (sleep), analgesia and anxiolysis as appropriate.

Sleep deprivation is a particular problem in the intensive care unit where sleep patterns are considerably disturbed and the average sleep time is less than 2 hours per day (5). Hypnosis is therefore an essential element of patient management as sleep deprivation can lead to a number of behavioral problems such as anxiety, hyperactivity, aggression, compromised immune response, hallucinations intensive care psychosis and increased sensitivity to pain (6,7). In terms of priority, however, the first consideration has to be the assessment and appropriate management of pain.

Prioritizing pain

Almost all patients in the critical care unit suffer pain and it is possible that even extreme pain in ventilated patients can go unrecognized for long periods of time due to an inability to adequately communicate their needs. Untreated pain can lead to significant physiological sequelae (8). Effective pain management is therefore an important aspect of patient care, leading to improved patient satisfaction, faster recovery times and a reduction in complications (8). The importance of addressing pain in critical care patients is emphasized by the Society of Critical Care Medicine (SCCM) whose practice guidelines recommend that adequate analgesia be a primary goal in the care of the critically ill (9).

Intravenous opiates are the current mainstay of analgesic therapy. While these agents provide highly effective pain relief, their use is associated with a number of additional effects (respiratory depression, hypotension, gastric retention, ileus, pruritus, nausea and vomiting) that prove problematic in critically ill patients (10). In an effort to avoid these significant adverse effects and concerns over the potential for additive effects, the adequacy of pain management can be compromised.

Morphine sulfate remains the most commonly used opioid, offering effective pain management at low cost. The fentanyl family of opioids is often used as an alternative in hemodynamically unstable patients, offering the benefit of potent analgesia with fewer adverse effects. These opiates have active metabolites; therefore the impaired clearance in critically ill patients may lead to accumulation and prolonged uncontrolled effects. Remifentanil, the newest agent in this family, has the benefit of being extremely receptor specific with a fast onset of action and clearance, with no active metabolite, and allows for accurate control of postoperative pain (11). However not only is it a fast onset agent it is also a fast offset agent. Therefore ongoing analgesic measures need to be taken prophylactically before the withdrawal of the drug.

Opiates have no real amnesic properties, although some debate on the benefit of this property continues. It is intuitive that patients experiencing the unpleasant nature of a critical illness, the critical care environment and the associated pain are best managed by aiming to ensure they have no recollection of the experience. However, it has been suggested that patients with no recall of their critical care period may not realize how ill they have been and therefore have unrealistic expectations of their recovery (12).

In order to determine an appropriate level of analgesia it is, of course, essential that regular patient assessment be conducted as a routine part of patient care. A number of behavioral observation systems have been developed and the verbal rating, visual analogue or numerical rating scales usually assess reports of pain. In addition, use of pictures describing pain levels is sometimes adopted. Picture scales have the benefit of being successfully used in children, illiterate or non-verbal patients or those who have difficulty manipulating or understanding visual analogue or numerical scales (13). Although these approaches to pain assessment are by nature highly subjective, physiological indicators such as tachycardia, increased blood pressure, palmar sweating and changes in endorphin and serotonin levels are not able to indicate intensity of pain (14,15,16). Therefore, while physiological signs are useful indications that a patient is suffering pain, particularly if they are non-verbal or semi-conscious, they are not considered suitable parameters for pain assessment in isolation.

The road to tranquility

In the past, heavily sedated patients were not uncommon in the majority of critical care units, the only signs of life emanating from the monitoring equipment they were connected to. Thankfully, excessive sedation is no longer considered acceptable for the majority of patients, as the incidence of unwanted adverse effects and prolonged recovery are so high (17,18). It is now generally considered that an ideal level of sedation maintains the patient in a cooperative, orientated and tranquil state when roused, but asleep when not disturbed (4,19).

For most patients, a certain degree of awareness is important in order to enable assessment of neurological function and to allow patients to communicate their needs to the care team, as isolation and frustration due to communication difficulties can lead to severe emotional reactions. A patient that is alert and aware is also better able to participate in his or her own care and to gain a sense of control. In addition, this situation is less worrying for relatives who will be reassured to see a loved one awake and responsive rather than unconscious for prolonged periods.

Despite recognition of the general goals of patient sedation, achieving an appropriate level of sedation can present a number of clinical and practical problems. Although there is little standardization of sedative approaches and objectives, an ideal level of patient consciousness has been defined as a state in which patients are able to respond to commands rather than painful stimuli (20). The absence of clear objectives or a common goal for sedative regimens is, however, apparent.

Approaches to patient assessment

As with any drug regimen, regular assessment of effect, patient status and emergent adverse effects is essential. In this respect, sedative and analgesic agents should be no exception. Despite this, patient assessment is by no means routine practice. A survey of Danish intensive care units has demonstrated that although sedatives and analgesic regimens were used routinely in ventilated patients in almost all of the 49 units surveyed, only 16% of the units used a sedation scoring system, the RSS (21). This situation is likely to reflect the approach in the majority of intensive care units. The real drive to the accurate control of sedation level by the use of a scoring system may be the economic impact that this can have on patient care. The controlled technique, targeting a sedation level, as opposed to prescribing a specific drug dose for infusion, may result in significantly less drug being administered. This can translate into cost savings, not only in pharmaceutical costs but also those costs associated with oversedation.

Ongoing patient assessment is essential to ascertain not only the efficacy of the management regimen but also to indicate where modifications are required. It is also fundamental to establishing a baseline on which individual management regimens can be based. From this baseline the efficacy of treatment and sedation regimens can be gauged and the level of discomfort and agitation that may indicate therapy adjustment can be determined. In addition, regular interaction with the patient provides reassurance and limits the feelings of isolation common in the intensive care setting. As a quantitative measure of reliable physiological endpoints is not currently an option, accurate assessment of depth of sedation can prove problematic and therefore a number of patient assessment instruments have been developed.

Sedation scoring systems

Since RSS was first presented in 1974 (1) it has become a universally recognized standard test of rousability of the sedated patient, providing a numerical ranking of a patient's level of consciousness. However the RSS level 1 does not differentiate between anxiety, delirium and agitation and level 6 does not discriminate between light general anesthesia and deep coma. Furthermore, the scale is not appropriate for the paralyzed patient. Despite these criticisms, the fact remains that the RSS has proven to be a practical and robust tool that has stood the test of time. In addition, the RSS remains the only instrument that has received any degree of general acceptance and utilization (22). The continued popularity of the RSS could, however, be considered more a factor of its widespread use and recognition as a 'common language', rather than the merits of the scale itself. In recognition of the limitations of the RSS, a number of new assessment instruments have been developed in recent years. The most frequently used and best validated are the Sedation-Agitation or Riker Scale, the Motor Assessment Scale, the COMFORT Scale and the use of the Bispectral Index or BIS monitor (23-27). Regular and routine use of an appropriate sedation scale has the potential not only to define an optimal endpoint for titration of sedation, but also to provide continuity of care. This approach to precise patient management, avoiding the problems of over and undersedation will result in a higher proportion of patients maintained in a calm, comfortable and cooperative state. In addition, the cost-effective use of drugs makes good economical sense.

Economic considerations

Perhaps the most profound impact on intensive care practice is likely to be an economic one. Cost-cutting exercises have led to an increased interest in assessing sedation levels and this is probably the major driving force behind using sedation scales in many units. While it is intuitive that rational drug use makes good financial sense, this theory has actually been confirmed by a recent study. A sedation guideline developed by the UK Intensive Care Society has been shown to have a significant effect on total sedative use and sedation costs without compromising patient outcome (28).

A New Approach to ICU Sedation

Alpha-2 adrenoceptor agonists have been used in veterinary anesthesia practice for many years. However, despite the knowledge that these agents reduce the release of norepinephrine and therefore have anesthetic properties, their use in humans has been very limited.

Alpha-2 receptors are located presynaptically in sympathetic nerve endings and in noradrenergic neurons in the CNS. The receptors in the locus coeruleus area of the upper brain stem and the substantia gelatinosa mediate the sedative effects. The imidazoline group of drugs (clonidine, medetomidine, dexmedetomidine, and mivazerol) has been the most thoroughly investigated as sedative, analgesic and anesthetic agents. Medetomidine has been used extensively in large animal veterinary practice with good success. The D-enantiomer, dexmedetomidine, has now been developed for clinical use in humans, and is a very potent and specific alpha-2 adrenoreceptor agonist.

Dexmedetomidine is extensively and rapidly metabolized into inactive metabolites that are mainly excreted in the urine. It is a lipophilic compound, which is extensively distributed in the tissues, with a half-life of 6 minutes. The elimination half-life is 2 hours.

Central Effects

Dexmedetomidine produces both sedative and analgesic properties by its agonist effects on the alpha-2 receptors in the brain and spinal cord. It was first introduced as an anesthetic sparing agent, and was demonstrated to reduce isoflurane requirements by up to 90% when delivered as an infusion during general surgery (29). It also may have a neuroprotective role as improved neurological outcome has been shown in a rat model of brain ischemia (30). Dexmedetomidine may also have a useful role in managing the patient undergoing a drug or alcohol withdrawal process.

Cardiovascular System.

The intravenous administration of dexmedetomidine causes a decrease in heart rate, a transient increase in blood pressure due to peripherally mediated α-2 receptor vasoconstriction. This is followed by a decrease in blood pressure as a result of a centrally mediated reduction in sympathetic tone. This reduction in sympathetic tone may have a beneficial cardioprotective effect in reducing the hemodynamic response to intubation or light anesthesia. Another α-2 agonist, mivazerol has been demonstrated to reduce episodes of myocardial ischemia in patients undergoing peripheral vascular surgery (31). The reduction in peri-operative oxygen consumption, as a result of these hemodynamic effects, may be very useful in protecting patients with coronary artery disease undergoing surgery.

Respiratory System.

Although dexmedetomidine is a powerful sedation agent with analgesic properties, it does not produce respiratory depression at clinically effective doses (32). This distinguishes this agent from virtually all other sedatives and provides for a unique safety factor in its use.

Neuroendocrine System.

The neuroendocrine response to stress is blunted by dexmedetomidine, as a result of its inhibition of sympathetic outflow and reduction in plasma catecholamines. It does not have any effect on ACTH secretion at therapeutic doses, unlike etomidate, another imidazole derivative drug.

Perioperative Use of Dexmedetomidine

Dexmedetomidine has been shown to be advantageous in an increasing number of perioperative situations. The following areas will be discussed:

- Awake craniotomy
- Bariatric surgery
- “Off-pump” & “Fast-Track” CABG

- Major vascular surgery
- Major spinal surgery
- Replacement for thoracic epidurals
- Regional plus sedation
- "Wake-up" procedures: carotid endarterectomy, spinal instrumentation
- Pediatric sedation
- Burns dressing changes
- Sole anesthetic agent for airway surgery

Sedation in the ICU

The advantages of a drug that provides sedation, anxiolysis and analgesia, without respiratory depression, makes it ideal for use in the intensive care unit. Dexmedetomidine can facilitate the extubation process by attenuating the hemodynamic responses and by not causing respiratory depression. This allows it to be continued after extubation providing continuity in the sedation therapy. Multiple studies have demonstrated its efficacy in this area. Another novel advantage of this agent is that the deeply sedated patient may be aroused and demonstrate normal cognitive ability. Therefore a neurological assessment could be performed whenever required. Sedation without cognitive impairment may have far-reaching effects von reducing the morbidity in ICU patients.

The time on mechanical ventilation and therefore the time spent in ICU may be reduced by the clinical advantages offered by dexmedetomidine.

Conclusion

The unique molecular pharmacology of this α-2 agonist provides sedation and analgesia without respiratory depression in a controlled manner by intravenous infusion. These properties may lend themselves to many areas of sedation and conscious sedation therapy in the ICU and perioperative period.

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