

Analgesia and sedation in high-risk critically ill patients: still waiting for evidence about remifentanyl

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Critically ill patients requiring invasive vital support such as mechanical ventilation almost uniformly show anxiety, agitation and pain during their Intensive Care Unit (ICU) stay. The use of analgesic and sedative drugs is essential to improve comfort, reduce anxiety and facilitate nursing care, despite the fact that these drugs present several side effects.

In the past decades, liberal doses of propofol and benzodiazepines were used to adapt patients to the harsh ICU environment through deep levels of sedation. Recently, evidence based medicine has shown that heavy sedation may increase mortality and morbidity:¹ new protocols have been proposed to change this cultural approach.² Spontaneous awakening and breathing trial,³ early mobility and physical therapy,⁴ analgesia-based sedation,⁵ the use of newer drugs with favorable pharmacokinetics⁶ and the use of an enteral approach⁷ are the most important recent innovations. They all share the new target of maximizing comfort and adaptation to invasive procedures while patients remain awake, interactive, and oriented.^{1, 8}

High-risk critically ill patients are the most difficult ICU population to take care of, for which any therapeutic intervention could have a significant role in changing the outcome.⁹ Both inadequate and excessive analgesic use has been associated with several disadvantages: nosocomial pneumonia, delirium, long-term psychological disorder, prolonged mechanical ventilation, higher risk of tracheostomy, higher risk of

requiring diagnostic imaging to clarify abnormal neurological status, and unnecessary prolonged ICU and hospital stay.¹⁰ Currently, morphine, sufentanil and fentanyl are the most commonly used analgesics in high-risk critically ill patients: the 2010 "Evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care" still suggest their use for analgesia extending beyond 72 hours. However, the duration of their effect may become unpredictable because of redistribution and accumulation with prolonged infusion, especially in patients with organ failure. In this context, the use of remifentanyl for analgesia-based sedation⁵ has been a significant innovation in recent years, "awakening" several intensivists to wake up their critical patients thanks to its manageability.

Remifentanyl is a strong selective μ -opioid receptor agonist, rapidly metabolized by non-specific plasma and tissue esterases into inactive metabolites; it has very short context-sensitive half-life (2-3 minutes) even after prolonged infusion or in patients with organ failure. Remifentanyl is easy to titrate and provides excellent analgesia: it allows higher doses administration than are normally used with traditional opioids without concerns about accumulation or delayed recovery.¹¹ However, more than the known side effects of opiates like hypotension, bradycardia, decreased respiratory drive, delirium, nausea and vomiting, ileus, sleep disruption, itch, and urinary retention, remifentanyl determined

thoracic rigidity after bolus administration; for this reason, it is used in continuous infusion. On the other hand, the very fast offset could lead to a greater incidence of pain, suddenly reported from patients, when its administering is not sufficiently tapered off.¹²

Several retrospective studies reported the clinical superiority of remifentanyl-based analgesoseda-tion, when compared to protocols using other opiates for analgesia plus propofol-based or mid-azolam-based sedation. However, when it was prospectively compared to other opiates in con-tinuous infusion (sufentanil, fentanyl), it failed to show substantial improvements of clinical outcomes, especially when considering patients ventilated for more than 72 hours.^{10, 13} Up to now, we lack the evidence that clinical improve-ments are due to the specific molecule rather than (more likely) to the “critically ill awakening”.

In the present issue of *Minerva Anestesiologica*, Futier *et al.* present a retrospective study¹⁴ including 1544 patients who required invasive mechanical ventilation in the ICU. In a before-after design, they compared the outcomes of opiates used according to local guidelines, particularly regarding the impact on mechanical ventilation days and ICU length of stay. The strengths of this paper are the high number of patients enrolled, the case-mix involving both medical and surgical patients, the comparison between the newly introduced remifentanyl with an opiate of relatively short half-life, like sufentanil. On the contrary, the before-after design is an intrinsic limitation, at least for the refinement in staff skills, as well as for a change in the use of sedatives (higher percentage of midazolam in the sufentanil phase). The main result coming from introducing remifentanyl was the decrease in mechanical ventilation days and ICU length of stay, with a higher achievement of sedation goals and similar costs for analgesic and sedative drugs. Once again, as already shown in the literature,¹⁵ these differences were significant only for short-stay ICU patients (<4 days).

Offering to the critically ill the best care for their pain is mandatory: nurses and physicians have to gauge it and provide effective measures to reach an adequate level of pain relief. Up to now it has not been conclusively determined whether

analgesia-based sedation is a more effective alternative compared to other sedative approaches (dexmedetomidine, propofol, enteral hydroxy-zine) to adapt patients to the necessary invasive procedures and to the ICU environment.

It seems incorrect to analyze together short- and long-ICU-stayers. The former could be more adequately treated with approaches coming from the operating theatre (short time from stop of drug infusion to patient awakening), where remifentanyl saves lives avoiding the unexpected late increases of sedative and respiratory depres-sant effects seen with longer half-life opiates. However, it could be pointless or even dangerous for the long-ICU-stayers, where analgesics have to be used only in case of pain or to decrease the respiratory drive, whereas agitation and anxiety should be treated with lower-side-effect seda-tives. In any case, remifentanyl is a “high-perfor-mance-drug”, with ultra-short onset and offset time and with unchanged context-sensitive half-life even after prolonged infusion. It has to be considered as an effective and manageable drug when facing the breakthrough pain in scheduled ICU procedures, or when patients need repeat-ed/rapid assessment of their neurological status (e.g. neurosurgical or comatose patients). Since recent literature has highlighted the need to keep patients awake, remifentanyl could represent an interesting alternative among the other analgesic and sedative drugs; anyway, even considering the paper published in the present issue of *Minerva Anestesiologica*, we still need evidence about the care of high-risk long-stay critically ill.

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