CRITICAL CARE

VIEWPOINT

Intensive care sedation: the past, present and the future

Yahya Shehabi*[1], Rinaldo Bellomo[2], Sangeeta Mehta[3], Richard Riker[4] and Jukka Takala[5]

Abstract

Despite the universal prescription of sedative drugs in the intensive care unit (ICU), current practice is not guided by high-level evidence. Landmark sedation trials have made significant contributions to our understanding of the problems associated with ICU sedation and have promoted changes to current practice. We identified challenges and limitations of clinical trials which reduced the generalizability and the universal adoption of key interventions. We present an international perspective regarding current sedation practice and a blueprint for future research, which seeks to avoid known limitations and generate much-needed high-level evidence to better guide clinicians' management and therapeutic choices of sedative agents.

Intensive care sedation: past, present, and future

The administration of sedative drugs is an almost universal intervention in mechanically ventilated intensive care unit (ICU) patients [1]. One might, therefore, expect that there is a strong body of epidemiologic knowledge about the use of such drugs to guide clinicians' current practice and therapeutic choices. However, despite a noticeable evolution in the field over the last 10 years, this is not the case [2-4]. One might also reasonably expect that there are multiple double-blind or open-label large (>1,000 patients) multicenter randomized controlled trials to guide clinicians in their choice of optimal therapy. This is also not the case. Furthermore, existing evidence has not been widely implemented [4].

There are several reasons for this. First, individual patient variability mandates dynamic and frequent changes in drug selection and dose in response to changing clinical situations [2,3]. Second, sedation is often undertaken by using a combination of drugs (benzodiazepines, propofol, narcotics, α_2 central receptor agonists, enteral sedatives, and antipsychotics), and each is administered dynamically in response to perceived and target sedation and analgesia. This additional layer of complexity makes trial design even more difficult and blinding of an intervention almost impossible. Third, the premise of many studies that achieving a given target level of sedation with one sedative versus another is not widely accepted as a means to achieve different clinical outcomes. Fourth, there is significant variability in the intensity of ICU nursing and medical bedside care and subsequently in sedation practices worldwide [4], making research findings in one context difficult to interpret and generalize. Finally, there is uncertainty about how best to diagnose delirium [5,6], a major outcome in most sedation studies. In this level-I data-poor environment, strong opinions abound, creating additional obstacles to the generation of higher-level evidence and the implementation of new recommendations.

In this point-of-view article, we seek to provide a global perspective on sedation to address important progress in the field and to highlight recent and imminent developments in high-quality evidence generation.

International sedation guidelines

In the 1980s and 1990s, sedation practice and drug selection for adult ICU patients were largely an extension of the practice of general anesthesia. Generally, the goal was deep sedation, and neuromuscular blocker use was not uncommon [7]. Because of the paucity of ICU-specific data regarding sedation, the first ICU sedation guidelines published in 1995 contained six recommendations and were based on 13 references [8]. Nevertheless, this pioneering effort recognized that adequate analgesia was a primary goal, that long-term administration of lorazepam had prolonged clinical effects, and that the greater acquisition costs of new sedatives (then midazolam and propofol) were potentially balanced by downstream clinical benefits with short-term use. The 2002 Society of Critical Care Medicine guidelines produced 28 recommendations based on 235 references [9]. This guideline

*Correspondence: y.shehabi@unsw.edu.au
[1]University of New South Wales Clinical School, Prince of Wales Hospital, Barker Street, Randwick, NSW 2035, Australia
Full list of author information is available at the end of the article

included an introduction to the assessment and treatment of delirium and drug-specific recommendations for various time frames and clinical situations. Both the 1992 and 2002 guidelines, however, recognized the dearth of high-quality trials. Though an improvement on the previous guidelines, the 2002 guidelines did not embrace new evidence outside of the US and thus had limited applicability. Hence, a number of country-specific guidelines appeared, reflecting newer information and local practices and matching individual formulary regulations [10,11].

The updated 2013 Society of Critical Care Medicine guidelines provide an unparalleled evaluation and review of the literature (more than 18,000 published articles) with 54 statements and recommendations [12]. Two important recommendations include an emphasis on the analgesia-first concept, or 'analgesia first sedation' [13], and the many benefits resulting from a lighter level of sedation for ICU patients. Additional aspects of the guidelines relate to an expanded understanding of the risk factors for and impact of delirium, and perhaps paradoxically, even more questions are raised about the management of this serious syndrome.

Sedative drugs in intensive care unit sedation

Many of the current drugs used in ICU sedation were initially introduced for general anesthesia or short-term sedation during regional anesthesia. This is why many of the currently used sedatives and analgesics have never been formally evaluated for safety and efficacy for ICU sedation. This also may explain the poor safety record of some sedative agents and the relatively late discovery of the adverse effects of ICU sedation.

Opioids have been an integral part of caring for critically ill patients since the early days of intensive care. The analgesic and sedative characteristics of morphine have been recognized since the 19th century, when it was used to comfort dying patients. Morphine is widely used in ICUs, and its sedative effects, especially at higher doses, may seem attractive in combining pain relief and sedation. The recent claim that the use of morphine alone represents 'no sedation' is clearly misleading [14], as morphine provides analgo-sedation. The effects, however, of long-term treatment with morphine or morphine-based regimens have not been formally evaluated in ICU patients. Despite well-known adverse effects (histamine release, hypotension, respiratory depression, tolerance and dependence, and accumulation of active metabolites) and long duration of action, morphine is likely to keep its place in the ICU because of familiarity, availability, and cost-effectiveness, at least in comforting dying patients, particularly in cost-restricted settings. Fentanyl is a shorter-acting opiate with no active metabolites; however, like morphine, it has a long context-sensitive half-life and accumulates in renal failure [15]. Although fentanyl has less-sedating effects than morphine, it potentiates the effects of sedative drugs and in high doses can produce somnolence and sedation [16]. Driven by the perceived cardiovascular stability and favorable kinetics [17,18], fentanyl appears to have replaced morphine to a large extent; whether this evolution in practice is clinically beneficial, however, remains untested.

The history of sedative use in the ICU has been long and complex. In the absence of long-term safety data, familiarity with short-term use and its apparent safety profile led to the introduction of etomidate as a continuous infusion for ICU sedation, with resulting adverse events including adrenal suppression and a 19% absolute increase in mortality in trauma patients [19,20]. Benzodiazepines, however, have the longest history and remain the most commonly used ICU sedative agents around the world. Their unpredictable accumulation, however, with prolonged sedation as a consequence, has been recognized for a long time [21,22]. It was, therefore, natural that the short-acting anesthetic propofol would be introduced for ICU sedation with great enthusiasm and expectations. Though allowing rapid awakening after short-term use, propofol also appeared to unpredictably accumulate after long-term use and to cause prolonged sedation [23]. Soon after its introduction, a serious adverse effect, the propofol infusion syndrome (PRIS), was recognized [24]. As originally described [24], PRIS was characterized by rhabdomyolysis, hyperkalemia, metabolic acidosis, and renal and cardiac failure and is associated with a high mortality.

Despite many years of benzodiazepines and propofol use, few studies compared these medications [25] and only recently have they been evaluated for safety and efficacy in large randomized controlled trials. This has been a direct consequence of the introduction of dexmedetomidine for ICU sedation. Dexmedetomidine, a sedative with high α_2-adrenoreceptor affinity and agonist action in the locus ceruleus, is the first sedative drug introduced for long-term ICU sedation to undergo formal evaluation for safety and efficacy according to modern drug development standards. This has necessitated comparisons with standard care sedation, and both midazolam and propofol have been used as comparators [26,27]. These trials have also provided insights into the comparative efficacy and safety profiles of these common sedatives. Dexmedetomidine has been shown to be non-inferior to both midazolam and propofol in maintaining light to moderate sedation [26,27]. It appears to shorten time to extubation and enhance arousability and patients' ability to communicate with caregivers. Dexmedetomidine may reduce delirium after long-term sedation as compared with midazolam [26] and also reduce the overall neurocognitive adverse

events of sedation, such as agitation, anxiety, and delirium, when compared with propofol [27]. These trials excluded patients with severe kidney and liver disease, thus limiting the generalizability of the findings. Furthermore, known side effects (such as bradycardia) and the acquisition cost of dexmedetomidine remain a concern. The safety and efficacy of dexmedetomidine, however, have not been evaluated in some ICU patient groups, such as patients with acute neurologic disorder (for example, stroke and head trauma).

Inhaled anesthetic agents such as sevoflurane and isoflurane have been advocated for ICU sedation [28]. To avoid repeating the etomidate story, safety assessment according to current drug development standards is mandatory before introducing new drugs for ICU sedation [29]. At the moment, even the most basic experimental safety data on the long-term effects of prolonged administration of inhalational anesthetics are lacking.

Sedative minimization and sedation depth

About 15 years ago, Kollef and colleagues [21] reported the association of continuous intravenous sedation with prolonged mechanical ventilation. Soon after, Brook and colleagues [30] demonstrated a significantly shorter ventilation time and ICU and hospital stays with the use of a sedative-analgesic protocol compared with usual sedation care in medical ICU patients. Over the last decade, sedation minimization strategies, including protocolized sedation (PS), have become the focus of strong research interest.

PS, which appears to be a promising approach, depends on the bedside clinicians titrating the individual patient's sedation needs to match identified specific goals using routine structured assessments. In a pre-post study, protocolized analgesia and sedation resulted in reduced sedative and opioid doses and reduced ventilation and ICU times [31]. The success of PS, however, depends on local practices, nurse-to-patient ratios, and the intensity of nurse training and expertise. This may explain why PS was not associated with benefits in an Australian ICU environment where usual care was already oriented toward sedative minimization [32]. By means of a modified sedation scale with a defined sedation protocol, 129 post-operative patients were randomly assigned to either light or heavy sedation [33]. The light sedation group received lower midazolam and morphine doses associated with 1-day and 1.5-day mean reductions in ventilation time and ICU days, respectively.

Another way to minimize sedation may be the use of programmed sedation interruptions. Daily sedation interruption (DSI) recommended in the 2002 guidelines became a key strategy after Kress and colleagues [34] reported significant reductions in ventilation time and ICU stay in a single-center 128-patient randomized trial. However, evaluation of DSI in subsequent randomized trials has produced inconsistent results. One trial was terminated early for safety concerns because the DSI group had a longer ventilation time and longer ICU and hospital lengths of stay compared with the sedation protocol group [35].

Girard and colleagues [36] combined DSI with daily spontaneous breathing trials (SBTs) in an open-label randomized trial and reported more days breathing without assistance and fewer days in the ICU and hospital and, although unexplained, suggested reduced mortality in the DSI/SBT group compared with the usual sedation care and SBT group. A limitation of this trial relates to a potential bias against the control group, given that sedatives were continued but not seemingly titrated to light sedation during the SBT, potentially leading to a longer ventilation time compared with the DSI group. Furthermore, unblinded research personnel were present during DSI in the trials by Kress and colleagues [34] and Girard and colleagues [36], creating serious potential for bias. In the trial by Girard and colleagues, the external validity of the experimental arm has also been questioned, given that the coordination of sedative titration with ventilator weaning is considered routine care in many ICUs outside the US and in many ICUs in North America.

Although DSI has many potential advantages (including the opportunity to cease infusions completely or to reduce dosage, perform a comprehensive neurological and delirium assessment, and assess for extubation readiness), it is not clear whether DSI offers any advantages when sedation is managed with a sedation protocol that targets light sedation. To address this question, Mehta and colleagues [37] conducted a multicenter randomized trial comparing PS with combined PS plus DSI in 423 critically ill mechanically ventilated medical and surgical patients. The authors found no difference in the primary outcome of duration of mechanical ventilation and no difference in ICU and hospital lengths of stay between the groups. Furthermore, the DSI group received higher daily opioid and benzodiazepines doses, and nurses reported higher workload with DSI. The enrolled patients, however, were primarily medical and were given benzodiazepines and this may reduce the generalizability of the findings. At present, although DSI appears to be safe, its effectiveness likely depends on the existing institutional sedation practice. If patients are kept lightly sedated, daily interruption does not appear to add further benefit and may increase nurse workload and drug use.

Limitations of current sedation research

The 2013 guidelines, albeit a comprehensive review of the evidence, uncovered a significant gap in our knowledge. Most clinical trials of sedation practice have been

Table 1. Salient features of key sedation trials conducted in the last 15 years

Authors (Year)	Design (Number)	Time to randomly assign	Main inclusion	Patients/intervention versus control	Time on treatment	Primary outcome	Main results
Mehta *et al*. [37] (2012)	Multicenter RCT open-label (423)	1 to 4 days	Ventilated >48 hours	Medical 80%+, DSI + PS versus PS. All patients received MDZ and received SBT.	Until extubated median 7 days	Time to extubation	No difference in outcomes
Jakob *et al*. [27] (2012)	Multicenter two RCTs Double-blind (998, 2 studies)	48 hours of sedation	Ventilated >48 hours	Medical Surgical and Trauma Dex versus MDZ and Dex versus Propofol. All patients DSI, SBT	Median 42 (23-72) hours for Dex	Time at target sedation RASS −3 to 0	No difference in primary outcome. Shorter time to extubation
Strøm *et al*. [14] (2010)	Single-center Unblinded RCT (140 but 113 analyzed)	24 hours after intubation	Ventilated >24 hours	General ICU patients Morphine versus propofol (first 48 hours) then MDZ. DSI conducted in all patients	Not given. Study staff intervened 2-5 days	Ventilator-free days at 28 days after intubation	More ventilator-free days, shorter ICU and hospital stays
Treggiari *et al*. [33] (2009)	Single-center Open-label RCT (129)	Up to 3 days	Ventilated >12 hours	Mainly post-surgical (80%+) Light sedation versus deep sedation using Ramsay scale	Mean days Light 2.9 versus deep 5.5	Post-traumatic stress at 28 days	Trend to lower post-traumatic stress
Skrobic *et al*. [31] (2010)	Single-center Pre and post (572 and 561)	24 hours after ICU admission	Admitted >24 hours	Protocolized analgesia and sedation with non-pharmacologic intervention (music)	Through ICU stay	Sedative and analgesic needs	Shorter ICU and hospital stays, less sub-syndromal delirium
Riker *et al*. [26] (2009)	Multicenter RCT double-blind (375 at 2:1)	Up to 96 hours	Ventilated >24 hours	Medical 85%+ Dex versus MDZ, rescue MDZ Sedation titration to RASS Fentanyl opioid of choice	Median days Dex 3.5 (2-5.2) versus MDZ 4.1 (2.8-6.1)	Time in target RASS −2 to +1	No difference in RASS range. Shorter ventilation time and less delirium
Girard *et al*. [30] (2008)	Multicenter RCT Unblinded (335)	2.2 to 4 days	Ventilated >12 hours	General ICU SAT and SBT versus usual sedation care and SBT Research personnel involved	Time to pass SBT 3.8 (1-14), 3.9 (1-11)	Ventilator-free days	More ventilator-free days and lower 12-month risk of death
De Wit *et al*. [35] (2008)	Single-center RCT unblinded (74)	Not reported	Ventilated in medical ICU	Medical respiratory ICU DSI versus sedation protocol	6.7 (4-10) days	Ventilation time	Terminated early; higher mortality longer vent time
Bucknall *et al*. [32] (2008)	Single-center RCT unblinded (312)	Not reported	Ventilated in ICU	Medical/surgical/trauma PS versus usual sedation practice	Ventilation hours 79 protocol 59 control	Ventilation time	No difference in outcomes
Pandharipande *et al*. [40] (2007)	2-center RCT double-blind (106)	48 hours after mechanical ventilation	Ventilated >24 hours	Medical 70%+/surgical Dex versus lorazepam Rescue propofol and fentanyl	5 (2-6) Dex versus 4 (2-6) lorazepam	Delirium-free days, coma-free days	Higher coma-free days but no effect on delirium
Carson *et al*. [25] (2006)	2-center RCT Open-label (132) over 56 months	1.5 days on average after ventilation	Ventilated >48 hours + lorazepam >10 mg/ hour	Medical ICU patients Lorazepam boluses versus propofol infusion with DSI	Not reported. Ventilation times 5.8 versus 8.4 days lorazepam	Ventilation time	Shorter ventilation time and ICU stay, more ventilation-free days
Kress *et al*. [34] (2000)	Single-center RCT unblinded (128)	Ventilated patients	Ventilated >48 hours and sedated	Medical ICU DSI started 48 hours after enrollment versus usual care. Research personnel involved	Not reported. Ventilation times 4.9 versus 7.3 days	Ventilation and ICU time	Reduced ventilation time and ICU stay
Brook *et al*. [30] (1999)	Single-center RCT unblinded (321)	Ventilated and in ICU >24 hours	Ventilated >24 hours	Medical ICU patients sedated with lorazepam. Nurse-implemented PS versus usual care	3.5 (4) days in protocol versus 5.6 (6.4) days controls	Ventilation time	Shorter ventilation time and ICU stay

Dex, dexmedetomidine; DSI, daily sedative interruption; ICU, intensive care unit; MDZ, midazolam; PS, protocolized sedation; RASS, Richmond Agitation Sedation Scale; RCT, randomized controlled trial; SAT, spontaneous awakening trial; SBT, spontaneous breathing trial.

inadequately powered and have not accounted for intensity of bedside care and thus lack external validity [14,33,34,38]. In addition, most shared significant limitations (Table 1). First, control groups did not reliably match current best practice, leading to misalignment with current practice. As such, these studies are seen to lack both relevance and validity. Second, clinical trials evaluating sedative agents have focused on comparisons of drug A and B, although patients are often sedated with a combination of drugs [26,27]. Third, the use of sedation monitoring and delirium assessment were not reliably applied. Fourth, random assignment did not occur until up to 96 hours after initiation of mechanical ventilation, leading to significant pre-enrolment sedative prescription, reduced duration of protocolized intervention, and reduced treatment separation between the experimental and control groups [26,27,34]. Fifth, few studies have assessed long-term patient-centered outcomes [36]. Sixth, the intervention was sometimes administered by research staff rather than clinical staff, thus limiting generalizability [33,34,36]. Finally, sedation strategy may have an impact on mortality [19,31,36]; however, there have not been any large phase III trials using mortality as the primary outcome. All of these aspects have resulted in a lack of conclusive evidence to guide clinicians in their daily practice and, thus, in variable adoption of many of the above interventions outside participating research centers. These problems are of particular relevance to delirium, and there is ongoing uncertainty regarding best preventive measures and management [12].

Delirium received significant attention in the 2013 Pain, Agitation, and Delirium (PAD) guidelines. The guidelines emphasized the value of light sedation, whenever clinically appropriate, as a possible way of preventing or attenuating delirium. None of the randomized trials comparing lighter and deeper sedation, however, led to a reduction in delirium with light sedation [14,36,37]. Recent data have also questioned the presumed link between drug-induced coma, deep sedation, and delirium [2,3,39].

The future of intensive care unit sedation research

To bridge the evidence gap, an evolutionary approach to sedation research is needed. A structured research program that describes current practice in detail and identifies possible modifiable risk factors is an important first step. Such multinational multicenter longitudinal cohort assessments of sedation practice have revealed a high prevalence of deep sedation early after initiation of mechanical ventilation; early deep sedation was strongly and independently associated with delayed extubation and long-term mortality (but not delirium) [2,3]. It is, therefore, imperative that any future intervention have specific key characteristics. First, it should be given early within minutes to hours of commencing sedation or mechanical ventilation. Second, the control group should align with best practice for the purpose of achieving relevance and external validity. Third, an integrated process of care (rather than specific drug A versus B) targeting light sedation should be investigated. Finally, investigators should use sedative agents shown to promote arousability, reduce ventilation duration, and attenuate delirium [26,27,40]. An innovative sedation strategy has been termed early goal-directed sedation and was recently tested for feasibility and safety in a pilot randomized trial [41]. This study suggested that early deep sedation, which was not addressed in any previous randomized trials, may be harmful and largely unjustified. The early goal-directed sedation concept will now be tested in an adequately powered, multinational multicenter randomized trial with a patient-centered outcome [42]. This trial will seek to address several of the key limitations and uncertainties of prior sedation research and current practice.

We acknowledge the comprehensive nature of the 2013 PAD guidelines; we believe they do provide a framework to adapt sedation practices to suit local and institutional needs. The guidelines have been appropriately non-prescriptive, and considering the limitations of many studies supporting PAD recommendations, we should be cautious about implementing strategies that are designed to force untested intervention bundles (that are based on a small number of randomized trials) into general practice. The second decade of the 21st century should be the decade of establishing high-level evidence for ICU sedation practice. The need is great, the time is right, the time is now.

Abbreviations

DSI, daily sedation interruption; ICU, intensive care unit; PAD, Pain, Agitation, and Delirium; PRIS, propofol infusion syndrome; PS, protocolized sedation; SBT, spontaneous breathing trial.

Competing interests

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Authors' contributions

YS contributed the concept, general outline, the manuscript plan, and final drafting of manuscript. Each author wrote an assigned section of the manuscript and critically reviewed and approved the final manuscript.

Author details

[1]University of New South Wales Clinical School, Prince of Wales Hospital, Barker Street, Randwick, NSW 2035, Australia, Australia. [2]Faculty of Medicine, University of Melbourne, Melbourne, Department Intensive Care Medicine, The Austin Hospital, 145 Studley Road, Heidelberg, Victoria 3084, Australia. [3]Medical/Surgical ICU, Mount Sinai Hospital, 600 University Avenue #18-216, Toronto, ON, Canada, M5G 1X5. [4]Tufts University School of Medicine, Neuroscience Institute and Department of Critical Care Medicine, Maine Medical Center, 22 Bramhall Street, Portland, ME 04102, USA. [5]Department of Intensive Care Medicine, University Hospital Bern (Inselspital), CH-3010 Bern, Switzerland.

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