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REVIEW

Sedation management in the post-COVID era: A personalised, patient-orientated approach

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ABSTRACT:

Intensive care patients are older, frailer, and more co-morbid than ever before, and remain at risk of a variety of adverse outcomes, both in ICU, and after discharge. Sedation and delirium play an intricate role in this complex system, and it can be difficult to determine if they are a contributor or consequence in any given situation. During the COVID-19 pandemic, the increased frequency of complex ventilatory management, including prone ventilation and neuromuscular blockade, necessitated deep sedation in many cases. In concert with infection control concerns and staffing pressures, the delivery of precision symptom- and patient-oriented sedation has waned in favour of strategies felt to be globally safe. Using the SPICE III study as a lens to understand both the importance of exploring heterogeneity of effect in large, complex RCTs of critically ill patients, and the importance of an individualised approach to sedation in the intensive care unit, we demonstrate the evolution of our understanding of sedation in this challenging environment. By following the principles that define the cornerstones of best contemporary sedation practice we can once more grow beyond the boundaries of clinical practice guidelines in the provision of personalised, patient-orientated sedation in the post-COVID intensive care unit.

Keywords: Hypnotics and sedatives; Delirium; Critical illness; Mechanical ventilation; Dexmedetomidine

INTRODUCTION

Advances in intensive care medicine have changed the demographics of the critically ill. This cohort of patients are older, with a greater burden of co-morbid disease, and are more likely to be clinically frail than ever before [1-3]. They present with incident and concurrent conditions which may have precluded surgical or critical care intervention in preceding decades [4,5]. Such patients are at risk of persistent critical illness, and a variety of post-intensive care syndromes [6-8], many of which carry profound implications for functional outcomes [9-11], the trajectory of organ function and failure over months and years [12-15], and medium to long term mortality [12,16,17]. Sedation and delirium play an intricate role in this complex system, and it can be difficult to determine if they are a contributor or consequence in any given situation. Different combinations and doses of sedative agents are likely to impact different patients with unique constellations of comorbidities at different points in their critical illness differently [18].

Prior to 2020, the approach to analgesia, sedation and delirium management in the ICU was shaped by clinical practice guidelines, such as PADIS-2018 [19]. While comprehensive, they encouraged a generalised approach, in the main based on observational data, or the small, generally uninformative single centre studies common to this space of the critical care literature. Steps were being taken to improve key methodological aspects of both clinician-initiated and industry-sponsored sedation trials [20], but the evidence base was produced in well-resourced settings, and the conditional recommendations made on their foundation could only apply to settings such as the severe acute respiratory syndrome coronavirus-2 induced COVID-19 pandemic in the broadest of brush strokes [21].

During the pandemic, the increased frequency of complex ventilatory management, including prone ventilation and neuromuscular blockade, necessitated deep sedation in many cases [22-25]. The need for strict patient isolation, staffing shortages, and the risks of droplet transmission in the event of self-extubation or circuit disruption increased the likelihood of the provision of sedation strategies that were felt to be globally safe, rather than being individually targeted to optimise patient outcome [26-28].

As the pandemic recedes, and elective surgery and non-COVID-19 diagnoses once more come to predominate in our ICUs internationally, it is time to re-examine the evidence for a patient-centred, targeted approach to sedation in the ICU [18].

KEY MESSAGES:

- Individualised symptom-oriented analgesia and sedation is a paradigm shift in ICU sedation from traditional one size fits all approach.
- While light sedation should always be promoted, a patient-oriented sedation target tailored to clinical complexity and considering relevant characteristics such as age, cognitive status and diagnosis, can be safely adopted.
- Multi-modal sedation can maximise the benefits and reduce harm associated with different agents when used in combination.
- A broad attention to good humane processes of care including sleep promotion, family visitation and de-escalation of medical care should be part of a personalised approach to cognitive wellbeing for ICU patients.

DEFINING LIGHT SEDATION

No universally accepted definition of light sedation exists, and such problems arise frequently when more nebulous diagnoses or concepts are being categorised for the purposes of prognostication or research. Moreover, the most commonly used tools to measure sedation are highly variably implemented worldwide. The 2013 precursor to the PADIS-2018 guidelines defined light sedation as defined light sedation as a score greater than or equal to –2 on the Richmond Agitation–Sedation Scale (RASS), with eye opening of at least 10 minutes duration [29]. The PADIS-2018 guidelines themselves based their definition on eight studies comparing sedation strategies targeting a priori defined light and deep sedation where sedation targets were objectively measured serially and systematically over time in the ICU [30-37]. Although these studies used a variety of scales and values (Table 1.), a RASS score of -2 to +1, or the conceptual equivalent from other scales, was considered by PADIS-2018 to be light sedation [19]. A comparison of the most frequently used scales demonstrates direct comparison to be challenging (Figure 1.). While these scales may be validated, with satisfactory inter-observer reliability [38], they may not be directly interchangeable, and they remain ordinal variables [39,40].

The Sedation Index, is a composite of RASS and need for assessment of depth of sedation, and measures sedation intensity. While not considered in the PADIS-2018 guideline, it was demonstrated to be independently associated with mortality, delirium, and prolonged intubation in an intensity-dependent manner over the first 48 hours of mechanical ventilation in a harmonised cohort of patients from the early longitudinal SPICE investigations [41]. It may be a more objective tool for both clinical and research purposes than the ordinal scales favoured to

Table 1. Studies and sedation scales used to define light sedation in the PADIS-2018 guidelines.

Study	Year	Scale	Definition of light sedation
[30] Pandharipande, et al.	2007	RASS	- 2 or greater
[31] Muller, et al.	2008	RSS	3-4
[32] Samuelson, et al.	2008	MAAS	3-4
[33] Treggiari.	2010	RSS	1-2
[34] Strom, et al.	2010	RSS	3-4
[35] Shehabi, et al.	2013	RASS	-2 to 1
[36] Bugedo, et al.	2013	RSAS	3-4
[37] Tanaka, et al.	2014	GCS	9 or greater

RASS: Richmond Agitation Sedation Scale; RSS: Ramsay Sedation Scale; MAAS: Motor Activity Assessment Scale; RSAS: Riker Sedation-Agitation Scale; GCS: Glasgow Coma Scale.

	Richmond Agitation Sedation Scale (RASS)			Ramsay Sedation Scale		Riker Sedation-Agitation Scale (SAS)		
	Score	Term	Description	Score	Description	Score	Term	Descriptor
↑ AGITATION	4	Combative	Overtly combative, violent, immediate danger to staff			7	Dangerous	Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
	3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive			6	Very agitated	Requiring restraint and frequent verbal reminding of limits, biting ETT
	2	Agitated	Frequent non-purposeful movement, fights ventilator	1	Patient is anxious and agitated or restless, or both	5	Agitated	Anxious or physically agitated, calms to verbal instructions
	1	Restless	Anxious but movements not aggressive vigorous					
CALM	**0**	**Alert and calm**		**2**	**Patient is co-operative, oriented, and tranquil**	**4**	**Calm and Cooperative**	**Calm, easily arousable, follows commands**
	-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)					
				3	Patient responds to commands only			
	-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)			3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
				4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus			
	-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)					
				5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	2	Very Sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
	-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation					
	-5	Unarousable	No response to voice or physical stimulation communicate or follow commands	6	Patient exhibits no response	1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands
↑ SEDATION								

Figure 1. Conceptual comparison of three commonly used sedation assessment scales: the Richmond Agitation Sedation Scale, the Ramsay Sedation Scale, and the Riker Sedation-Agitation Scale.

date. In the absence of a unifying definition, understanding the sedation targets for any study exploring the impact of sedation strategies in the critically ill remains crucial to appropriately interpreting its findings.

LIGHT SEDATION SHOULD BE THE NORM

In 2018, meta-analysis of data from 4500 patients across 9 clinically and statistically heterogenous trials had suggested that early light sedation was associated with a lower reported mortality, incidence of delirium, and duration of mechanical ventilation and ICU stay when compared to deep sedation [42]. While methodologically imperfect, this work provided a platform upon which to normalise the practice of early light sedation.

The relationship between early light sedation and improved outcomes was strengthened by the results of a cohort analysis of over 5000 Brazilian patients, which demonstrated reduced mortality in patients achieving a targeted RASS score of -3 to 0 by day 2 when adjusted for illness severity [43]. This was a secondary analysis of the complex CHECKLIST-ICU study, a prospective cohort study assessing work climate, care processes, and clinical outcomes in 118 Brazilian ICUs followed by a cluster randomised RCT where units were randomised to routine care or the introduction of daily checklist and goals setting during multidisciplinary rounds [44]. The presence of specialist intensive care physicians was associated with achieving sedation targets, and such targets were more likely to be achieved with increasing duration of ventilation, in keeping with the then prevalent belief that patients should be deeply sedated early in their acute critical illness [43].

The Re-evaluation of Systemic Early Neuromuscular Blockade (ROSE) trial from the PETAL Clinical Trials Network was an attempt to demonstrate the benefit of early paralysis in severe ARDS [45], building on the mortality advantage demonstrated in the earlier ARDS et Curarisation Systematique (ACURASYS) trial [46]. ROSE randomised 1006 of a planned 1408 patients to either 48h of continuous neuromuscular blockade and deep seda-

tion, or usual care with light sedation targets, before being stopped at the second interim analysis for futility. Light sedation was defined as a RASS score of -1 to 0, a Riker Sedation–Agitation Scale (RSAS) score of 3 to 4, and/or a Ramsay Sedation Scale (RSS) score of 2 to 3 [45]. No difference in mortality was demonstrated between groups at 90-days or at 1 year, nor were any differences demonstrated in patient-centred secondary outcomes. Substantially more adverse cardiovascular events occurred in the deep sedation group. The study was terminated early, and so was underpowered. It is probable that ICU-acquired weakness would have been significantly less common in the light sedation group had the study run to completion (27.5% vs 46.8%, between group difference: -19.4%, 95% CI -38.2 to 0.6) [45].

It should be noted that, in contrast to the ACURASYS cohort, a substantial proportion of patients screened for inclusion in ROSE were already receiving continuous neuromuscular blockade [47]. The ROSE study population may then represent patients without the severest forms of ARDS, with fewer complicating factors, or those without clear evidence of desynchrony, where the apparent benefit of paralysis was questionable.

However, light sedation is not the same as no sedation, as the Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients (NONSEDA) study from 8 Scandinavian centres demonstrated, just as the COVID-19 pandemic took hold [48]. 700 patients of 710 randomised within 24 hours of intubation were included in an intention-to-treat analysis of no sedation compared to off-label, unblinded, light sedation with daily interruption.

Light sedation was defined as a score of −2 to −3 on the RASS, and achieved with continuous infusion of propofol for the first 48h, replaced with midazolam thereafter. While the non-sedated group did receive less propofol and midazolam, they probably received more morphine over the first 7 days in the ICU.

The primary outcome, 90-day mortality, was 5.4% (95%CI -2.2% to 12.2%, p = 0.65) greater in the non-sedated group, though this was not statistically significant. The study is likely to have been underpowered for this outcome, having over-estimated the original effect size [49], despite being based on an earlier RCT [34].

More than twice as many non-sedated patients accidentally self-extubated and required extubation within 24h compared to those in the lightly sedated arm (8.9% vs 4.0%, p=0.01). In the non-sedated group, more than 50% more episodes of accidental removal of equipment occurred compared to lightly sedated patients (15.2% vs 9.1%, p=0.01). There was a suggestion of reduced thromboembolic risk in the non-sedation group, and these patients appeared to have fewer delirium or coma free days, though this was limited to those patients who "succeeded" at non-sedation.

42.8% of those randomised to the non-sedation arm experienced "failure of non-sedation" according to the authors. These patients, primarily male, required rescue sedation, and had longer ICU and hospital stays, and fewer days alive without sedation, coma, delirium, organ support, or mechanical ventilation, though mortality and long-term outcomes did not differ between non-sedation "failures" and "successes" [50].

In aggregate, these studies, among others, demonstrated that targeting light sedation in ventilated patients was safe, and limited the complications observed with removing sedation completely in this group. However, they offered little evidence regarding the choice of agent best suited to provide such controlled sedation strategies.

DEXMEDETOMIDNE AS AN ALTERNATIVE SEDATIVE AGENT

Alpha-2 adrenergic agonists have been used in veterinary practice as sedatives and anaesthetic agents for more than 50 years [51]. Over the last 20 years, peri-operative sedation has undergone a paradigm shift through the use of dexmedetomidine, a highly specific D-enantiomeric preparation of medetomidine [52], with sedative [53], anxiolytic [54], and anti-noiciceptive [55] actions. By moving away from the traditional gabaminergic approach to sedation with benzodiazepines and propofol in mechanically ventilated critically ill patients, and by reducing opioid requirements, maintaining arousal, improving sleep quality and avoiding respiratory depression, dexmedetomidine may allow lighter sedation [41], reduce the incidence of agitation and delirium [56,57], and speed liberation from ventilation [58].

Dexmedetomidine acts through the widely expressed family of alpha2-adrenoceptor subtypes and agents binding to these receptors being reported to induce a variety of beneficial effects [59]. These include the stimulation of the cholinergic anti-inflammatory pathway [60], with a reduction in pro-inflammatory cytokine release being demonstrated on treatment with dexmedetomidine in multiple animal models [61,62], and in the critically ill [63,64]. By mitigating the renal, neural, vascular and cardiogenic inflammatory responses, it may protect against subsequent organ dysfunction driven by inflammation in patients with sepsis and following major cardiac or non-cardiac surgery [59].

In addition to these anti-inflammatory effects, dexmedetomidine is recognised as a global sympatholytic agent, acting centrally and peripherally [65-67], as well as indirectly by influencing vasopressin release [67]. The sympathetic overactivity observed in sepsis is associated with immunosuppression, microcirculatory and metabolic abnormalities, and myocardial and hepatic dysfunction [68-72] and its ablation may offer a degree of protection [73]. However, the well documented side effects of dexmedetomidine at the concentrations and doses used clinically include hypotension as a result of this sympatholysis [74], as well as a multi-modal bradycardia, mediated by heightened vagal tone [75], reduced sympathetic drive and the baroreceptor reflex [76].

Dexmedetomidine is a complex agent, and the evidence for its use across different populations has varied depending on the question being asked and the outcome being studied. In a recent, comprehensive systematic review with a robust, multi-source search strategy, data from 11,997 patients across 77 trials were synthesised to determine if dexmedetomidine reduces delirium com-

pared to conventional sedation strategies in critically-ill patients requiring mechanical ventilation. The answer was yes: dexmedetomidine, with moderate certainty, decreased the incidence of delirium, with an absolute risk reduction of 11% (95% CI 6 – 15%), or a number needed to treat of 23. Meta-regression indicated this effect was independent of age. Dexmedetomidine also reduced the risk of agitation (RR 0.59, 95% CI 0.40 to 0.87; 21 trials, n = 6032 patients) [77].

In this meta-analysis of parallel-group RCTs including mechanically ventilated adults receiving dexmedetomidine vs another sedative/usual care/placebo, fewer patients receiving dexmedetomidine required supplemental propofol or analgesia and there was a modest reduction in the number of ventilation-free days by day 28 (MD 1.08 days, 95% CI: 0 to 2.17 days). A similarly modest reduction in ICU length of stay was demonstrated, and this may have been mediated by the significant reduction in mean depth of sedation and increase in the proportion of time spent at a higher RASS score.

While no difference in mortality was demonstrated between groups, 30-day mortality was only reported in 16 trials, representing less than 20% of the patient cohort, and the non-standard reporting measure of mortality at longest follow-up reported in a substantially larger cohort of studies (41 studies, n = 9234 patients). However, only 25% of trials reporting mortality were at low risk of bias and less than 30% of the 77 included trials were thought to be at low risk of bias over all. Dexmedetomidine, compared to other agents, appears to significantly increase the risk of bradycardia (RR 2.39, 95% CI 1.82 to 3.13; 36 trials, n = 8965 patients), but not severe bradycardia or the need for intervention in the smaller number of trials recording this. It similarly increased the risk of hypotension when compared to other sedating agents (RR 1.32, 95% CI 1.07 to 1.63; 40 trials, n = 9188 patients), though again there was no significant increase in the number of patients requiring intervention for the observed hypotension. The incidence of agitation was reduced with dexmedetomidine compared with other sedatives, but the risk of self-extubation increased [77].

With multi-modal sedative, analgesic, and anxiolytic effects that appear to reduce the risk of delirium, time on the ventilator, and in ICU, dexmedetomidine is an important drug for providing a personalised approach to sedation. While no mortality advantage was demonstrated, and an increased risk of adverse events not requiring specific intervention was noted, it remains a useful addition to the post-COVID intensivist's sedation armamentarium.

INSIGHTS FROM THE SPICE III TRIAL

For fifteen years, the Sedation Practice in Intensive Care Evaluation (SPICE) program has explored the management of some or all aspects of sedation practice with the aim of providing clinically optimised sedation to all patients, irrespective of demographic or diagnosis [18,78,79]. SPICE III is the largest RCT of sedation practice by an order of magnitude [80], and has provided a wealth of information regarding the management of sedation in the critically ill.

SPICE III enrolled 4000 patients over the age of 18 without significant neurological insult requiring sedation who were intubated and expected to require ongoing mechanical ventilation for at least a further 24 hours were randomised to open-label dexmedetomidine or usual care within 12 hours of initiation of invasive ventilation. They were mainly male (61.6% overall), and sick, with a mean APACHE II score > 20, and less than 30% had received an operation. More than 60% of the cohort had suspected or proven sepsis. While 98% of those in the usual care arm received propofol or midazolam with 11.5% receiving dexmedetomidine, 65% of patients in the intervention arm received supplemental propofol, 3% midazolam, and 7% both. Similar proportions of patients (78.5% vs 80.7%) in each arm received fentanyl.

Study treatment was initiated promptly, within less than 5 hours from eligibility in both groups, and continued for up to 28 days, including or readmission and re-escalation of sedation requirements. Exacting trial design to a pre-published protocol and limited attrition contributed to a high degree of internal validity, despite the open-label nature of drug administration. The trial was fiercely pragmatic, comparing the addition of dexmedetomidine to usual care and allowing the use of multiple agents to reach sedation targets, as well as the use of deep sedation. There was no protocolised approach to sedation interruption, or the provision of other organ support. The patient cohort was recruited from 74 ICUs in 8 countries, providing robust external validity.

The use of early dexmedetomidine in this group of patients was not associated, overall, with a difference in 90- or 180-day mortality when compared to usual care, nor was it associated with obtained measures of quality of life or cognitive function. However, it was associated with a meaningful reduction in both the number of days free from coma or delirium (Adjusted Risk Difference 1.0 day; 95% CI: 0.5 to 1.5 days) or ventilation (Adjusted Risk Difference 1.0 day; 95% CI: 0.4 to 1.6 days).

Six pre-specified clinically relevant subgroup analyses were performed to explore for potential heterogeneity of effect (HTE) across age, illness severity, geographical region, degree of hypoxia on admission, presence of suspected sepsis, and admission following operative intervention. While the point estimates suggested HTE across all of the subgroups (Table 2.), after correction for multiple comparisons, only age continued to demonstrate HTE. Early dexmedetomidine use favoured lower mortality in older patients, and suggested an increased mortality in younger patients. This divergent effect was noted on either side of the median age of 63.7 years.

HETEROGENEITY OF TREATMENT EFFECT

RCTs provide average estimates of treatment effects when interventions are applied to a population [81]. SPICE III reports the difference in average outcomes between those exposed to dexmedetomidine and those who are managed with usual care [80]. There is an assumption that all of the individuals within each arm of the study will be similar enough that the average treatment effect in the

Table 2. Heterogeneity of effect in the primary outcome in SPICE III.

Subgroups	% Risk Difference (95% CI) in 90d Mortality	
Age	**≤ Median**	**> Median**
(Median = 63.7 years)	4.4 (0.8 to 7.9)	−4.4 (−8.7 to −0.1)
APACHE II Score	**≤ Median**	**> Median**
(Median = 21)	−1.9 (−5.4 to 1.5)	1.1 (−3.2 to 5.5)
PaO_2:FiO_2 Ratio	**≤ Median**	**> Median**
(Median = 198 mmHg)	0.8 (−3.7 to 5.2)	1.6 (−5.7 to 2.5)
Sepsis	**Yes**	**No**
	1.1 (−2.6 to 4.8)	2.0 (−6.4 to 2.4)
Operative Admission	**Yes**	**No**
	−2.3 (−7.2 to 2.7)	0.8 (−2.6 to 4.3)
Overall Risk Difference	**−0.2 (−1.4 to 1.1)**	

APACHE II: Acute Physiology and Chronic Health Evaluation II Score

PaO_2:FiO_2: Ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen concentration (mmHg)

study population will be reflective of the treatment effect of any individual within it. An individual patient cannot be both exposed and unexposed to the intervention, so their individual treatment effect will never be able to be observed.

These differences in treatment effect between individuals – the HTE – are important to understand. From one perspective, they form the basis of personalised medicine. From another, as would appear to be the case in SPICE III, understanding that a net "negative" result, or one showing no difference in the primary outcome, may be the average result of benefit in one sub-group cancelling the harm caused by the intervention in another [81].

HTE can be explored using modern analytic techniques. Two important post-hoc analyses of the SPICE III data have provided powerful insights into the questions raised by the initial analysis of the RCT data [82,83]. The first, is a Bayesian attempt to quantify the HTE of early dexmedetomidine use according to age categories and algorithmically determined clinical subgroups to identify patients who have a high probability of differential 90-day mortality [82].

Gender, illness severity score, PaO_2/FiO_2 ratio, categorised source of admission, as well as type and diagnosis, and details regarding the sedation received were identified as being clinically relevant variables by which computational algorithm could "cluster" patients into groups without pre-determined classification or streaming. HTE was assessed across clusters and by age group (above 65) using Bayesian hierarchical modelling.

Two clusters of patients were identified. The first, cluster 1, represented 30% of the cohort, and were operative admissions with cardiovascular or general surgical diagnoses, and were more likely to have received propofol. Cluster 2 formed the majority (70%), and were admitted from the emergency department with sepsis or respiratory diagnoses, higher illness severity scores and lower PaO_2/FiO_2 ratios. They were less likely to receive propofol than other additional sedative agents. The proportion of patients allocated to the dexmedetomidine arm of the study was similar in both clusters.

Older patients allocated to the dexmedetomidine arm demonstrated a very high (>99%) probability of reduced 90-day mortality. In older patients, regardless of cluster-assignment, or the choice of prior, a high (>90%) probability of increased coma and delirium-free days, and ventilator-free days was demonstrated. Moreover, patients in cluster 1 who received early dexmedetomidine had a lower 90-day mortality. However, non-operative patients receiving early dexmedetomidine had an increased 90-day mortality, which increased with increasing illness severity. A similar result was shown in cluster 2, the non-operative group of mainly septic patients.

A major limitation to Bayesian approaches is limited clinician familiarity, and slow adoption of such analyses as being equivalent to frequentist techniques in influencing clinical decision making [84-86]. This is despite over a decade of discussion [84] and several recent well publicised re-analyses of critical care studies utilising such techniques, including ANDROMEDA-SHOCK [87] and EOLIA [88]. However, Bayesian techniques offer powerful insights into HTE that are impossible to obtain in the conventional frequentist analysis of an RCT. As the authors clearly state, these conclusions must only be considered hypothesis generating, providing the rationale and estimates for the generation of future high-level evidence [82].

EXPLORING EFFECT AND CAUSALITY

Patients aged 65 or older who were randomised to the dexmedetomidine arm of SPICE III were more likely to survive than younger patients. More than 85% of patients in this arm received supplemental propofol to achieve the targeted sedation aim [89]. It was thought possible that, given their different adverse effect profile, preferentially increasing the dose of propofol or dexmedetomidine may have different associations with mortality in older and younger patients and that this may explain some of the observed heterogeneity of effect.

The 1,177 patients randomised to the dexmedetomidine arm in SPICE III who also received propofol were identified, then stratified by age for inclusion in a secondary double stratification resampling analysis. This is a technique for obtaining subgroups of patients with matched mean characteristics for one ranking variable, but different mean characteristics for another for subsequent comparison [83]. This type of analysis may be familiar from explorations of the association between driving pressure and ventilator-associated lung injury [90].

Younger patients received significantly higher hourly rates of both propofol (median dose 0.50 [IQR: 0.25–0.87] vs. 0.33 [IQR: 0.14–0.62] mg/kg/h; P<0.001) and dexmedetomidine (median dose 0.54 [IQR: 0.35–0.72] vs. 0.44 [IQR: 0.27–0.64] μg/kg/h; P <0.001) to achieve a similar Sedation Index over the first seven days of invasive ventilation [83]. The Sedation Index, is a composite of RASS and need for assessment of depth of sedation, and measures sedation intensity. It was demonstrated to be independently associated with mortality, delirium, and prolonged intubation in an intensity dependent manner over the first 48 hours of mechanical ventilation in a harmonised cohort of patients from the early longitudinal SPICE investigations [41]. Depth of sedation as measured by Sedation Index was once more demonstrated to be independently associated with mortality in both older (HR 1.24, 95% CI 1.15 – 1.33; p <0.001) and younger patients (HR 1.49, 95% CI 1.36 – 1.63; p <0.001) in reanalysis of the SPICE II cohort [83].

In younger patients where the dose of dexmedetomidine remained steady and the dose of propofol incrementally increased to meet sedation targets a reduced risk of mortality was observed. Conversely, in this patient group where the dose of propofol remained constant and the dose of dexmedetomidine was up titrated to achieve sedation goals, an increased risk of mortality was observed. At these higher doses, direct cardiovascular adverse events, or the suppression of plasma catecholamine concentrations may be responsible for the harm observed. In the older patient group sedation targets were met without exposure to the higher doses of either drug experienced by younger patients; this may explain why no association between drug infusion rates and mortality was demonstrated [83].

As SPICE III was unblinded, and used usual care as a comparator, the analytic strata may not represent clinically homogenous groups of patients where the adjustments to sedative administration were being performed for uniform reasons. Bias may have been introduced, both regarding who was given supplemental propofol, and then how it was used. However, unmeasured confounding was explored using E-values. These are a relatively recent addition to the statistical armamentarium, providing a method of performing sensitivity analyses in observational studies while minimising assumptions [91]. They help assess how robust the findings of the study result are, in the setting of the measured covariates, by determining the strength of association with both intervention and outcome that an unmeasured confounder would have to have to overturn the study result. It requires no assumptions regarding the nature or magnitude of the unmeasured confounder, but its meaning is defined by, and must be interpreted in the context of, the study of origin [92]. In this secondary analysis, the E-values were high. This implies that any unknown or unrecognised confounders would have to have a substantial effect to negate these associations with mortality in younger patients [83]. By deciding if unmeasured confounding on this scale is even plausible, then the "E-value" provides a measure related to the evidence for causality [91].

THE ROAD AHEAD

SPICE III demonstrated that, within the construct of a large, multi-centre RCT with high internal validity, the use of dexmedetomidine was associated with reduced mortality in patients over the age of 65, with post-operative patients irrespective of age, or patients with medical or surgical cardiovascular diagnoses. Within this setting and subgroups, and in those suffering from sepsis, the use of dexmedetomidine was also associated with more delirium and coma-free days in the majority of patients. In younger patients, the observed difference in mortality may have been, in part, due to escalation of the dose of dexmedetomidine when using combination dexmedetomidine and propofol therapy to achieve targeted deep sedation [80,82,83].

SPICE III clearly shows that the potential benefits of dexmedetomidine therapy depend on optimal timing and dosing, and on how the drug is handled in concert with other sedative agents. Strong associations are suggested between dexmedetomidine and outcomes. However, until robust high-level evidence is available to validate the beneficial effect in these subgroups these findings can only provide guidance in the clinical use of dexmedetomidine – particularly in situations where the risk of harm is perceived to be high.

To provide clinicians with this evidence in older patients, SPICE IV will explore the potential mortality advantage of early sedation with dexmedetomidine in a prospective, multi-centre, double-blind, placebo-controlled, randomized trial of 3,500 ventilated critically-ill patients over the age of 65. More than 30 sites internationally are contributing to the study to maximise its external validity. While the primary outcome will be all-cause 90-day mortality, in addition to coma- and delirium-associated outcome measures, renal and health economic analyses will also be performed [93].

PERSONALISED PATIENT-ORIENTATED SEDATION

So, what do these findings mean for the clinician at the bedside regarding the post-pandemic management of the critically ill ventilated patient requiring sedation? While clinical practice guidelines provided a generalised approach, current evidence calls for a more personalised strategy than these one-size-fits-all recommendations.

First: Regardless of the depth of sedation required for any particular clinical scenario, there MUST be a sedation target set for each patient. This must be reviewed at least twice a day, aiming for the lightest sedation level necessary to achieve safety, comfort and facilitate need-

ed therapeutic interventions [18]. The SPICE III, ROSE and other trials, demonstrated a common trend towards deeper level of sedation in the first 48 hours of critical illness management [42,43,45,48,80]. While this may be a clinically desirable goal, light sedation to an awake, communicating and comfortable patient should be an immediate priority once the storm of initial instability has passed [79]. In particular, this ensures that a vital aspect of humane patient care – the provision of appropriate and adequate analgesia – is addressed early in the intensive care management journey. Deep sedation can mask pain, and untreated pain is associated with a variety of adverse outcomes [18].

Second: Many agents are available to the intensivist trying to achieve optimal sedation, each of which have important pharmacokinetic and pharmacodynamic features that must be considered; the most common are summarised in Table 3. The potential interplay between agent, the patient, their current condition, and the interventions they currently require, all contribute to the

Table 3. Common sedative agents used in the critically ill.

	Route	Typical Dosing[a]	Onset[b]	Half-Life[c]	Notes
Antipsychotics					
Haloperidol	IV bolus	0.5-5mg max 15mg/24h	3-20min	20h	Use lower doses in elderly patients Contraindicated in Parkinson's Disease
	PO	1-5mg q12h to q8h	2-6h		Risk of Neuroleptic Malignant Syndrome Risk of QTc prolongation
Olanzapine	IM, SL	2.5-10mg q12h to q8h	6h	30h	Contraindicated in Parkinson's Disease Risk of Neuroleptic Malignant Syndrome Risk of QTc prolongation
Quetiapine	PO	12.5-50mg q12h	90min	6h	Use lower doses in elderly patients Higher doses with drug dependence Risk of Neuroleptic Malignant Syndrome Risk of QTc prolongation
Benzodiazepines					
Midazolam	IV bolus IV infusion	1-2.5 mg 1-5 mg/hr	2-3 min	2-6h	Active metabolites contributing to activity Associated with delirium Accumulates in renal/hepatic impairment
Lorazepam	IV bolus	1-2mg q6h max 6mg/24h	5-20min	8-14h + with age	Associated with delirium Prolonged sedation
	IV infusion	2-6mg/h			Dose reduction in the elderly
	PO	2-4mg q6h	2h		Propylene glycol toxicity at high dose At risk of paraoxical stimulation
Anaesthetic Agents					
Propofol	IV bolus	0.5-1mg/kg	30-60 sec	3-10 min	Synergystic with other agents
	IV infusion	1-3 mg/kg/h		Dose-dependent	Risk of hypotension ++ with bolus dose Risk of propofol infusion syndrome Risk of hyperlipidaemia and zinc depletion
Ketamine	IV bolus	0.5-2 mg/kg	30-60 sec	5-10 min	Analgesic/anaesthetic properties
	IV infusion	5-20 μg/kg/min for analgesia		180min	Bronchodilation Risk of tachycardia and hypertension
		10-50 μg/kg/min for anaesthesia			Risk of emergence phenomena Controversial in cases of elevated ICP Causes sialorrea Accumulates with hepatic impairment
α2-Agonists					
Dexmedetomedine	IV infusion	0.2 - 1.0 μg/kg/h	15-20min	2h	Low dose: 15% drop in heart rate and blood pressure >0.7μg/kg/h: hypertension Accumulates with hepatic impairment
Clonidine	IV bolus IV infusion	50 - 150 μg q6h 10-30 μg/h	10-15min	6-7h	Less neurospecific Bradycardia, hypotension Rebound hypertension Accumulates with renal impairment

[a]: Information from Australian Medicines Handbook, https://amhonline.amh.net.au.acs.hcn.com.au/, accessed 5th Dec 2023 and DRUGBANK Online, https://go.drugbank.com/, accessed 5th Dec 2023; Dosing is given in around-the-clock format of qXh, where qXh refers to "quaque X hora," or "give every X hours."; [b]: Time to onset of IV infusions will depend on a variety of patient, illness and administration factors; [c]: Half-life of bolus administration may represent distribution time; elimination half-life in critically ill patients will be subject to a variety of factors.

rational selection of the most appropriate pharmacotherapy. Patient related factors to be considered include age [94,95], admission diagnosis [19,96], prior exposure to antipsychotics or chronic pain medications [97], acute on chronic organ dysfunction [98,99], and alcohol intake [19]. Intervention related factors including controlled ventilation, prone ventilation, neuromuscular blockade, extracorporeal support and prospective surgical or airway intervention [45,100]. Dexmedetomidine is the preferred primary sedative for older patients, operative admissions, and those with a previous history of delirium, exposure to antipsychotics, or potential alcohol dependence. Propofol and or incremental small boluses of midazolam are preferred primary agents for achieving deeper levels of sedation, particularly for younger patients admitted with non-operative diagnoses [83]. The use of additional enteral atypical antipsychotics such as quetiapine or parenteral haloperidol could also be used in cases where conventional sedative agents prove inadequate. The concept of multimodal sedation is an attractive one in this context, where combinations of dexmedetomidine, propofol and/or antipsychotic can lessen the total dose and minimise the risk of adverse events, while providing the benefits of each agent [101] .

Third: Prescription of sedative agents by medical staff must be accompanied by an understanding of the needs of the multidisciplinary team, including those providing around the clock care. The goals of sedation, the targets being aimed for, and the rescue strategies in place for when these targets are not being achieved must be clearly communicated to those who are expected to deliver this therapy [102]. This focus on communication must also extend to both patients and their families, who may not understand why they or their loved ones are awake, but still require a breathing tube or a ventilator [103,104]. Adherence to the principles of early appropriately timed physical therapy should always be encouraged, with recent evidence demonstrating that, much like sedation, early mobilisation strategies must needs be moderated, and institution and patient specific [105].

Finally: All the above principles aim to restore normal homeostasis in the broadest sense, and most importantly, a human element to the management of critical illness, with vigilant attention to good processes of care. Sleep promotion techniques, day-night orientation, family visitation and de-medicalisation of care should all be a priority to a personalised targeted sedation approach [19].

CONCLUSION

SPICE III can be used as a lens to understand both the importance of exploring heterogeneity of effect in large, complex RCTs of critically ill patients, and the importance of an individualised approach to sedation in the intensive care unit. Our understanding of sedation in this challenging environment has grown beyond clinical practice guidelines. Before COVID-19, we were the closest we have ever been to delivering precision symptom- and patient-oriented sedation. We can be again, provided we follow the principles that define the cornerstones of best contemporary sedation practice.

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