Annals of Pharmacotherapy
1–5

DOI: 10.1177/1060028019890672
journals.sagepub.com/home/aop
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Reconsidering Dexmedetomidine for Sedation in the Critically Ill: Implications of the SPICE III Trial

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Abstract

Dexmedetomidine is a sedative agent that has gained popularity for use in the intensive care unit over the past 20 years. Guidelines recommend dexmedetomidine as a first-line agent to achieve light sedation in mechanically ventilated adults. Recently, the SPICE III (Sedation Practice in Intensive Care Evaluation III) trial was published. This was a randomized controlled trial comparing initial sedation with dexmedetomidine with usual care sedation in adult patients receiving mechanical ventilation. The results of this trial have both validated and contradicted previous findings about dexmedetomidine. This editorial examines the merits of the SPICE III trial and the role of dexmedetomidine in practice following its publication.

Keywords

sedation, mechanical ventilation, intensive care

Introduction

Dexmedetomidine, a central α-2 agonist medication, was approved by the US Food and Drug Administration for short-term (less than 24 hours) sedation of nonintubated patients prior to and/or during surgical and other procedures in 1999. Since that time, this agent has gained popularity for use in mechanically ventilated patients in the intensive care unit (ICU). The appealing qualities of dexmedetomidine include the lack of respiratory depression and inability to yield deep sedation, which current sedation guidelines recommend to avoid.[1] Several randomized controlled trials have been conducted comparing dexmedetomidine monotherapy sedation with sedation using other agents, which are summarized in Table 1.[2-4]

Current sedation guidelines recommend use of propofol or dexmedetomidine over a benzodiazepine for sedation in critically ill, mechanically ventilated adults.[1] However, this is a conditional recommendation with low quality of evidence. Existing literature is limited by small sample size. Additionally, only 1 previous study has compared dexmedetomidine with propofol as a sedative agent. Consequently, the precise role of dexmedetomidine remains to be determined. Here, we discuss the implications of the recently completed SPICE III (Sedation Practice in Intensive Care Evaluation III) trial within the context of the existing literature regarding use of dexmedetomidine in the ICU.

SPICE III

The SPICE III trial compared the use of dexmedetomidine with usual care (propofol or midazolam or a combination of the two) for sedation therapy in mechanically ventilated patients.[5] This open-label, randomized trial enrolled 3904 patients (dexmedetomidine: n = 1948; usual care: n = 1956). The primary outcome was mortality at 90 days postrandomization. Secondary outcomes included 180-day comparisons of mortality, cognitive function, and quality of life.

Results from the study revealed no difference in 90-day mortality (dexmedetomidine: 29.1%; usual care: 29.1%, $P = 0.98$). There was also no difference between the cohorts with respect to cognitive function at 180 days, quality of life, or 180-day mortality. The dexmedetomidine group had a median of 24 days free of coma or delirium compared with 23 coma or delirium-free days for the usual care cohort (adjusted risk difference, 1 day; 95% CI, 0.5-1.5). Similarly, the dexmedetomidine group had 1 more day free of mechanical ventilation (23 days [interquartile range, IQR = 0-26] vs 22 days [IQR = 0-25]; adjusted risk difference, 1 day; 95% CI, 0.4-1.6). The clinical significance of this outcome is questionable given that other outcomes were similar.

SPICE III is the largest randomized controlled trial to examine dexmedetomidine for sedation, enrolling approximately 8 times as many patients as the next largest trial.[4,5] Although the primary outcome in previous studies was time

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Table 1. Comparison of Outcomes in Randomized Controlled Trials for Dexmedetomidine Sedation.[a]

Study Name (Year)	Study Medications	Number of Patients	Time in Goal Sedation	Delirium Prevalence	Time to Extubation	ICU Length of Stay	Bradycardia	Hypotension
MENDS (2007)[2]	Dexmedetomidine vs lorazepam	107	N/A	79% vs 82% ($P = 0.65$)	N/A	7.5 vs 9 Days ($P = 0.92$)	17% vs 4% ($P = 0.03$)	25% vs 20%[b] ($P = 0.51$)
SEDCOM (2009)[3]	Dexmedetomidine vs midazolam	366	77.3% vs 75.1% ($P = 0.18$)	54% vs 76.6% ($P < 0.01$)	3.7 vs 5.6 Days ($P = 0.01$)	5.9 vs 7.6 Days ($P = 0.24$)	42.4% vs 18.9% ($P < 0.001$)	56.1% vs 55.1% ($P = 1.00$)
MIDEX (2012)[4]	Dexmedetomidine vs midazolam	500	60.7% vs 56.6% ($P = 0.15$)	7.7% vs 10% ($P = 0.43$)	4.2 vs 6.1 Days ($P = 0.01$)	8.8 vs 10.1 Days ($P = 0.27$)	14.2% vs 5.2% ($P < 0.001$)	20.7% vs 11.6% ($P = 0.007$)
PRODEX (2012)[4]	Dexmedetomidine vs propofol	498	64.6% vs 64.7% ($P = 0.97$)	4.9% vs 9.7% ($P = 0.056$)	2.9 vs 3.9 Days ($P = 0.04$)	6.8 vs 7.7 Days ($P = 0.54$)	13.0% vs 10.1% ($P = 0.328$)	13.0% vs 13.4% ($P = 1.00$)
SPICE III (2019)[5]	Dexmedetomidine vs usual care	3904	56.6% vs 51.8% (P value not reported)[c]	40.7% vs 42.5% ($P = 0.26$)	N/A	6.0 vs 6.3 Days (P value not reported)	5.1% vs 0.5% ($P < 0.0001$)	2.7% vs 0.5% ($P < 0.0001$)

Abbreviations: ICU, intensive care unit; SPICE III, Sedation Practice in Intensive Care Evaluation III.
[a]Dexmedetomidine group is represented first in each cell.
[b]Defined as incidence of systolic blood pressures less than 80 mm Hg.
[c]First 48 hours following initiation of study drug only.

in goal sedation or days free from delirium and coma, the primary outcome of SPICE III was mortality. Previous trials did not demonstrate a tendency toward lower mortality with dexmedetomidine sedation, although they were not powered to detect this outcome. However, other trials examining dexmedetomidine in sepsis have associated use of the agent with lower mortality.[6,7] Thus, the choice of mortality as the primary outcome of SPICE III is reasonable. Finally, SPICE III was the first randomized controlled trial to examine the effects of dexmedetomidine sedation for up to 180 days postrandomization.

Sedation

Sedation goals in previous trials did not allow investigators to target deep sedation.[2-4] The Dexmedetomidine vs Midazolam for Sedation of Critically Ill Patients (SEDCOM) study had a Richmond Agitation Sedation Score (RASS) target of −2 to +1 for all patients.[3] The Dexmedetomidine vs Midazolam for Sedation During Prolonged Mechanical Ventilation (MIDEX) and Dexmedetomidine vs Propofol for Sedation During Prolonged Mechanical Ventilation (PRODEX) studies excluded patients who required deep sedation.[4] Although the desired sedation target in the SPICE III trial was light sedation (RASS −2 to +1), deep sedation (RASS −5 to −3) was allowed if deemed necessary by the treating clinician. The proportion of all patients in whom deep sedation was indicated was approximately 60% on day 1 and approximately 50% on day 2.[5] The inclusion and high incidence of deep sedation in SPICE III have important implications for study findings. The SPICE investigators have previously demonstrated an association of deep sedation with poor outcomes, including higher incidence of delirium and longer length of ICU stay.[8,9] One study showed that deep sedation (RASS −3 to −5) within the first 48 hours of ICU stay was independently associated with a greater time to extubation and hospital death.[8] A subsequent study examining the association between sedation intensity (defined as the sum of negative RASS scores divided by number of RASS measurements) and outcomes found that a higher sedation intensity was a predictor of 180-day mortality, delirium, and greater time to extubation.[9] A companion editorial to the publication of the SPICE III trial has a raised a concern regarding the proportion of patients in the study who were targeted for deep sedation.[10] Deep sedation may have independently influenced outcomes in the SPICE III trial, confounding the effects of sedative agent used. A subgroup analysis of SPICE III that included patients in whom deep sedation was not indicated could provide more insight into how dexmedetomidine is best utilized.

The need to pursue deep sedation required adjunctive therapy in SPICE III. Use of additional sedation is to be expected when deep sedation is desired because therapy with dexmedetomidine may not achieve deep sedation.[3,11] In SPICE III, more than 70% of patients in the dexmedetomidine cohort received additional propofol or midazolam to reach goal sedation in the first 48 hours following randomization compared with 20% of patients who received both multiple agents in the usual care cohort. Additionally, more than 50% of the dexmedetomidine cohort continued to receive propofol at study day 10 despite an indication for deep sedation in less than 30% of patients on the same study day.[5] The frequent use of propofol on study day 10 suggests that even when light sedation was targeted, dexmedetomidine monotherapy was often inadequate to achieve sedation goals. This confirms previous findings. In prior trials, use of rescue sedation in dexmedetomidine cohorts of patients ranged from 43.8% (MIDEX) to 72.5% (PRODEX).[3,4] Furthermore, discontinuation of study drug because of inadequate sedation was significantly greater in the dexmedetomidine cohort in both the MIDEX (dexmedetomidine: 9%; midazolam: 4%; $P = 0.02$) and PRODEX (dexmedetomidine: 14%; propofol: 5%; $P < 0.001$) trials.[4]

The maximum dose of dexmedetomidine used in SPICE III was 1.5 µg/kg/h, which is comparable to the maximum dose of 1.4 to 1.5 µg/kg/h allowed in previous trials.[2-5] Although these doses are in excess of the maximum dose of 0.7 µg/kg/h recommended by the dexmedetomidine product labeling, some investigators advocate for examining doses of dexmedetomidine in excess of 1.5 µg/kg/h in future trials.[5] Retrospective literature suggests that doses of dexmedetomidine >0.7 µg/kg/h are not associated with a greater incidence of adverse effects, but there may be no increase in sedation efficacy.[12]

The results of SPICE III suggest that when deep sedation is indicated, dexmedetomidine monotherapy is inadequate. This is not a surprising finding given the need for adjunctive sedation therapy in patients targeted for light sedation in previous trials. Thus, the role of dexmedetomidine as a sedative should be limited to patients in whom light sedation is desired.

Adverse Events

In the SPICE III trial, there were significantly more adverse events in the dexmedetomidine cohort compared with the usual care cohort (9.6% vs 1.8%, respectively; $P < 0.0001$).[5] Consistent with previous studies, bradycardia and hypotension were the most frequent adverse events in the dexmedetomidine group. However, the rates of both hypotension and bradycardia observed in the dexmedetomidine group in SPICE III were lower than in previous trials (Table 1).[2-4] This finding is unexpected considering that many patients in the dexmedetomidine cohort of SPICE III also received propofol, which can cause additive bradycardia and

hypotension. According to the SPICE III study protocol, adverse events were reported by site investigators, but data were not systematically collected.[5] Incidence of bradycardia and hypotension were likely underreported, and the adverse event rates in SPICE III should be interpreted with caution. SPICE III did not allow for bolus doses of dexmedetomidine to be administered, which also could have contributed to the low rate of adverse events. Of note, 14 patients (0.7%) in the dexmedetomidine group experienced a prolonged sinus pause (asystole), leading to the use of atropine, epinephrine, or cardiac massage in 7 of the events. There were no details provided regarding dose or duration of dexmedetomidine in these patients. There were 2 episodes (0.1%) of prolonged sinus pause in the usual care cohort.[5] Although rare, episodes of asystole should prompt clinicians to carefully consider use of dexmedetomidine in patients who might be at risk, such as patients with heart block or bradycardia. Strategies to reduce rates of adverse events associated with dexmedetomidine may include avoiding use of loading doses, waiting at least 30 minutes between dose titrations, and keeping maximum infusion rates at or below 0.7 µg/kg/h.[3,12,13]

Delirium

The SEDCOM study showed that dexmedetomidine was associated with lower prevalence of delirium relative to midazolam (54% vs 76.6%, $P < 0.01$).[3] However, prevalence of delirium was similar between midazolam and dexmedetomidine in the MIDEX trial.[4] In the PRODEX trial, delirium occurred with greater frequency in the propofol cohort compared with the dexmedetomidine cohort, but the absolute difference was smaller than what was observed in SEDCOM (9.7% vs 4.6% respectively, $P = 0.056$).[4] In SPICE III, patients in the dexmedetomidine group had 1 more coma or delirium-free day (24 days [IQR = 11-26]) compared with the usual care group (23 days [IQR = 10-26]). Although patients in the dexmedetomidine group had more coma-free days (25 days [IQR = 14-27] vs 24 days [IQR = 14-26]), outcomes regarding delirium-free days were not reported. It is possible that no difference in delirium-free days existed. Additionally, there was no difference in the proportion of patients who experienced delirium between the 2 cohorts (dexmedetomidine, n = 796 [40.7%], vs usual care, n = 835 [42.5%]; $P = 0.26$).[5] Thus, the impressive delirium reduction benefits of dexmedetomidine seen in the SEDCOM study have not been repeated in subsequent studies. Furthermore, the marginal benefit of dexmedetomidine regarding decreased days of delirium/coma in SPICE III did not translate into a decrease in length of ICU stay, an improvement in long-term cognitive function, or mortality.

Current guidelines recommend dexmedetomidine as an agent that can be used to treat delirium in mechanically ventilated adults in whom agitation is precluding weaning/extubation based on the results of a single, small randomized controlled trial. Because SPICE III randomized patients to dexmedetomidine or usual care within 12 hours of requiring mechanical ventilation, it is not well designed to assess this indication for dexmedetomidine. Additional high-quality research is necessary to assess the efficacy of dexmedetomidine compared with alternative therapy to facilitate extubation in agitated patients and prevent intubation in nonintubated, agitated patients.

Conclusion

The SPICE III trial, the largest study ever to examine dexmedetomidine sedation in the critically ill, demonstrates that early sedation with dexmedetomidine is not associated with a reduction in mortality. The results are confounded by a high prevalence of deep sedation and frequent use of additional sedative medications. However, SPICE III does confirm some previously identified characteristics regarding dexmedetomidine use as a sedative agent in patients receiving mechanical ventilation. First, dexmedetomidine as a sole agent does not reliably provide adequate sedation in all patients and may be insufficient as a sole agent when light sedation is targeted. Second, there are a greater number of adverse events associated with the use of dexmedetomidine when compared with alternative sedatives. In other instances, the findings from SPICE III contradicted the results of prior studies. The presumed benefit of a decrease in the incidence of delirium with dexmedetomidine use was not seen in SPICE III. Additionally, SPICE III did not find a difference in duration of ICU length of stay. The accumulated efficacy and safety data suggest that current guidelines will need to be updated to address the limitations of dexmedetomidine, and its place as an option of first choice in the management of sedation in all patients receiving mechanical ventilation needs to be reconsidered. Future research with dexmedetomidine in the critically ill should focus on its specific benefits and risks in subpopulations.

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