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SPECIAL FEATURE

Dexmedetomidine for Sedation in Patients Undergoing Mechanical Ventilation in the ICU

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The need for sedation and analgesia is common in patients requiring invasive mechanical ventilation in the intensive care unit (ICU). Previously, benzodiazepine infusions were commonly used, but this prompted concern for the development of delirium and long-term neurocognitive deficits. Recent trials have explored alternative sedative agents that might lead to better outcomes for patients. Subsequently, many have moved away from benzodiazepine infusions, using propofol instead. The use of dexmedetomidine has increased as an alternative to propofol and benzodiazepines, although the use of ketamine also has been increasing. This special feature will focus on dexmedetomidine as a sedative for invasive mechanical ventilation in the ICU.

PHARMACOLOGY OF DEXMEDETOMIDINE

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist.[1,2] It was initially approved in the United States in 1999 for short-term sedation of intubated patients, with expansion of this indication to include perioperative and procedural sedation in 2008. Dexmedetomidine acts within both the central nervous system and spinal cord to cause salutary and adverse effects. The locus coeruleus within the pons mediates vigilance and arousal via synthesis of norepinephrine (NE). Presynaptic activation by dexmedetomidine leads to decreased NE efflux into the locus coeruleus, while post-synaptic agonism causes hyperpolarization of neuronal membranes leading to sedation. Unlike GABA-ergic sedatives such as benzodiazepines

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and propofol, there is no associated respiratory depression. Activation of α-2 receptors in the rostral ventrolateral medulla combined with parasympathetic activation in the nucleus ambiguous mediates bradycardia and vasodilatory hypotension. Within the spinal cord, descending medullo-spinal nociceptive pathways are repressed, and the release of excitatory neurotransmitters in the dorsal horn is decreased, mediating analgesia. Dexmedetomidine is lipophilic and highly protein-bound, leading to a large volume of distribution. Infusions of dexmedetomidine at doses 0.2 mcg/kg/hour to 1.4 mcg/kg/hour demonstrate linear kinetics, with a rapid distribution half-life of about six minutes. It has extensive hepatic metabolism to inactive metabolites primarily excreted into the urine.

TRIALS OF DEXMEDETOMIDINE FOR SEDATION

The 2002 clinical practice guidelines for the use of sedatives in the ICU recommended lorazepam, a benzodiazepine, be used for sedation after adequate analgesia had been achieved.[3] However, there were concerns that use of benzodiazepines might lead to delirium, brain dysfunction, increased ICU length of stay, and duration of mechanical ventilation. This led to the search for alternative sedation strategies. In 2007, the MENDS trial compared the effect of dexmedetomidine vs. lorazepam on delirium as a primary outcome.[4] This study further evaluated the effects of these medications on mechanical ventilation, ICU length of stay, hospital length of stay, neurocognitive decline, and mortality. This study included 103 patients requiring sedation for invasive mechanical ventilation and showed that when compared with lorazepam, dexmedetomidine led to more coma- and delirium-free days (7 vs. 3 days, $P = 0.01$), driven primarily by coma-free days. Although not statistically significant, there were trends toward decreased duration of mechanical ventilation and 28-day mortality. There was a higher incidence of bradycardia and heavier reliance on fentanyl in the dexmedetomidine group compared with lorazepam. The median cost of care was noted to be $22,500 higher in the dexmedetomidine group. In showing improved outcomes with dexmedetomidine, this seminal study opened the door for further studies of alternatives to benzodiazepines for sedation.

Subsequently, many other trials evaluated the role of dexmedetomidine for sedation in the ICU. The SEDCOM study, published in 2009, was a prospective, double-blind, randomized controlled trial that enrolled 375 adults who were expected to require sedation for mechanical ventilation for at least 72 hours.[5] Notable exclusion criteria included the use of neuromuscular blockade other than for induction for intubation, liver disease, cardiac dysfunction, and the need for two or more vasopressors. There was no difference in the primary outcome of time at the targeted sedation level between the dexmedetomidine group and the control group receiving midazolam. However, at similar levels of sedation, patients receiving dexmedetomidine had a lower prevalence of delirium (54% vs. 76.6%, $P < 0.001$) and decreased time to extubation (3.7 vs. 5.6 days, $P = 0.01$). Neither ICU length of stay nor 30-day mortality was statistically different between the two groups, but the dexmedetomidine group again had a higher rate of bradycardia (42.2% vs. 18.9%, $P < 0.001$) as well as hyperglycemia (56.6% vs. 42.6%, $P = 0.02$). Unexpectedly, the dexmedetomidine group also evidenced a lower risk of infection (10.2% vs. 19.7%, $P = 0.02$). This finding raised the question of whether dexmedetomidine might have a special role in patients with sepsis.

The MIDEX and PRODEX studies published in 2012 compared the ability of dexmedetomidine with midazolam and propofol, respectively, to reduce the duration of mechanical ventilation while maintaining sedation.[6] Each study enrolled about 500 adult patients who were expected to need mechanical ventilation for at least 24 hours. In the MIDEX trial, the duration of mechanical ventilation for patients receiving dexmedetomidine was less than for those on midazolam (123 vs. 164 hours, $P = 0.03$). The median ICU and hospital lengths of stay were similar. However,

patients on dexmedetomidine were better able to participate with nursing care.

In the PRODEX trial, the duration of mechanical ventilation was similar between the two groups, but the median time to extubation was less in the dexmedetomidine group (93 vs. 69 hours, $P = 0.01$). Patients receiving dexmedetomidine again were better able to participate with their care. Patients on dexmedetomidine had a higher prevalence of severe cardiovascular instability (5.8% vs. 3.2%, $P = 0.02$) compared with those who received propofol. The conclusions from these studies were that dexmedetomidine was noninferior to either midazolam or propofol for long-term sedation in the ICU and may enable patients to liberate from mechanical ventilation faster. They did not evaluate outcomes such as mortality.

Two more recent studies asked whether dexmedetomidine compared with usual care improved mortality in patients requiring sedation in the ICU. The DESIRE study, published in 2017, randomized 201 patients with sepsis and the need for sedation for mechanical ventilation to either dexmedetomidine or usual care consisting of either midazolam or propofol.[7] While not reaching statistical significance, this study hinted at a trend toward decreased 28-day mortality (19% vs. 28%, $P = 0.14$) and more ventilator-free days (20 vs. 18 days, $P = 0.2$) in the dexmedetomidine group compared with usual care. The SPICE III investigators enrolled 4,000 patients in the ICU on mechanical ventilation requiring sedation to receive either dexmedetomidine or usual care.[8] This study was powered with a 90% chance to detect a 4.5% change in 90-day mortality assuming a baseline 26% mortality rate. Despite the larger enrollment, no change in 90-day mortality was seen. Furthermore, there was no difference in several metrics of cognitive function. A one-day decrease in coma- or delirium-free days and a one-day increase in ventilator-free days was noted in the dexmedetomidine group. Of note, 1,235 of the 1,910 patients in the dexmedetomidine group also received propofol to achieve sedation targets, limiting interpretation of this study. There also was a dichotomy of outcomes when stratified by age, with younger patients benefiting more from usual care, while older patients did better with dexmedetomidine.

The most recent study to evaluate the effect of dexmedetomidine on ICU outcomes was the MENDS2 trial published in 2021.[9] This was a multicenter, randomized, double-blind trial in 422 adults with sepsis and the need for mechanical ventilation. Patients were randomized 1:1 to dexmedetomidine or propofol, with the primary outcome being days alive without delirium or coma within the 14-day intervention period. Secondary outcomes included ventilator-free days within 28 days, mortality at 90 days, and cognitive status. This study did not demonstrate a difference in number of days alive without delirium or any of the secondary outcomes. Notably, there was substantial midazolam exposure in both the dexmedetomidine and propofol groups (53% and 43%, respectively) that likely blunted differences in outcomes between the two groups. In addition, 42% of each group received antipsychotics, showing additional medications were needed for sedation.

These studies together suggest that dexmedetomidine can be used for sedation in patients requiring invasive mechanical ventilation. Although no clear mortality benefit has been found consistently, some studies show a trend toward earlier extubation and decreased delirium or coma, with the most recent MENDS2 study being a notable exception. It should be stated that patients randomized to the dexmedetomidine arms in these trials often required additional sedatives, and in some studies, higher doses of narcotic pain medications to achieve equal levels of sedation.

[Dexmedetomidine represents an alternative to propofol and benzodiazepines for sedation in patients requiring mechanical ventilation.]

USE OF DEXMEDETOMIDINE IN PATIENTS WITH SEPSIS REQUIRING MECHANICAL VENTILATION

Since most sedatives lead to hypotension, there is concern about their use in the context of sepsis and vasopressor support. In fact, the SEDCOM trial excluded patients taking two or more vasopressors, but, interestingly, noted a lower rate of infection in patients receiving dexmedetomidine.[5] In contrast, there were experimental data that dexmedetomidine might blunt inflammation in rat models of sepsis.[10] This led to reevaluations of multiple studies focusing specifically on patients with sepsis who also required sedation and mechanical ventilation. A subgroup analysis of the MENDS study identified 63 patients with sepsis who had been randomized to either lorazepam or dexmedetomidine.[11] While the original study showed statistically significant improvement in delirium- and coma-free days with dexmedetomidine, in septic patients, there also were improvements in mechanical ventilator-free days (15.2 vs. 10.1 days,

Table 1: Studies Comparing Dexmedetomidine with Other Sedatives in Patients Requiring Mechanical Ventilation

Study	n	Comparison with Dexmedetomidine	Primary Outcome	Result	Comment
MENDS[4]	103	Lorazepam	Delirium and sedation	Decreased coma-free days with dexmedetomidine	More fentanyl required with dexmedetomidine
SEDCOM[5]	366	Midazolam	Sedation	Similar time at target sedation	Less delirium/MV with dexmedetomidine
MIDEX[6]	501	Midazolam	Sedation and duration of MV	Noninferior for sedation, shorter duration of MV	Similar hospital LOS
PRODEX[6]	500	Propofol	Sedation and duration of MV	Noninferior for sedation, earlier time to extubation	Similar rates of hypotension
DESIRE[7]	201	Usual care	Mortality- and MV-free days	No difference in primary outcome	Patients with sepsis on MV
SPICE III[8]	3,904	Usual care	90-day mortality	No difference in primary outcome	Many patients on dexmedetomidine received propofol
MENDS2[9]	422	Propofol	Days alive without delirium/coma	No difference in primary outcome	Duration of MV, 90-day mortality similar

MV: mechanical ventilation; LOS: length of stay

P = 0.03) and 28-day mortality (165 vs. 41%, *P* = 0.03). Subgroup analysis of the SPICE III trial showed that less vasopressor was required to achieve target mean arterial pressure in patients receiving dexmedetomidine.[12] A prespecified analysis of the DESIRE trial[13] compared 201 septic patients receiving sedation for mechanical ventilation. While there was no change in mortality, there were statistically significant decreases in C-reactive peptide levels and procalcitonin in patients receiving dexmedetomidine compared with usual care. These studies confirm that dexmedetomidine is a safe sedative in patients with sepsis and further suggest that it may have anti-inflammatory effects.

CONCLUSIONS

Dexmedetomidine represents an alternative to propofol and benzodiazepines for sedation in patients requiring mechanical ventilation. Common side effects include bradycardia and hypotension; despite this, it appears safe in patients with sepsis. Compared with other common sedatives, dexmedetomidine may reduce delirium and may facilitate earlier extubation, but study results are notably mixed. (*See Table 1.*) ■

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ABSTRACT & COMMENTARY

Is There a Role for Intermediate-Dose Anticoagulation for Critically Ill COVID-19 Patients?

By Kathryn Radigan, MD, MSc

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SYNOPSIS: In a multicenter, randomized clinical trial of critically ill COVID-19 patients, intermediate-dose compared to standard-dose prophylactic anticoagulation did not result in significant differences in the rates of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days.

SOURCE: INSPIRATION Investigators, Sadeghipour P, Talasaz AH, Rashidi F, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: The INSPIRATION randomized clinical trial. *JAMA* 2021;325:1620-1630.

Thrombotic complications are not uncommon in critically ill patients with COVID-19. The INSPIRATION investigators conducted a multicenter, randomized clinical trial that included 562 critically ill COVID-19 patients across Iran, with 10 enrolling centers in Tehran and Tabriz, between July 29 and Nov. 19, 2020. The trial had a 2 × 2 factorial design that compared intermediate-dose vs. standard-dose prophylactic anticoagulation (first hypothesis) and statin therapy vs. matching placebo (second hypothesis; not addressed in this publication). Eligible patients were allocated in a 1:1 ratio. Enoxaparin was the primary anticoagulant agent in both groups. For patients weighing less than 120 kg and with a creatinine clearance greater than 30 mL/min, enoxaparin at 1 mg/kg daily was assigned as intermediate-dose anticoagulation. The control group standard-dose prophylactic anticoagulation regimen was enoxaparin 40 mg daily. Predefined modifications were advised according to body weight and creatinine clearance. In the case of severe kidney insufficiency, unfractionated heparin was used.

Patients admitted to the intensive care unit (ICU) with a polymerase chain reaction (PCR)-confirmed COVID-19 test within seven days of hospitalization were included in the trial, but patients with a life expectancy of less than 24 hours, an established indication for therapeutic-dose anticoagulation, weight less than 40 kg, pregnancy, history of heparin-induced thrombocytopenia, platelet count < 50×10^3/μL, or overt bleeding were excluded. The primary efficacy outcome was a composite of adjudicated acute venous thromboembolism (VTE), arterial thrombosis, treatment with extracorporeal membrane oxygenation (ECMO), or all-cause mortality within 30 days of enrollment. Secondary efficacy outcomes included all-cause mortality, adjudicated VTE, and ventilator-free days. Prespecified safety outcomes included major bleeding according to the Bleeding Academic Research Consortium (type 3 or 5 definition), powered for noninferiority (a noninferiority margin of 1.8 based on odds ratio), and platelet count < 20×10^3/μL.

The primary analysis included 562 of 600 randomized patients (93.7%). The primary efficacy outcome of acute VTE, arterial thrombosis, ECMO treatment, or all-cause 30-day mortality occurred in 126 patients (45.7%) in the intermediate-dose group and 126 patients (44.1%) in the standard-dose prophylaxis group (absolute risk difference 1.5%; 95% confidence interval [CI], –6.6% to 9.8%; odds ratio 1.06, 95% CI, 0.76-1.48; $P = 0.70$). Seven patients (2.5%) in the intermediate-dose group and four patients (1.4%) in the standard-dose prophylaxis group experienced major bleeding (risk difference 1.1%, one-sided 97.5% CI, $-\infty$ to 3.4%; odds ratio 1.83, one-sided 97.5% CI, 0.00-5.93), not meeting the noninferiority criteria (P for noninferiority > 0.99). Patients assigned to the intermediate-dose group were the only patients who experienced severe thrombocytopenia, defined as a platelet count < 20×10^3/μL (6 vs. 0 patients; risk difference 2.2%, 95% CI, 0.4%-3.8%; $P = 0.01$). These results fail to support the routine use of intermediate-dose prophylactic anticoagulation in critically ill COVID-19 patients.

■ COMMENTARY

More recently, the United States has reported more than 40 million COVID-19 cases and more than 600,000 deaths.[1] It is now well-established that

when patients are infected with COVID-19, they often experience profound inflammation with a coinciding prothrombotic state.[2] A number of studies that included ICU patients early in the pandemic reported higher rates of VTE. These studies reported a broad range of VTE incidence (up to 42% in one study), with pulmonary embolism as the most common form, despite prophylactic-dose anticoagulation.[3-5] A meta-analysis of studies in hospitalized patients with COVID-19 raised further concerns and found an overall VTE prevalence of 40.3% with ultrasound screening, 9.5% without screening. A subgroup analysis revealed an overall VTE prevalence of 22.7% in ICU patients.[6] In light of these data, intermediate-dose prophylactic anticoagulation was proposed and often used in an attempt to reduce VTE and optimize mortality. This practice persisted in many institutions until this study reported that, compared with standard-dose, intermediate-dose prophylactic anticoagulation did not result in improved outcomes.

Although the INSPIRATION Investigators studied intermediate-dose vs. standard-dose prophylactic anticoagulation, the REMAP-CAP, ACTIV-4a, and ATTACC trials randomized severely ill hospitalized COVID-19 patients to therapeutic-dose anticoagulation vs. standard-dose prophylactic anticoagulation.[7] The percentage of patients who survived to hospital discharge was similar in both anticoagulation strategy groups (62.7% and 64.5%, respectively; adjusted odds ratio, 0.84, 95% credible interval, 0.64 to 1.11). The investigators concluded that therapeutic-dose anticoagulation also was not beneficial.

Obesity is one of the strongest predictors of severe disease and mortality in COVID-19.[8] Although the authors described the trial as a comparison between intermediate-dose and standard-dose thromboprophylaxis, it is important to note that the authors actually compared two weight-based low molecular-weight heparin (LMWH) thromboprophylaxis dosing protocols that differ between individuals < 120 kg and ≥ 120 kg. The dose of anticoagulation was escalated for patients who weighed > 120 kg or who had a body mass index (BMI) > 35 to enoxaparin 0.6 mg/kg twice daily in the intermediate-dose group and 40 mg twice daily in the standard-dose group. It also is important to note that the number patients weighing > 120 kg was very limited in the trial. For the REMAP-CAP, ACTIV-4a, ATTACC trials, investigators also escalated the dose of anticoagulation for patients with a BMI ≥ 40 or weight ≥ 120 kg. Although weight-based prophylaxis dosing is practiced by most, both trials specifically included two weight-based thromboprophylaxis dosing protocols that differ between individuals < 120 kg and ≥ 120 kg.

Although it is clear that anticoagulation was altered appropriately for the obese patients, the optimal dose of anticoagulation and whether this optimal dose is superior to standard-dose prophylactic anticoagulation remains unclear. As detailed, the researchers used an intermediate dose of anticoagulation, but why this regimen was chosen over other potential regimens is uncertain.[9-11] The REMAP-CAP, ACTIV-4a, and ATTACC trials attempted to address these issues further and compared therapeutic anticoagulation and usual-care thromboprophylaxis anticoagulation. Unfortunately, these trials were limited in that a substantial majority of the patients who were enrolled in the severe-disease cohort were in the United Kingdom, where the national practice guidelines changed during the trial, and the usual-care thromboprophylaxis group was transformed to an intermediate-dose thromboprophylaxis group.[12] As a result of these modifications and the fact that the method of standard prophylaxis was left to the physicians' discretion, 22.4% of patients in the therapeutic-dose group did not receive a therapeutic dose, whereas 51.7% of the patients in the control group received intermediate-dose anticoagulation.

Even though the rates of VTE were noted to be higher early in the pandemic, and patients often were placed on higher doses of prophylactic anticoagulation as a result, a number of subsequent randomized trials did not consistently find that higher doses of prophylactic anticoagulation (both intermediate-dose and therapeutic-dose) resulted in a lower risk of VTE in critically ill patients. Instead, a number of trials observed a decline in rates of VTE, which was thought to be because of decreased severity of illness as a result of better knowledge on how to treat COVID-19 patients.[13] Essentially, baseline VTE risk declined, and as a result, the number of events was lower than expected in both the standard-dose and higher-dose anticoagulation groups.

The most recent National Institutes of Health guidelines state, "There is currently insufficient evidence to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial."[14] Since the most recent update to these guidelines, it is worth mentioning that the REMAP-CAP, ACTIV-4a, and ATTACC trials recently found that non-critically ill COVID-19 patients treated with therapeutic-dose anticoagulation

increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support compared with usual-care thromboprophylaxis.[7] Further studies are needed to guide whether there are additional subgroups of COVID-19 patients that may benefit from higher-dose anticoagulation strategies. For now, until data support otherwise, prophylactic rather than higher doses of anticoagulation are recommended for critically ill COVID-19 patients. ■

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b. Paid Circulation *(By Mail and Outside the Mail)*	(1)	Mailed Outside-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)	41	39
	(2)	Mailed In-County Paid Subscriptions Stated on PS Form 3541 *(Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)*	0	0
	(3)	Paid Distribution Outside the Mails Including Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid Distribution Outside USPS®	1	2
	(4)	Paid Distribution by Other Classes of Mail Through the USPS (e.g., First-Class Mail®)	16	23
c. Total Paid Distribution *[Sum of 15b (1), (2), (3), and (4)]* ▶			58	64
d. Free or Nominal Rate Distribution *(By Mail and Outside the Mail)*	(1)	Free or Nominal Rate Outside-County Copies included on PS Form 3541	0	0
	(2)	Free or Nominal Rate In-County Copies Included on PS Form 3541	0	0
	(3)	Free or Nominal Rate Copies Mailed at Other Classes Through the USPS (e.g., First-Class Mail)	0	0
	(4)	Free or Nominal Rate Distribution Outside the Mail *(Carriers or other means)*	2	2
e. Total Free or Nominal Rate Distribution *(Sum of 15d (1), (2), (3) and (4))*			2	2
f. Total Distribution *(Sum of 15c and 15e)* ▶			60	66
g. Copies not Distributed *(See Instructions to Publishers #4 (page #3))* ▶			8	8
h. Total *(Sum of 15f and g)*			68	74
i. Percent Paid *(15c divided by 15f times 100)* ▶			97%	97%

* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.

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(All Periodicals Publications Except Requester Publications)

16. Electronic Copy Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Paid Electronic Copies ▶		
b. Total Paid Print Copies (Line 15c) + Paid Electronic Copies (Line 16a) ▶		
c. Total Print Distribution (Line 15f) + Paid Electronic Copies (Line 16a) ▶		
d. Percent Paid (Both Print & Electronic Copies) (16b divided by 16c × 100) ▶		

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18. Signature and Title of Editor, Publisher, Business Manager, or Owner: DocuSigned by: Kay Kraft — Chief Executive Officer — Date: 29-Sep-2021

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CME/CE QUESTIONS

1. **Dexmedetomidine is a:**
   a. benzodiazepine.
   b. GABA antagonist.
   c. long-acting narcotic.
   d. α-2 agonist.

2. **Compared with propofol, clinical trials of dexmedetomidine show which of the following?**
   a. A higher prevalence of tachycardia
   b. Similar mortality
   c. Trends toward later extubation
   d. A decreased need for analgesia

3. **Which of the following is part of the National Institutes of Health guidelines regarding the use of venous thromboembolism (VTE) prophylaxis in patients hospitalized with COVID-19?**
   a. Therapeutic anticoagulation dosing is recommended.
   b. Intermediate-dosing (higher than prophylactic, lower than therapeutic) is recommended.
   c. Given the increased risk of bleeding, no VTE prophylaxis is recommended.
   d. There is insufficient evidence to recommend for or against higher than prophylactic dosing.

4. **In the INSPIRATION trial, which of the following was included in the composite primary efficacy outcome?**
   a. Mortality within 90 days
   b. Arterial thrombosis
   c. Intubation and mechanical ventilation
   d. Bowel ischemia

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.