Dexmedetomidine (DEX) is a selective alpha-2-adrenergic agonist that received Food and Drug Administration approval in 1999 for sedation of mechanically ventilated patients in the ICU for up to 24 hours. DEX lacks depressive respiratory effects and allows patients to be more arousable and interactive in comparison with other sedatives. This potentially can reduce the risk for developing delirium because deeper sedation (e.g., comatose state) is a risk factor for the development of delirium.5,9

The pathophysiology of delirium is complex and not well defined; it can be due to inflammatory changes in the brain or comorbid conditions leading to changes in the blood-brain barrier.10,11 Beyond changes to the brain, delirium also can be related to changes in neurotransmitters (reduced cholinergic activity or increased catecholamine serotonergic activity). DEX lacks anticholinergic activity, which can reduce the occurrence of delirium.12 While the 2002 PAD Guidelines described DEX as a new sedative agent with limited data to support its use in critically ill patients,13 the 2013 PAD Guidelines now suggest that DEX may be preferred over benzodiazepines for sedation in adult ICU patients with delirium in order to reduce the duration of delirium.1

The objective of this review was to evaluate recent clinical studies involving the use of DEX infusion for the treatment of delirium in adult ICU patients.

LITERATURE REVIEW

A literature search was conducted to identify peer-reviewed articles in MEDLINE (1966–June 2016) using the terms sedation, analgesic, dexmedetomidine, delirium, and critically ill adult patients. Two landmark studies were influential in the recommendation of DEX administration beyond 24 hours.5,9 One pilot study and one randomized clinical trial evaluating the use of DEX in the treatment of delirium in adult patients in the ICU were identified.14,15

Patients in the ICU, especially those requiring mechanical ventilation, often need continuous administration of sedative and analgesic agents to facilitate care and maintain comfort.13,16–21 Benzodiazepines, such as lorazepam or midazolam, are commonly used sedatives in patients requiring mechanical ventilation. It is uncertain whether benzodiazepine use is a risk factor for the development of ICU delirium because the causes of delirium are multifactorial (e.g., disease related, iatrogenic, environmental).1 The ACCM suggestion regarding DEX use in patients with delirium was extrapolated from several studies, including two multicenter, double-blind, randomized controlled trials comparing DEX sedation with benzodiazepines in ICU patients requiring mechanical ventilation beyond 24 hours.8,9

In the Maximizing Efficacy of Target Sedation and Reducing Neurological Dysfunction study (MENDS), Pandharipande et al. compared continuous infusions of DEX (0.15–1.5 mcg/kg per hour) or lorazepam (1–10 mg per hour) for up to 120 hours in 106 mechanically ventilated medical/surgical ICU patients.8 Patients were included if they required mechanical ventilation for more than 24 hours. Delirium was assessed using the Confusion

INTRODUCTION

Intensive care unit (ICU) delirium often presents acutely and manifests with an altered level of consciousness and changes in cognition. ICU patients with acute delirium can present with agitation, hallucinations, and/or delusions (hyperactive delirium); lethargy, confusion, and/or sedation ( hypoactive delirium); or a combination of hypoactive and hyperactive symptoms. Hypoactive delirium often goes unrecognized, compared with hyperactive delirium.1

ICU delirium can persist throughout a patient’s admission and has been associated with adverse clinical patient outcomes, including longer length of hospital stay and higher incidence of mortality.5–7

In 2013, the American College of Critical Care Medicine (ACCM) revised and published its “Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit” (PAD Guidelines), which concluded that atypical antipsychotics, such as quetiapine, may reduce the duration of delirium in adult ICU patients, but that more trials were needed to determine whether antipsychotics were actually beneficial in this patient population.1

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Off-Label Use of Dexmedetomidine for the Treatment of Delirium in the Intensive Care Unit

Assessment Method for the ICU (CAM-ICU), and coma was defined as a Richmond Agitation–Sedation Scale (RASS) score of −4 to −5. The researchers found that patients receiving DEX had a greater combined endpoint of delirium-free and coma-free days compared with the lorazepam patients (seven days versus three days; \( P = 0.01 \)); however, this significance was likely driven by coma-free days.

In the Safety and Efficacy of Dexmedetomidine Compared With Midazolam (SEDCOM) study, Riker et al. compared DEX with midazolam in medical/surgical ICU patients requiring sedation beyond 24 hours for mechanical ventilation.9 Delirium was assessed daily utilizing the CAM-ICU. Patients were given an optional loading dose of DEX (1 mcg/kg) or midazolam (0.05 mg/kg). A maintenance intravenous (IV) infusion at 0.8 mcg/kg per hour for DEX or at 0.06 mg/kg per hour for midazolam was initiated. Fewer patients receiving DEX developed delirium (54% versus 76.6%; \( P < 0.001 \)), and those patients had longer mean delirium-free days (2.5 days versus 1.7 days; \( P = 0.002 \)).

The MENDS and SEDCOM trials demonstrated reductions in the prevalence of delirium in patients receiving DEX compared with patients receiving benzodiazepines for sedation for mechanical ventilation beyond 24 hours. These studies were instrumental in the ACCM suggestion that “in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of DEX rather than benzodiazepine infusions be administered for sedation to reduce the duration of delirium in these patients.”14 However, it is not clear from the available data if DEX is associated with a lower risk of developing ICU delirium or if it actually helps to prevent or treat ICU delirium.

Once an ICU patient presents with signs and symptoms of delirium, commonly used pharmacological options include antipsychotics, such as haloperidol or quetiapine, although the evidence for the effectiveness and benefit of these agents is limited. Although DEX may be associated with a lower prevalence of delirium in ICU patients, it is unclear if DEX is a viable treatment option for patients with ICU delirium. Data regarding the use of DEX for the treatment of delirium not related to alcohol or benzodiazepine withdrawal are limited to two studies.14,15,22-27

In a randomized, open-label, parallel-group pilot study, Reade et al. compared DEX with haloperidol for the treatment of ICU-associated delirious agitation in mechanically ventilated patients.14 The study evaluated 20 patients who required continued mechanical ventilation solely due to agitated delirium. Patients were randomized to receive an infusion of haloperidol (0.5–2.0 mg per hour) or DEX (0.2–0.7 mcg/kg per hour) with an optional loading dose of 2.5 mg haloperidol or 1.0 mcg/kg DEX. The median time to extubation and ICU discharge for the DEX group was shorter compared with the haloperidol group (19.9 hours versus 42.5 hours; \( P = 0.016 \); and 1.5 days versus 6.5 days; \( P = 0.004 \)). The median time to achieve a RASS of −2 to 1 was not significantly different between the DEX and the haloperidol groups (four hours versus 18 hours; \( P = 0.071 \)).

Because delirium based on an Intensive Care Delirium Screening Checklist (ICDSC) score of 4 or greater was not an inclusion criterion prior to enrollment in the study, only 30% of the DEX group and 40% of the haloperidol group had delirium based on the ICDSC score. The lack of blinding and the relatively small percentage of patients who had delirium were obvious limitations. It remains unclear whether the patients who received DEX benefited because of the treatment of delirium or because of the sedative effects of DEX. Based on this study, the usefulness of DEX for the treatment of delirium, especially hyperactive delirium, is inconclusive.

Reade et al. addressed the limitations from their pilot study and recently published a double-blind, placebo-controlled, parallel-group randomized clinical trial to determine the effectiveness of DEX compared with standard care in mechanically ventilated patients with agitated delirium in the ICU.15 Patients were included if they had delirium based on CAM-ICU evaluation and were excluded if they were already receiving DEX for sedation. DEX IV infusion was initiated at 0.5 mcg/kg per hour up to a maximum rate of 1.5 mcg/kg per hour to target a RASS score of 0 or physician-prescribed goal. The primary outcome was the number of ventilator-free hours during the ICU admission and was limited to the seven days following randomization. The DEX group had longer ventilator-free hours compared with the placebo group (median, 144.8 hours versus 127.5 hours; \( P = 0.01 \)). The patients in the DEX group were removed from mechanical ventilation sooner (median, 21.9 hours versus 44.3 hours; \( P < 0.001 \)) and had a shorter time to resolution of delirium (median, 23.3 hours versus 40.0 hours; \( P = 0.01 \)).

DISCUSSION

In both the MENDS and SEDCOM trials, delirium was less prevalent with DEX administration compared with benzodiazepine administration in mechanically ventilated patients requiring sedation.59 Although patients receiving DEX had fewer days on mechanical ventilation compared with patients receiving benzodiazepines, there was no significant difference in the number of days in the ICU. However, these studies were not powered to evaluate the clinical implications of a lower prevalence of delirium, such as length of hospital stay and mortality. It is important to recognize that the lower number of days on mechanical ventilation was seen in institutions where the practice parameters included light-to-moderate sedation goals and daily arousal assessment.

Two studies by Reade et al. reported the effects of DEX compared with haloperidol or placebo in the management of mechanically ventilated patients in the ICU with agitated delirium.14,15 In both studies, the median times to extubation were lower in the DEX groups, although lengths of ICU stay were not significantly shorter. In the placebo-controlled trial, time to resolution of delirium was shorter in the DEX group. However, it is unclear if DEX is associated with an antidelirium effect or if it is associated with decreased use of medications prone to cause delirium. These studies were not designed to provide supportive data for the treatment of hypoactive delirium.
Clinical interventions (e.g., atypical antipsychotics, DEX, early mobilization) to reduce delirium duration in the critically ill have not been shown to reduce short-term mortality. Evidence such as mortality data, ICU length of stay, and mechanical ventilation-free days will require randomized controlled trials evaluating DEX in critically ill patients with delirium. Previous trials also demonstrated that hemodynamic effects (e.g., hypotension, hypertension, bradycardia) were the most frequently reported adverse events. Hypotension is associated with continuous infusion and can be reversed by DEX dose reduction, aggressive fluid replacement therapy, or vasopressor administration. Transient hypertension is associated with rapid administration or bolus doses of DEX. DEX would not be an ideal option in the setting of hemodynamic instability.

**CONCLUSION**

DEX appears to offer some advantages for patients with ICU delirium over other sedatives in regard to prevalence of delirium; however, further studies are required before any definitive conclusions can be reached.

**REFERENCES**