Commentary

Dexmedetomidine for hyperactive delirium: worth further study

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In their recent work, reported in *Critical Care Medicine*, Carrasco *et al*. have investigated dexmedetomidine as a rescue agent for treatment of hyperactive delirium refractory to continuous intravenous haloperidol in non-intubated intensive care unit (ICU) patients. The authors address a highly significant critical care issue of delirium with a medical ICU incidence of 50% to 80% (1). A variety of risk factors have been identified for delirium; the most well established risk factors include pre-existing dementia, severity of illness, history of alcoholism, history of hypertension and ICU medications such as benzodiazepines (1). Ultimately, delirium portends poor ICU outcomes of worsened long term cognition, increased length of ICU and hospital stay, increased length of mechanical ventilation, higher mortality and higher healthcare costs (2-10). Despite best efforts, the field, as of the 2013 Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Adult Patients in the ICU (PAD guidelines), continues to lack definitive data regarding prevention and treatment methods for ICU delirium.

Nonpharmacologic interventions such as early mobilization are the only PAD guideline suggested delirium prevention method; there are no recommendations for pharmacologic prevention strategies due to a lack of evidence. Specifically, there is a lack of data supporting use of haloperidol, atypical antipsychotics or dexmedetomidine for delirium prevention. There is a recommendation to use dexmedetomidine rather than continuous intravenous infusions of benzodiazepines for sedation in mechanically ventilated ICU patients. Daily sedative interruption is also recommended. There is level C evidence that atypical antipsychotics may reduce the duration of delirium once it occurs.

In this context, the authors sough to evaluate the clinical effectiveness, safety and cost of dexmedetomidine as a rescue agent after use of haloperidol for the treatment of agitated delirium. They cited appropriate expert guidelines (11,12) and common ICU practice as the reason for starting their treatment protocol with haloperidol and suggest that this work is a first step in establishing the safety and efficacy of dexmedetomidine in the treatment of hyperactive delirium.

Study procedures

The study was a nonrandomized controlled trial with a quasi-experimental design. Patients were prospectively included as they met study criteria. Enrolled subjects were critically ill patients admitted to a combination medical-surgical ICU; all patients were subject to a nonpharmacologic delirium prevention protocol consistent with PAD guidelines and including elements of risk assessment, reorientation, cognitive stimulation, sleep promotion (nonpharmacologic), early mobilization, early removal of devices/restraints and provision of sensory aids. Investigators screened and enrolled patients with hyperactive delirium and trialed haloperidol to a maximal cumulative dose of 30 mg. Their delirium screening tools, the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC), are the most valid and reliable monitoring tools in adult ICU patients (evidence A, PAD guidelines). Following subject enrollment, haloperidol was given at doses of 2.5

to 5.0 mg every 10 to 30 minutes until either a Richmond Agitation Sedation Scale (RASS) score of 0 or 30 mg total dosing occurred. Responders, patients who achieved a RASS score of 0, were maintained with haloperidol infusion of 0.5 to 1.0 mg per hour and followed for resolution of delirium, drug failure or serious adverse event (over-sedation or QTc lengthening). Patients who did not respond to haloperidol were termed nonresponders (RASS greater than 0 after 30 mg haloperidol) and were rescued with dexmedetomidine infusion titrated until RASS 0 was achieved or to a maximum dose of 0.7 μg per kilogram per minute. Nonresponders were maintained on dexmedetomidine until resolution of delirium or serious adverse event occurrence. Outcomes as described below were monitored and analyzed. Patients with drug failure or serious adverse effects were excluded from further participation in the study and received medications as selected by their primary physician team.

Group comparisons were started at the time of the patient first achieving the goal RASS 0 score; after this was achieved, the drugs were adjusted to maintain RASS between –2 and 0 and ICDSC less than 4. Analgesia was achieved in both patient groups with scheduled paracetamol and as needed metamizole or morphine. The primary study endpoint was the quality of sedation defined as the percentage of total sedation time that the patient was maintained at RASS –2 to 0 or ICDSC less than 4. The primary safety endpoint was excess sedation (RASS equal or less than –3). A cost benefit analysis looked at both pharmaceutical cost (primary) and monetary cost of care during and after delirium treatment (secondary).

Study findings

Of 808 consecutive admissions, 154 (19%) patients developed hyperactive delirium; 132 of these patients proceeded into the study. Forty-six of the enrolled patients did not respond to haloperidol and were rescued with dexmedetomidine. The responder and nonresponder groups were similar in terms of demographics, illness severity and time from ICU admission to onset of delirium; the nonresponder group had a nonsignificant trend towards worse RASS scores and higher rates of restraint use at the time of delirium diagnosis. The authors did not identify any risk factors that may have contributed to haloperidol failure.

Regarding clinical effectiveness, dexmedetomidine use resulted in a higher percentage of sedation time at RASS and ICDSC goals which met the authors' definition of better quality of sedation and greater stability of sedative effect. The mean sedation time required was slightly longer in the haloperidol group. In addition, dexmedetomidine patients received less "as needed" analgesia. These findings are not surprising given the pharmacokinetics of haloperidol and dexmedetomidine and the analgesic properties of dexmedetomidine.

The authors also report that the haloperidol responder group had ten additional later failures of therapy due to either oversedation or QTc prolongation; the dexmedetomidine group had no oversedation during treatment, again this is likely a function of the long half-life of haloperidol and the high doses used. ICU and in-hospital mortality were rare and appeared unrelated to study drug administration. After including the cost of increased ICU and hospital length of stay, the authors demonstrated a cost savings of $4,370 per patient for the dexmedetomidine group.

Commentary

It is now well documented in the literature that delirium has significant implications for both short and long-term patient outcomes. Hyperactive or agitated delirium is a subset of the broader category of delirium, which unlike hypoactive delirium, is easily recognized by clinicians due to its characteristic features. While there is an absence of strong evidence to support pharmacologic strategies to prevent or treat delirium, ICU providers need to provide treatment for agitated patients in order to maintain a safe environment. Based on studies of psychotic patients, but without any evidence in critically ill patients, ICU physicians often prescribe centrally acting, sedative drugs that have potential for adverse effects and a high rate of outpatient carryover (13).

Haloperidol, along with atypical antipsychotics, is commonly used for treatment of agitated delirium despite a lack of evidence that it shortens the duration of delirium (14). At best, haloperidol is converting hyperactive delirium into hypoactive delirium (15). In addition, there are clearly patients with delirium who cannot safely receive haloperidol or who do not respond to haloperidol. Given the evidence for harm with benzodiazepine use, dexmedetomidine with both anxiolytic and analgesic properties is a reasonable choice for treatment of agitation. However, dexmedetomidine is commonly restricted in use do to a high up front medication cost and perhaps due to provider lack of familiarity with this newer agent.

In this work, the authors instituted appropriate guideline based nonpharmacologic primary delirium prevention. They used well validated definitions of agitated delirium with RASS +1 to +4 and CAM ICU positive or ICDSC 4 to 8. All study subjects were initially treated with an intravenous bolus haloperidol titration until control of agitation or a maximal cumulative dose of 30 mg. While the authors justify their maximum dose, there is much literature to suggest that doses this high are unnecessary and lead to increased adverse reactions, especially in older patients. Brain imaging studies have demonstrated that dopamine receptors are saturated with about 10 mg per day of haloperidol (16). Their observation of drug failure with haloperidol causing oversedation in ten subjects is a known side effect of the drug especially at the high doses at which it was given.

Despite this study being nonrandomized and their use of high doses of haloperidol as a comparator to dexmedetomidine, this work is a first step in the direction of establishing the utility of dexmedetomidine in the treatment of hyperactive delirium. The authors have demonstrated favorable outcomes from effectiveness, safety and cost viewpoints. The primary clinical endpoint appears to be sedation rather than delirium resolution and so dexmedetomidine may treat the agitation but not resolve the delirium. Future work should investigate the effectiveness of dexmedetomidine as a first line agent for hyperactive delirium treatment.

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Footnote

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