Editorial

REDUCE trial: using haloperidol to prevent delirium has no beneficial effect in critically ill patients

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Delirium is a common clinical syndrome in intensive care unit (ICU) patients, characterized by acute impairment of attention and cognition with a fluctuating course (1). The onset of delirium is associated with an increased duration of mechanical ventilation, prolonged ICU and hospital stay and increased overall costs of care (2,3). Furthermore, delirium may lead to impaired mental health that persists after hospital discharge (4). The prevention of delirium during ICU stay could lead to meaningful benefits to patients and reduced costs of hospital care.

Recently, a meta-analysis including 10 randomized controlled trials recruiting 1,861 surgical patients demonstrated that Haloperidol (≥5 mg/d) may significantly reduce the incidence of post-operative delirium compared to placebo or second-generation antipsychotics (5). The purpose of the REDUCE trial was to determine if Haloperidol could prevent the onset of delirium in ICU patients and thereby lead to improved survival after critical illness.

Study design

The REDUCE trial was conducted across 21 ICUs in the Netherlands. All major design features of the REDUCE trial were robust: (I) allocation concealment was maintained by the use of pharmacist controlled randomization; (II) blinding of clinicians, patients and outcome adjudicators was attained by using an identical placebo control and; (III) the primary outcome (day 28 survival time) was reported for all randomized patients.

Initially, the REDUCE trial started as a comparison between three different treatment groups: Patients were randomized to either 1 mg haloperidol q8h, 2 mg haloperidol q8h or Placebo q8h. A pre-planned interim analysis was conducted and the 1 mg haloperidol q8h group met pre-defined criteria for futility so recruitment into this group was stopped. Because the pre-planned stopping rules were appropriate, there are no methodological concerns arising from stopping recruitment to into the 1 mg haloperidol q8h group. The remainder of this editorial will focus on results obtained from comparing the 2 mg Haloperidol q8h group to the Placebo q8h group.

The primary outcome, survival time until study day 28, was standardized across all sites. Secondary outcomes were also pre-defined and standardized in the study protocol. Patients would be considered to have new-onset delirium if they had either one positive Confusion Assessment Method (CAM-ICU) result or if they scored four or higher on the Intensive Care delirium Screening Checklist (ICDSC). Both CAM-ICU and ICDSC are accepted as valid screening tools

for delirium diagnosis in critically ill patients (6). Only one study site used the ICDSC. Interpreted in the context of the primary outcome, use of a different validated screening tool at one site to diagnose a secondary outcome is unlikely be a source of major bias.

Patient population

Adult critically ill patients without delirium were recruited into REDUCE if they were expected to remain in the study ICU at least two days. Patients were excluded if they already had delirium, Parkinson disease, dementia, a history of alcohol abuse, a psychiatric disease or an acute neurological condition. Complete details of exclusion criteria are reported in the primary manuscript and Supplement.

The study intervention was started immediately after patients were deemed eligible, within 24 h of ICU admission. It was continued until discharge from ICU, occurrence of delirium or day 28 after enrollment. If delirium occurred, the blinded study intervention was discontinued and the patient was started on open-label Haloperidol treatment, with the dose increased if the severity of delirium increased, up to 5 mg every 8 hours. As delirium improved, the dose of Haloperidol decreased by half each day and was stopped when signs of delirium disappeared. Other sedative agents could be used in refractory cases.

Findings

The primary outcome, the number of days that patients survived up to study day 28, did not differ between the two groups (median difference 0 days; 95% CI, 0 to 0; P=0.93; HR 1.003; 95% CI, 0.78 to 1.30; P=0.82). Furthermore, there was no difference in the number of survivors at day 28 (83.3% 2 mg Haloperidol *vs.* 82.7% Placebo, 0.6% difference, 95% CI, –3.4% to 4.6%), and at day 90 (79.1% 2 mg Haloperidol *vs.* 78.6% Placebo, 0.5% difference, 95% CI, –3.9–4.8%).

Prophylactic treatment with 2 mg Haloperidol q8h did not prevent the onset of delirium (33% 2 mg Haloperidol *vs.* 33% Placebo, difference 0.4%, 95% CI, –4.6% to 5.4%) and did not alter delirium/coma-free days (median difference, 0 days, IQR 0 to 0 days).

There were no differences between the two groups in the duration of mechanical ventilation, length of ICU or hospital stay, ICU readmission, use of body restraints, unplanned removal of tubes, reintubation rates, number of adverse events or any other outcomes. The results of predefined subgroup analysis and per-protocol analysis were all in line with the intention to treat results presented above.

Commentary

The REDUCE trial was a well-conducted, pragmatic, large scale, multi-centered clinical trial undertaken to investigate whether Haloperidol, administered to ICU patients who did not have delirium, could improve duration of survival after critical illness. The secondary aim of the REDUCE trial was to determine whether any increase in duration of survival was attributable to a reduction in the onset of delirium.

Based on the results of the REDUCE trial, critically ill patients without delirium do not benefit from prophylactic treatment with Haloperidol.

Implications for clinical ICU practice

The negative results of the REDUCE trial are consistent with previous negative clinical trials conducted in critically ill patients (7). Outside of clinical trials research protocols, there does not appear to be high-level evidence of benefit from using Haloperidol in general ICU patients who do not have delirium.

If I cannot use Haloperidol to prevent delirium, should I consider other options for my ICU patients?

Recently published RCTs demonstrate that low-dose dexmedetomidine may decrease the incidence of delirium in elderly surgical patients admitted to the ICU (8) and general medical ICU patients (9). Dexmedetomidine is therefore a promising agent for the prevention of delirium in ICU patients, however studies reporting long term outcomes post-ICU discharge are needed.

Interestingly, the REDUCE protocol recommended the use of non-pharmacological methods for delirium prevention in all patients (Haloperidol and Placebo treated patients). These methods included the implementation of early mobilization, improving patient circadian rhythm, noise reduction, reduction of sedation and benzodiazepines, awakening trials, and use of hearing and visual aids (6). Study Supplement 2 eTable 2 reports that 70% of participating sites implemented all of the above methods, with 90% of hospitals implementing at least five specific

methods whilst 100% of hospitals implemented at least two methods.

Although these non-pharmacological approaches appear attractive and may be relatively inexpensive, many clinical trials are ongoing to validate their effectiveness in critically ill patients. For example, current ongoing clinical trials are recruiting patients to evaluate the use of light therapy (NCT01727375), daily interruption of sedative infusions (NCT00714194), nursing and physical therapy interventions (NCT03002701) and melatonin (ACTRN12616000436471) on the prevention of delirium in the ICU. Results of these ongoing clinical trials may lead to more widespread use of these specific interventions.

Should I use Haloperidol for treating delirium in my ICU patients?

The results of the REDUCE trial do not provide any guidance on the use of Haloperidol for treating delirium. The 2013 American College of Critical Care Medicine's Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium recognizes there is no published evidence that treatment with Haloperidol reduces the duration of delirium in adult ICU patients (10).

Caveats for over-interpretation and implications for future research

Supplement 2 eFigure 2b reports the presence of a treatment interaction in a subgroup of patients. eFigure 2b suggests that patients who received treatment with Haloperidol for three days or less had improved survival until study day 90 ($P_{interaction}$=0.08). We caution the reader on the over-interpretation of this finding (11). First, it is important to consider that eFigure 2a, 2b and 2c reported a total of 20 subgroup analyses. To minimize the potential for false positive results, most clinical trials report only three to five subgroup analyses. Second, patients were not randomized to short duration *vs.* long duration of Haloperidol treatment, so this subgroup result carries the same weight as an observational study. Third, there is no physiological basis for this finding. Figure 2c does not provide any evidence that patients who received Haloperidol for a shorter duration of time had less delirium ($P_{interaction}$=0.84). Whilst it may be possible to use the results from these subgroup analyses to guide future research directions, they should not be used to guide clinical care.

Conclusions

The REDUCE trial is a well conducted clinical trial that provides convincing evidence that Haloperidol has no beneficial effect on promoting survival and preventing occurrence of delirium in critically ill patients with high risk of delirium.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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