ICU
MANAGEMENT & PRACTICE

LIVES2018: Are dopamine antagonists useful in preventing ICU delirium?

There are conflicting data on the effects of antipsychotic medications on delirium in patients in the intensive care unit (ICU). A new study shows that the use of haloperidol or ziprasidone, as compared with placebo, in patients with acute respiratory failure or shock and hypoactive or hyperactive delirium in the ICU did not significantly alter the duration of delirium. The findings were presented at the European Society of Intensive Medicine congress, LIVES 2018.

"In this double-blind, randomised, placebo-controlled trial of intravenous antipsychotic medications for the treatment of delirium in the ICU, there was no evidence that either haloperidol or ziprasidone led to a shorter duration of delirium and coma. Patients who received treatment with up to 20 mg of haloperidol per day or up to 40 mg of ziprasidone per day and those who received placebo had similar outcomes, including survival and lengths of stay in the ICU and hospital," according to the study published online in The New England Journal of Medicine.

Delirium is the most common manifestation of acute brain dysfunction during critical illness, affecting 50 to 75% of ICU patients who receive mechanical ventilation. Delirium can interfere with medical care: hyperactive delirium can lead to unplanned removal of devices, whereas hypoactive delirium prevents participation in nursing interventions and physical therapy.

Haloperidol, a typical antipsychotic medication, is often used to treat hyperactive delirium in the ICU, and surveys suggest that the drug is also used to treat hypoactive delirium despite two small randomised trials that showed no evidence that haloperidol results in a shorter duration of delirium in the ICU than placebo. Atypical antipsychotic medications, such as olanzapine, quetiapine, and ziprasidone, are also used for this purpose, and one placebo- controlled trial has suggested a benefit, whereas another showed no evidence of benefit.

The current study aimed to examine the effects of haloperidol or ziprasidone on delirium during critical illness. The volume and dose of a trial drug or placebo was halved or doubled at 12-hour intervals on the basis of the presence or absence of delirium, as detected with the use of the Confusion Assessment Method for the ICU, and of side effects of the intervention. The primary end point was the number of days alive without delirium or coma during the 14-day intervention period.

Written informed consent was obtained from 1,183 patients or their authorised representatives for this study. Delirium developed in 566 patients (48%), of whom 89% had hypoactive delirium and 11% had hyperactive delirium. Of the 566 patients, 184 were randomly assigned to receive placebo, 192 to receive haloperidol, and 190 to receive ziprasidone. The median duration of exposure to a trial drug or placebo was 4 days (interquartile range, 3 to 7). The median number of days alive without delirium or coma was 8.5 (95% confidence interval [CI], 5.6 to 9.9) in the placebo group, 7.9 (95% CI, 4.4 to 9.6) in the haloperidol group, and 8.7 (95% CI, 5.9 to 10.0) in the ziprasidone group (P=0.26 for overall effect across trial groups).

Data showed that the use of haloperidol or ziprasidone, as compared with placebo, had no significant effect on the primary end point (odds ratios, 0.88 [95% CI, 0.64 to 1.21] and 1.04 [95% CI, 0.73 to 1.48], respectively). There were no significant between-group differences with respect to the secondary end points or the frequency of extrapyramidal symptoms.

"One possible reason that we found no evidence that the use of haloperidol or ziprasidone resulted in a fewer days with delirium or coma than placebo is that the mechanism of brain dysfunction that is considered to be targeted by antipsychotic medications — increased dopamine signalling — may not play a major role in the pathogenesis of delirium during critical illness," researchers note. "Another possible reason is that heterogeneous mechanisms may be responsible for delirium in critically ill patients."

An accompanying editorial by Thomas P. Bleck, MD, MCCM (Section of Neurocritical Care, Department of Neurological Sciences, Rush Medical College, Chicago) discusses why the trial has failed to show benefits of dopamine antagonist drugs in ICU delirium.

"Why did the trial fail to show benefit? It is likely that our concept of delirium is flawed. The neurochemistry of sudden alteration in mentation is complex and involves several neurotransmitters as well as structural, immunologic, and network alterations and possible brain infection that is not clinically evident," Dr. Bleck says.

An interesting finding of the trial, Dr. Bleck notes, was that an added bolus of placebo was just as effective as an added bolus of an active rescue medication. This could be because the majority of patients in the trial had hypoactive delirium, for which the drugs may not have an effect.

"The investigators deserve credit for conducting a difficult trial," the author says, "but it would have been astounding if there were a single magic bullet for the restitution of normal brain function in ICU patients with delirium."

Wes Ely, Professor of Medicine at Vanderbilt University School of Medicine presented the MIND-USA results at the European Society of Intensive Medicine congress, LIVES 2018.

Ely emphasised to delegates that the key goal to managing/preventing delirium is to get patients naturally tired, for example by mobilising.

J. Randall Curtis commented on Twitter: "Anti-psychotics don't reduce delirium in the ICU. We need to stop using them so often! Nice work from Ely and team should change our clinical practice."

Source: The New England Journal of Medicine
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