Randomised controlled trial

Placebo might be superior to antipsychotics in management of delirium in the palliative care setting

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Commentary on: Agar MR, Lawlor PG, Quinn S, *et al*. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. *JAMA Intern Med* 2017;177:34–42.

Context

The need for controlled trials evaluating the efficacy of antipsychotics in the management of delirium has been recognised since the Practice Guidelines for the treatment of patients with delirium were introduced in 1999.[1] Since then, only few relevant studies have been published. In contrast to the Practice Guidelines, which favoured psychopharmacological management, the National Institute for Health and Care Excellence Guidelines solely recommend psychopharmacological management for distress.[2] To date, it has not yet been clearly defined what the distressing symptoms of delirium are. Considering this controversy and the necessity of further studies in this domain, the most beneficial approach for delirious patients remains unclear.[3 4]

Methods

In this multicentre, randomised clinical trial in the palliative care setting, haloperidol or risperidone were evaluated versus placebo in a double-blind design between 2008 and 2016. The doses were age adjusted and titrated as required, administered every 12 hours over a course of 72 hours. In addition to the standard approach, management of delirium precipitants and supportive care, as well as subcutaneous midazolam as needed for severe distress or safety were provided. Based on the Nursing Delirium Screening Scale (Nu-DESC)-defined items for distress (behavioural, communication and perceptual items), the primary outcome was set as the mean group difference of improvement between management regimens. Secondary outcomes were delirium severity, midazolam requirement, extrapyramidal side effects, sedation and survival.

Findings

In total, 247 patients—more than 80 in each arm—were included in this intention-to-treat analysis. Both risperidone and haloperidol arms had higher delirium scores (0.48 units and 0.24 units, respectively) based on the Nu-DESC defined items (items 2, 3 and 4) than placebo at 72 hours of management (1-unit decrease deemed minimum clinically significant). Similarly, based on the Memorial Delirium Assessment Scale, the improvement in the placebo arm was greater. Compared with placebo, both risperidone and haloperidol were factors associated with delirium in multivariable analysis at the endpoint. Furthermore, in both active arms, extrapyramidal side effects occurred at higher rates (almost 1 more mean effect per day), and death was greater (HR 1.29 (95% CI 0.91 to 1.84) for risperidone and HR 1.73 (95% CI 1.20 to 2.50) for haloperidol). Midazolam use (for immediate distress or safety symptoms) was also significantly lower among those on placebo.

Commentary

Undoubtedly, this was a comprehensive study, including 247 patients over a period of 6 years including numerous parameters in a randomised controlled design. The main result was the superiority of placebo versus risperidone and haloperidol.

There are several limitations of the study. The assumption in the power analysis was a reduction of Nu-DESC scores of 1 over the course of management, which was not achieved. Furthermore, the measurement of distressing symptoms of delirium was based on consensus using the Nu-DESC behavioural, communication and perceptual items. To what extent these items reflect distress has not yet been evaluated. In addition, the management course over 72 hours was short as the literature indicates delirium resolution takes up to 7 days and a longer observation period would have been preferable.

The requirement for titration was greater, and mean doses higher in the active arms, midazolam rescue requirement was lower in the placebo arm and the Richmond Agitation and Sedation Scale scores were lower in the haloperidol arm. All of these could also indicate that delirium was not the same between arms.

Among others, type and severity of illness cause persistent or irreversible delirium[5]; considering the palliative care setting, patients were likely very ill; however, irreversible delirium was not included, and the proportion in management arms was not determined. Although antipsychotics increase mortality in the elderly with dementia, it is unclear whether the administration of few doses caused mortality in the given time and population studied or other causes prevailed.

Finally, patients exclusively had mild to moderate delirium; the effects of elimination of delirium precipitants and supportive care in these types of delirium are not known. In antidepressant trials, for example, the active arms failed to distinguish from placebo in milder forms.[6]

Implications for practice

Although this remarkable study indicates the superiority of placebo over risperidone or haloperidol in the management of delirium, potential confounding effects cannot be excluded. Therefore, it would be premature to conclude that delirious palliative care patients should solely be managed with placebo. In the interest of the well-being of the patient, an individualised approach implementing all management options—including antipsychotics if required—remains favourable.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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