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Evaluating interventions to reduce the risk of postoperative delirium

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This editorial accompanies: Restricted *versus* liberal intraoperative benzodiazepine use in cardiac anaesthesia for reducing delirium (B-Free Pilot): a pilot, multicentre, randomised, cluster crossover trial by Spence et al., *Br J Anaesth* 2020:125: 38–46, doi: 10.1016/j.bja.2020.03.030

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Postoperative delirium is a form of acute brain dysfunction that sits on a spectrum of perioperative neurocognitive disorders, manifesting within 30 days of surgery.[1] There are acute and fluctuating disturbances in attention and awareness, with hyperactive (agitation), hypoactive (inactivity), and mixed forms.[2] Delirium is distressing to patients and their families, an extra burden for healthcare workers, and is associated with increased healthcare costs.[3] Postoperative delirium is also associated with a decline in both cognitive and functional performance in the weeks to months after surgery.[4,5]

Postoperative delirium is estimated to occur in up to 65% of older patients after surgery,[6,7] but the reported incidence is highly dependent on how it is diagnosed and screened.[1] The Confusion Assessment Method for the ICU (ICU-CAM) is a widely used tool validated in the ICU setting that identifies delirium on the basis of an acute change or fluctuating course of mental status plus inattention and either altered level of consciousness or disorganised thinking.[8] ICU-CAM should ideally be administered by trained staff, twice a day, for at least 5 days after surgery if wanting to detect all delirium cases.[9,10]

Risk factors for delirium include advanced age, comorbidity, extent of surgery, and postoperative pain.[10–12] Most risk factors are non-modifiable so there has been great interest in evaluating potential preventative measures or treatments. But with the possible exception of dexmedetomidine,[13] there is no convincing evidence that pharmacological prevention or

treatment is effective.[14–16] Nevertheless, many experts and professional bodies recommend avoiding the use of benzodiazepines and other sedatives in those at risk of postoperative delirium.[7,10,17] Large clinical trials are clearly needed, but key components of such a trial require multidisciplinary and consumer consultation, and identification of the specific trial methodologies that allow researchers to fully evaluate such an intervention. A pilot trial is an important early step in this process.[18]

In this issue of the *British Journal of Anaesthesia*, Spence and colleagues[19] present their results of a pilot randomised cluster crossover trial evaluating *intraoperative* benzodiazepine restriction for cardiac surgery. They included four, 4-week crossover periods in their design, requiring clinicians to crossover three times between treatment periods, meaning that each of the two hospitals involved in the study would be obliged to use a 'liberal' and 'restricted' approach to intraoperative benzodiazepine administration on two occasions. Their primary goal was to test the feasibility (treatment adherence, reliable detection of postoperative delirium in a setting of routine care) of a future large-scale trial, and to determine the incidence of intraoperative awareness during the restricted benzodiazepine periods.[19] Most key methodological features of the study design, and its reporting on a publicly accessible trial registration website,[20] were according to best practice. All process (except intraoperative drug administration data) and outcome data were obtained from electronic medical records; this enhanced the efficiency of the trial, but to some extent limited the quality of the data.

Spence and colleagues[19] enrolled 800 cardiac surgical patients of which they detected 127 patients (15.9%) with delirium. Most (91%) had received intraoperative benzodiazepines during their standard care (liberal) periods, and this was reduced to 12% during the restricted benzodiazepine periods. A total of 740 (93%) had at least one postoperative delirium assessment per day in the ICU, and only 1 of 521 patients screened had intraoperative awareness detected (incidence 0.2%); this patient had received intraoperative benzodiazepine. While not a statistically significant difference, there was a suggestion that patients in the benzodiazepine restriction period received more preoperative and postoperative benzodiazepines. They concluded that their study demonstrated the feasibility of a future large, multicentre, randomised, trial.

Pilot studies are useful for many reasons, and testing feasibility is one important aim.[18,21,22] Other purposes may include testing proof-of-concept (preliminary efficacy), typically done using surrogate markers of effect, refining methodology including dose selection for pharmacological studies, and estimates of effect for sample size calculation. There are recommendations for reporting pilot studies.[23] The rationale for a feasibility or 'vanguard' trial is to investigate areas of uncertainty about a future definitive trial.[23] Criteria should be established to assess recruitment potential, reliable and complete delivery of the proposed intervention, multisite/international collaboration, safety, and data collection.

Spence and colleagues[19] had, importantly, predetermined their feasibility criteria.[18] The two key criteria were to show that at least 80% of patients would receive care that complied with the assigned benzodiazepine administration policy, and at least 95% of patients would have at least one delirium assessment completed in the ICU during the study period. The authors did not provide 95% confidence intervals for these two results, but the denominator (n=411) allows the calculation of the lower 95% confidence limit, these being 84.9% for treatment group compliance and 94.7% for ICU delirium assessment, respectively. Although the latter sits just outside the prespecified criterion, it is reasonable to conclude that feasibility was confirmed in their study.

There are, however, important weaknesses of this feasibility trial, some of which were identified by the authors themselves. The most crucial was that they did not control for preoperative or postoperative benzodiazepine administration, or the total dose administered. Patients assigned to the restricted benzodiazepine group were freely able to receive such medications before or after surgery, including as part of a sedation regimen in the ICU. In fact, close to 15% of patients in the restricted benzodiazepine group received a benzodiazepine before operation and 13% after operation. That is, there was *treatment contamination* that jeopardised the internal validity of the trial. Furthermore, the mean midazolam equivalent dose administered in the liberal benzodiazepine group was only 5.2 mg. Both these features would dilute any treatment effect, and artificially inflate the estimate of the likely compliance in a future large-scale trial. Another important issue is that the authors relied upon the clinical assessments of delirium done as part of routine care in the two trial sites, and it is unclear what level of staff training and expertise existed in this process. The incidence of delirium reported (15.9%) is extremely low relative to other recent reports, suggesting many episodes of delirium may have been missed. Clinical trials evaluating postoperative delirium should assess patients twice a day over (at least) 5 days, using a validated tool such as the ICU-CAM.

The information provided by Spence and colleagues will assist those considering their own interventional trials aimed at reducing the risk and impact of postoperative delirium. Large clinical trials are clearly needed; we are one step closer to finding effective solutions.

Declaration of interest

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