Editorial

Low dose dexmedetomidine for the prophylaxis of perioperative ICU delirium—how much evidence is enough?

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Few clinical trials in critical care medicine suggest clinicians should do something most would not have previously considered. The recently published randomised, placebo-controlled, 2-hospital blinded study of low dose, non-titrated dexmedetomidine in 700 elective surgical patients >65 years old admitted to an intensive care unit in the immediate postoperative period (1) is such a trial. Su *et al.* showed dexmedetomidine 0.1 mcg/kg/hr (a very low dose, well below that used for sedation in most patients) from the time of ICU admission to 8 am on the first postoperative day was associated with a reduction in the incidence of postoperative delirium of >50% (from 23% to 9%, P<0.0001), along with universally congruent benefit in secondary outcomes such as subjective sleep quality and pain, daily prevalence of delirium on days 1–3, time to extubation (in the approximately 50% of patients who were intubated at the time of randomisation), and length of ICU stay, all without any observable increase in bradycardia or hypotension, adverse effects related to dexmedetomidine at higher doses. The beneficial effect of dexmedetomidine was observed both in patients who were, and who were not, intubated at the time of ICU admission. Patients who received dexmedetomidine for longer had greater benefit—plausibly interpreted as a dose-dependent effect. Notably, there was only one observed difference in the use of intercurrent sedatives (the median total propofol dose in the dexmedetomidine group was approximately 75% of that in the placebo group), suggesting that the mechanism of benefit was not avoidance of deliriogenic sedatives but rather a direct anti-delirium effect of dexmedetomidine.

Intensivists have learnt to be sceptical of trials showing benefit of novel interventions (2). Initial enthusiasm for intensive glycaemic control (3), early goal directed therapy (EGDT) for severe sepsis (4), corticosteroids for acute respiratory distress syndrome (ARDS) (5,6) and septic shock (7), drotrecogin alfa for severe sepsis (8), and higher-than-conventional dialysis dose (9), none of which were supported by larger multicentre studies (10-15), has led to a nihilistic attitude towards the first study of an intervention to show positive results. This attitude is typified by the Lancet editorial that accompanied the paper (16).

However, the Su *et al.* trial differs from the quoted examples in several respects. Unlike the very unwell patients in the first EGDT trial (4), Su's patients were typical of those admitted to ICUs after elective surgery in much of the world. As would be expected, 30-day mortality was very low (0.3–1.1% in the dexmedetomidine and placebo groups, respectively), as were time to extubation (4.6–6.9 hours) and length of ICU stay (20.9–21.5 hours). The incidence of delirium in control patients (23%) was high, but no higher than in several other studies quoted in the manuscript. Unlike the first intensive glycaemic control trial in which all patients received dextrose infusions (3), intercurrent interventions were typical of contemporary practice: for example, half the trial patients received a small dose of intraoperative midazolam; approximately 90% had either patient-controlled intravenous or epidural anaesthesia; and propofol was more commonly chosen (approximately 50%) than midazolam (<10%) as a postoperative sedative. The balance of beneficial and adverse effects in an individual patient can be assessed during a dexmedetomidine infusion, unlike corticosteroids for which this balance might not be

apparent until long after the drug is discontinued. Unlike the EGDT (4) and dialysis-dose trials (9), Su's patients and staff were blinded; unlike the first drotrecogin trial (8), the drug manufacturer had no role in the conduct of the study. And, unlike many of these other examples, the trial was conducted in more than one centre, with all the benefits this entails (2).

The accompanying *Lancet* editorial (16) is circumspect, stating "clinical implementation without verification of safety and effectiveness would be premature". Hence the title of this commentary: "*how much evidence is enough?*" Addressing the editorialists' criticisms in turn: first, the biological plausibility of a sub-sedative dose of dexmedetomidine as a prophylactic anti-delirium agent. Evidence is accumulating that dexmedetomidine might be directly neuroprotective: for example, in animal models of traumatic brain injury (17) and ischaemia (18). Whether a sub-sedative dose in humans is sufficient to cause such an effect is unknown, but only studies such as that of Su *et al.* will provide the answer. Second, the concern is raised that family members provided consent for 58% of trial participants—a figure not reported in the manuscript or supplemental material, and so presumably the result of a personal communication. However, patients were not recruited until ICU admission, and 55% were intubated at that time. Presumably none of the intubated patients could be approached for consent, implying that almost all of those who were not intubated were not delirious and so could consent for themselves. The trial authors note the weakness of not assessing formally for delirium at study baseline in intubated patients. They also note the lack of prognostic significance of very early postoperative delirium, which accords with similar findings with "sedation-related" delirium in a general ICU population (19). Even if some patients were delirious, this does not impact the validity of the trial unless there was a difference between groups—unlikely given the large study size and the absence of any other group characteristics suggesting this. Finally, the use of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), developed to identify delirium in intubated patients, is criticised for its lack of sensitivity in patients who are not intubated. This is correct (20), but the lesser sensitivity is not marked, and once again would have affected both trial groups equally. Furthermore, the incidence of delirium was approximately that expected from the literature.

Some questions do remain when deciding whether to implement Su's low-dose, non-titrated dexmedetomidine protocol in clinical practice. No cost-effectiveness analysis is presented in the manuscript. Dexmedetomidine is expensive (for example in Canada in 2014, full sedation with dexmedetomidine cost $452/day, compared to $126/day for midazolam and $230/day for propofol) (21). While the infusion rate used by Su *et al.* was only 10–20% that required for sedation, at least one ampoule per patient would still be required. Time to extubation was reduced from a median (IQR) of 6.9 (5.2–8.6) hours to 4.6 (3.4–5.8) hours, which was statistically significant (P=0.031) and most likely of patient benefit, but probably not associated with any cost savings. Similarly, ICU length of stay was shortened, but the difference in medians was only 0.6 hours—also unlikely to result in cost savings. The manuscript does not report if there was a reduction in the proportion of patients who had atypically long lengths of ICU stay, in whom cost savings might have been apparent. More patients in the dexmedetomidine group were discharged from hospital within 7 days (23.7%) *vs.* the placebo group (17.1%) (P=0.032), but this outcome is not listed in the published study protocol or in *the Chinese Clinical Trial Registry* and so could possibly be just one of several exploratory post-hoc endpoints, susceptible to the statistical problem of multiple comparisons. There is little information on how the results differed between patients who were intubated and not intubated at the time of study inclusion, other than to note that the reduction in the incidence of delirium in the dexmedetomidine group was significant (although of lesser magnitude in the non-intubated patients) regardless of intubation status. Logically, cost-effectiveness might differ according to whether a patient is intubated at the time of ICU admission. It is also not known whether certain patient characteristics, such as age, duration of anaesthesia, type of surgery, chronic alcoholism, and comorbidity (all of which were recorded and presented in the manuscript or appendix) identified patients at particularly high risk of delirium, or who had particular benefit with dexmedetomidine. In hospitals where dexmedetomidine remains expensive and where non-reimbursed drug expenditure is a major consideration, the trial's tenuous suggestions of cost-effectiveness in the study cohort as a whole will be insufficient for many clinicians to apply low-dose dexmedetomidine to every patient who would have been eligible for the study.

Su *et al.* suggest that "a larger study will be required to rule out possible safety concerns". Most critical care studies of this size, having found statistically significant improvements in some adverse events (such as tachycardia

requiring intervention, hypertension requiring intervention, and hypoxaemia) and no significant differences in others (such as bradycardia or hypotension), would not call for further, larger, studies. Trials that used dexmedetomidine at much higher doses in general ICU populations found a higher incidence of bradycardia (and also less delirium) with dexmedetomidine than with benzodiazepines (22,23), but this bradycardia appeared transient and seldom required treatment. However, the protocol used by Su *et al.* administered dexmedetomidine at low dose to every postoperative patient >65 years, many of whom would have been at a very low risk of delirium. No drug is universally "safe", so logically there must be some patients in whom the risks of delirium and its consequences are less than the risk of the drug. Given this, further information on safety is indeed warranted. However, the adverse effects of dexmedetomidine (bradycardia and hypotension) should be short-lived and readily treated in an ICU—as appears to have been the case in this trial. Whether establishing safety requires another even larger phase III effectiveness trial, or whether post-marketing surveillance would be sufficient, is a matter for regulators and trial funding agencies.

An enticing question is whether dexmedetomidine at this dose mandates presence in an intensive care unit. Perioperative delirium in the ICU is a small fraction of that experienced in the general hospital wards. Dexmedetomidine can be administered by routes other than continuous infusion, raising the possibility that in general wards, where possible technical errors might make the administration of sedative infusions unsafe, dose-equivalent dexmedetomidine by another route might be similarly efficacious, safe, and potentially cost effective.

Unlike the *Lancet* editorialists (16), I think that this large, multicentre blinded trial with patient-centred outcomes provides sufficient evidence of clinical effectiveness. No alternative approach to pharmacological delirium prophylaxis is endorsed by evidence-based guidelines for such patients (24), and the negative associations of delirium are sufficiently well-established to warrant treatment. To me, the only reason not implement the Su *et al.* protocol today in my ICU is cost. I will, however, apply results of the Su *et al.* trial to patients at the highest risk of postoperative delirium, but (as with most ICU interventions) I will modify individual treatment based on response. To ignore the results of a 700-patient blinded, multicentre, placebo-controlled trial of a registered drug in common use worldwide, which found the intervention more than halved the incidence of the serious condition it was hypothesised to prevent, with universally congruent secondary outcomes, biological plausibility and alignment with trial results in other contexts, would be to strike at the entire rationale for performing trials and for evidence-based medicine.

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Footnote

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Conflicts of Interest: I have been paid to speak at events, once in 2009 and once in 2016, organised by the manufacturers of dexmedetomidine (Hospira Australia Pty Ltd. and Pfizer Australia Ltd.). Hospira Australia Pty Ltd. has provided unrestricted grant funding for two clinical trials in which I am a Chief Investigator.

Comment on: Su X, Meng ZT, Wu XH, *et al*. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1893-902.

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