

Dexmedetomidine: what next?

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Drs. McLaughlin and Marik have summarised very well the problem of critical illness delirium and how the results of our trial (Dexmedetomidine to Lessen ICU Agitation: 'DahLIA') add to the existing body of evidence supporting dexmedetomidine as a useful drug for its treatment. Our study was confined to patients with both agitation and delirium at the time of randomisation, as we reasoned that the sedative properties of dexmedetomidine would have the greatest benefit in agitated patients. However, both delirium and agitation are fluctuating conditions, and it is likely that in the absence of treatment many of our patients would have manifest both hyperactive and hypoactive forms of delirium at different times. As we noted in the trial manuscript, we cannot say whether the benefit observed with dexmedetomidine was due to a direct anti-delirium effect or due to the reduction in other sedatives, many of which are thought to have a deliriogenic effect. Theoretically, patients with hypoactive delirium should have required little or no sedation. If dexmedetomidine works only by reducing the use of other sedatives, one would therefore expect it to be less effective in patients with long periods of hypoactive delirium. However, in practice, continuous sedative infusions are sometimes titrated at infrequent intervals (especially at night) and being randomised to dexmedetomidine may have resulted in more frequent sedative titration. The bottom line is that we do not know if our results were solely due to a sedative-sparing effect of dexmedetomidine.

In favour of a direct anti-delirium effect of dexmedetomidine are a small number of studies examining dexmedetomidine as a neuroprotective agent. When applied directly to traumatised hippocampal slice cultures, dexmedetomidine exerted a neuroprotective effect (1). In a

rat model of focal ischaemia, dexmedetomidine (compared to saline) reduced infarct size despite also inducing mild hypotension (2), an effect that appears mediated by NF- κ B and COX-2 (3). Clinically, randomisation to intraoperative dexmedetomidine infusion compared to placebo, in the context of standard anaesthesia care including propofol induction and sevoflurane maintenance, was associated with less postoperative confusion, and serum levels of TNF- α , NSE and IL-6 were less (4).

Our trial enrolled patients who could not be extubated only because the degree of their agitation and delirium made lessening their sedation unsafe. By definition, then, they were largely recovered from their initial critical illness. We chose this restrictive entry criterion to increase the dexmedetomidine signal-to-noise ratio: a more eclectic mix of patients at various stages of their critical illness would have had a more diverse range of times to extubation (or ventilator-free hours in the subsequent seven days)—that is, 'noise' through which it would have been more difficult to appreciate any signal. Our trial therefore does not convincingly show that dexmedetomidine is a useful adjunct for treating agitation and delirium earlier in critical illness. However, there is no reason to expect that it would not help in this context, and the various dexmedetomidine-as-sedative trials [including the one containing a subgroup analysis of the 60% of patients with delirium at time of trial entry (5)] suggest that it would be beneficial.

At the doses used in our trial, dexmedetomidine preserves airway reflexes and respiratory drive, making it suitable to continue after extubation. This raises the question of its possible utility in patients who are not initially intubated. Anaesthetists have found dexmedetomidine useful for monitored anaesthesia care in non-intubated patients (6),

and dexmedetomidine was found to be more effective than midazolam in a small randomised trial amongst patients intolerant of non-invasive ventilation (7). There is only one description of dexmedetomidine use on general wards: in 33 postoperative gynaecology patients randomised to dexmedetomidine or placebo, infusion of low-dose dexmedetomidine on a general ward was safe and was associated with lower reported pain scores (8). Many non-intubated, non-critically ill patients with agitated delirium are frail and elderly, so conducting such a trial would require considerable caution; nonetheless, there is currently no data showing such an approach would be unsafe.

There is some concern that dexmedetomidine, an α_2 agonist, might be contraindicated in critically ill patients who are already hypotensive. This was not observed in the DahLIA trial, but our patients had essentially recovered from their critical illness at the time of trial entry. However, prolonged sympathetic stimulation in response to septic shock might cause reduced adrenergic-receptor responsiveness, which might be reversed by an α_2 agonist. While this argument seems counterintuitive, two experimental series in an ovine sepsis model have demonstrated improved pressor responsiveness with both dexmedetomidine and clonidine (another α_2 agonist) (9,10). As with all sedatives, the haemodynamic effects of dexmedetomidine must be monitored and the drug titrated accordingly. There is little evidence that dexmedetomidine causes more hypotension than alternative sedatives such as propofol or midazolam.

It is important to note that our trial protocol added dexmedetomidine to standard care. Some clinicians have reflected to the trial authors that their experience of dexmedetomidine is less positive than we reported. This may or may not be true if dexmedetomidine is used as a single agent: we did not test this in the trial. Intensive care medicine has the luxury of immediacy of response, making titration of therapy paramount and persisting with strategies that are ineffective in a particular patient illogical. We showed that, on average, adding dexmedetomidine to standard care (including sedation, opioid analgesia and antipsychotic drugs) and reducing the doses of other sedatives if possible was beneficial. This is a quite different strategy to thinking that 'dexmedetomidine cures delirium'.

What are the remaining questions regarding the role of dexmedetomidine in the 'ICU cognitive triad' of sedation, analgesia and delirium control (11)? The qualitatively different, seemingly lighter, sedation produced by dexmedetomidine suggests it may be useful in a multimodal

strategy to target maximal interactivity from very early in the ICU stay. This strategy, compared to standard care, is currently the subject of a 5000-patient randomised controlled trial (Early Goal Directed Sedation compared with standard care in mechanically ventilated critically ill patients: 'SPICE' NCT01728558). The questions about use as an anti-delirium agent earlier in the ICU stay and in non-agitated delirium are valid, but many (including many of the DahLIA investigators) would now lack equipoise for such a trial. The possible utility of dexmedetomidine in delirious patients who have never been intubated is particularly enticing, especially if it could be shown that such patients could be nursed safely outside of intensive care units.

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Footnote

Conflicts of Interest: Dr. Reade reported receiving single fee of a \$1,000 in 2009 to contribute to a Hospira clinician advisory board preparing guidelines for the use of dexmedetomidine.

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