Editorial

Dexmedetomidine: magic bullet or firing blanks?

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Introduction

Postoperative delirium (POD) is a major source of morbidity after both cardiac and major non-cardiac surgery. It is common, occurring in 4–54% of patients, depending on patient's age, comorbidities, and type of surgery (1). POD is linked to accelerated functional decline, and an increase in relative risk of death by 10–20% for every 48 hours of duration of POD (2). Potential practices for reducing the incidence and severity of POD are therefore a major area of active research during the perioperative period. A recently published randomised controlled trial by Su *et al*. (3) has shed new light on the place of dexmedetomidine for POD prophylaxis.

In a well-designed and powered double-blinded randomised controlled trial, these authors selected 700 elderly patients having major non-cardiac surgery under general anesthesia, and receiving either 0.1 µg/kg/hr of dexmedetomidine or placebo (intravenous normal saline), from the Intensive Care Unit (ICU) admission immediately after surgery, until 8 am the next morning. The inclusion criteria were pragmatic: intubated and non-intubated patients were included, with no selection as to type of surgery. Standard contraindications to dexmedetomidine administration were used as exclusion criteria. A wide variety of pain management techniques (including epidural, opioid-based intravenous patient controlled analgesia, and oral opioids) and sedatives (propofol, midazolam, haloperidol) were employed as standard care.

The primary endpoint was the incidence of POD, which was assessed by the Confusion Assessment Method for ICU twice daily during the first 7 postoperative days. POD was reduced in the dexmedetomidine group by the absolute of 14% (9% *vs*. 23%; P<0.0001). The secondary endpoints of time to extubation (4.6 *vs*. 6.9 hours; P<0.0001) and incidence of non-delirium complications (14.9% *vs*. 20.9%; P<0.039) were also significantly lower in the dexmedetomidine group. The intervention group were also less likely to have pain on movement for at least the first 6 hours after surgery [non-verbal rating scale (NRS): 1; P<0.0001], with faster extubation, and better subjective sleep quality (NRS: 2 on day 1, 1 days 2–3; P<0.0001). Length of ICU and hospital stay, as well as all cause 30-day mortality were similar between the two groups.

These findings are similar to previous studies on dexmedetomidine (4-6) *vs*. propofol or benzodiazepines (GABA-agonists) for sedation of mechanically ventilated patients in ICU. However, these studies have all used dexmedetomidine as sedatives, at doses (0.2–1.4 mcg/kg/hr), instead of GABAergic agents (propofol and benzodiazepines). The current study by Su *et al*. (3) is qualitatively different—it uses sub-sedative doses of dexmedetomidine for the first time, as an adjunct to GABAergic agents, the doses of which were not substantially different between study groups. This raises a number of interesting questions: if the effect on delirium reduction is not simply due to reduction in GABAergic drug use, what is the pharmacological effect? Is there a pathological effect caused by the surgery, general anesthesia, or postoperative care that induces delirium, which dexmedetomidine actively prevents and/or treats?

Surgical insult as a cause of delirium

The tissue trauma associated with major surgery causes significant release of major inflammatory mediators, interleukins and cytokines (7). High postoperative levels of Interleukin-6, procalcitonin and C-reactive protein are independent risk factors for delirium in elderly patients (8-10). Animal models have shown that surgically-induced

inflammation is associated with cognitive impairment (11), and is mediated by α_5-subunit containing $GABA_A$ receptors ($\alpha_5GABA_A$rs) (12). It has also been suggested that dexmedetomidine may have a neuroprotective effect through inhibiting α_{2A}-receptors (13,14), as well as through an anticholinergic pathway (15). In addition, dexmedetomidine has direct anti-inflammatory effects on microglia, but these are seen only at concentrations an order of magnitude higher than used clinically (16).

Hypoxia-reperfusion and ensuing glutamate-mediated excitotoxic neuronal death is another mechanism by which major surgery may cause POD and postoperative cognitive dysfunction. This is supported by the observation that factors which are associated with reduced cerebral oxygen delivery, such as major blood transfusion, anemia, and more equivocally hypoxia and hypotension, even if not sustained long enough to cause overt neurological injury, are potent risk-factors for delirium (17). Dexmedetomidine has a protective effect against this form of neurological injury, at least in animal models (14).

A clinically available, safe, effective drug which can reduce perioperative neurological injury via a direct mechanism would be a major breakthrough for perioperative care of patients undergoing major surgery. However, given the low doses involved, this study lends weight to the hypothesis that dexmedetomidine exerts its anti-delirium effect via a subtler mechanism.

General anesthetic agents and delirium

Volatile anesthetic agents, propofol, etomidate, barbiturates and benzodiazepines ($GABA_A$ergic agents) are all $GABA_A$ receptor agonists. The $GABA_A$ receptor is α_5 subunit transmembrane ligand-binding chloride channel, widely distributed throughout the central nervous system, with a wide variety of different isoforms. It is responsible for the reduction in synaptic transmission of the $GABA_A$ergic agents. However, significant numbers of these receptors, particularly the α_5 and δ isoforms, are located extra-synaptically, in areas of the brain associated with hypnotic states. They produce a continuous low-amplitude inhibitory current, which is modulated by the $GABA_A$ergic agents. The precise location and pharmacological behaviour of these receptors can give us some insight into the effect of anesthetic drugs. For example, the hippocampus contains high concentrations of $\alpha_5GABA_A$rs, where they have been demonstrated to be responsible for the amnestic effects of isoflurane. δ subunit containing forms are highly expressed in the thalamus, where they produce hypnotic effects (18). Importantly, the memory-impairing effects caused by α_5GABA_Ar agonists persist long-after the clinical effects of anesthetic agents have passed (19), leading to post-anesthetic memory deficits, and inhibition of $\alpha_5GABA_A$rs immediately reverses this effect (20-22). Interestingly, one group has reported that the α_5GABA_Ar itself is involved in the process by which systemic inflammation induces long-term memory deficits, a process which did not take place in α_5GABA_Ar knockout mice (12). This raises the possibility that postoperative cognitive dysfunction is a result of a "double-hit" mechanism: surgical inflammatory neurological damage, facilitated and enhanced by anesthetic α_5GABA_Ar agonism.

As fascinating as these neuroscientific insights are, we are still some way for having functioning anatomical, physiological and pharmacological model of how hypnotic drugs affect the human brain *in vivo*. Nonetheless, it does appear that anesthesia drug-induced long-term memory impairment contributes substantially to the process of POD, through an extra-synaptic $GABA_A$ mediated mechanism.

To sleep, per-chance to dream?

Sleep-deprivation is a potent cause of short-term memory deficit, disorientation, reduced higher cognitive abilities and parallels the clinical features of POD (23). During natural sleep, the brain cycles through periods or rapid-eye-movement (REM) and non-REM sleep. Both are required for processing of memories and recovery of cognition, and deep, slow-wave, non-REM in particular is associated with physiological repair of neurons which have become damaged (for instance, by surgical inflammation or anesthesia drugs). However, patients in ICU rarely experience sufficient of either of these states, and generally achieve light non-REM sleep, if any (23).

One of the unique properties of dexmedetomidine sedation is its similarity to natural sleep, both clinically, and in laboratory studies, as well as in electroencephalogram and functional magnetic resonance imaging studies (24,25). Benzodiazepines cause a state of sedation which is unlike natural sleep, and while propofol does induce some of the endogenous sleep pathways, its GABAergic properties produce a state more akin to coma. This invites the speculation that some of the delirium-reducing properties of dexmedetomidine may be due to promotion of more natural sleep.

Indeed, in the study by Su *et al.* (3), dexmedetomidine-treated subjects had much better subjective sleep quality on all

of the first three postoperative days, although the effect was strongest for the first night, while the drug was being infused. This effect was striking, in spite of the relatively low dose of dexmedetomidine used, and raises the question as to whether doses which are sub-therapeutic for sedation, may have some undefined role in enhancing sleep homeostasis. This would not be the first time an anesthetic drug was found to have different properties in different dose ranges: ketamine, for example, has been shown to have a profound analgesic effect at doses much lower than used for anesthesia (26), presumably through a neuronal priming or anti-windup mechanism. Clearly more studies are called for.

Summary

For the first time, a well-powered randomised controlled trial has been conducted demonstrating a clinically significant reduction in POD with the use of dexmedetomidine at doses much lower than previously described. While the potential mechanisms by which this effect is induced are not fully clarified, this study adds significantly to the evidence supporting the routine use of dexmedetomidine in anesthesia for major surgery in the elderly. Moreover, if the efficacy of dexmedetomidine in this dose range can be confirmed by other multi-centre trials, the door for its routine use will be wide open.

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Footnote

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