

# Delirium and cognitive decline after surgery: a randomised controlled trial of anaesthetic management to improve postoperative mental health outcome

MTV Chan \*, T Gin

## KEY MESSAGE

For every 23 elderly (aged  $\geq 65$  years) patients undergoing major colorectal surgery, anaesthetic delivery titrated according to the bispectral electroencephalographic index prevents an episode of postoperative mental disturbance.

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MTV Chan \*, T Gin

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong

\* Principal applicant and corresponding author: mtvchan@cuhk.edu.hk

Previous clinical trials and animal experiments have suggested that long-lasting exposure to general anaesthetics may lead to postoperative mental disturbance. Intraoperative monitoring of processed electroencephalogram (EEG), such as the bispectral index (BIS), has been shown to facilitate titration of anaesthetic drug delivery.<sup>1,2</sup> The BIS monitor analyses raw EEG signals and displays a dimensionless number, ranging from 0 (isoelectric EEG) to 100 (fully awake), to indicate the depth of anaesthesia. By aiming at a BIS value between 40 and 60 during anaesthesia, the doses of hypnotic agents administered can be reduced by 11% to 27%.<sup>3,4</sup> However, it is unclear whether a lower dose of anaesthetics with BIS monitoring will minimise anaesthetic side effects, leading to an improvement of cognitive function after surgery. We have recently published study to evaluate the impact of BIS-guided anaesthesia on postoperative mental health in elderly patients undergoing major surgery.<sup>5</sup>

The Cognitive Dysfunction after Anesthesia (CODA) Trial recruited 921 patients aged  $\geq 65$  years having general anaesthesia for major colorectal surgery. Patients were randomised to receive either BIS-guided anaesthesia ( $n=462$ ) or routine care ( $n=459$ ), in which anaesthetic drug administration was titrated according to clinical judgement. All patients were interviewed before surgery and at 30 days and 3 months after surgery for objective neuropsychology assessments. A cognitive failure questionnaire was used to measure subjective change in perception, memory, and motor function. Patients were monitored daily after surgery until discharge to detect complications and occurrence of delirium using the Confusion Assessment Method criteria.

Anaesthesia guided by BIS reduced anaesthetic drug dosage as indicated by a reduced volatile

anaesthetic concentration by 29.7% (95% confidence intervals [CI], 25.9-32.8,  $P<0.001$ ) and estimated propofol effect site concentration by 20.7% (95% CI, 12.1-31.9,  $P<0.001$ ). The mean  $\pm$  standard deviation BIS value during surgery was higher in the BIS-guided group than in the routine care group ( $53.2 \pm 8.9$  vs  $38.6 \pm 6.5$ ,  $P<0.001$ ). The amount of time when BIS  $<40$  was also lower in the former than latter ( $7.2 \pm 7.8$  vs  $22.8 \pm 7.3$  minutes,  $P<0.001$ ).

Compared with routine care, BIS-guided anaesthesia decreased the risk of postoperative cognitive decline (14.7% vs 10.2%,  $P=0.02$ , Fig), and the number needed to treat was 23 (95% CI, 6-391). The benefit of BIS monitoring was unchanged after adjusting for age, gender, education status, average BIS value during anaesthesia, and postoperative delirium while in hospital (adjusted odds ratio, 0.67; 95% CI, 0.32-0.98;  $P=0.025$ ). Compared with routine care, BIS-guided anaesthesia decreased the rate of postoperative delirium (24.1% vs 15.6%,  $P=0.001$ , Fig). Thus, BIS-guided anaesthesia decreased the risk of postoperative delirium during initial hospitalisation by 35% and cognitive decline at 3 months after surgery by 31%. The CODA Trial highlighted the potential harmful effects of deep anaesthesia, commonly defined as BIS of  $<40$ .<sup>6</sup> However, a randomised controlled trial comparing two distinct levels of anaesthetic depth is needed to establish the causal relationship. In collaboration with the Australian and New Zealand College of Anaesthetists Trials Group, we have initiated the Balanced Trial (Australian New Zealand Clinical Trials Registry No: ACTRN12612000632897) to determine the impact of light versus deep general anaesthesia on postoperative adverse outcomes (including delirium and other mental disturbance), in 6500 moderate to high risk patients having major

non-cardiac surgery.<sup>7</sup>

In conclusion, the CODA Trial indicated that for every 1000 patients undergoing major surgery, BIS-guided anaesthesia prevented 83 patients from suffering delirium during hospital admission and 23 patients from postoperative cognitive decline at 3 months after surgery. Given that intra-operative low BIS values, a long period of deep anaesthesia (BIS <40), and large doses of anaesthetic were predictors of postoperative cognitive dysfunction, BIS monitoring with careful titration of anaesthetics should prevent unintentional deep anaesthesia and may be useful for improving postoperative cognitive performance in the elderly.

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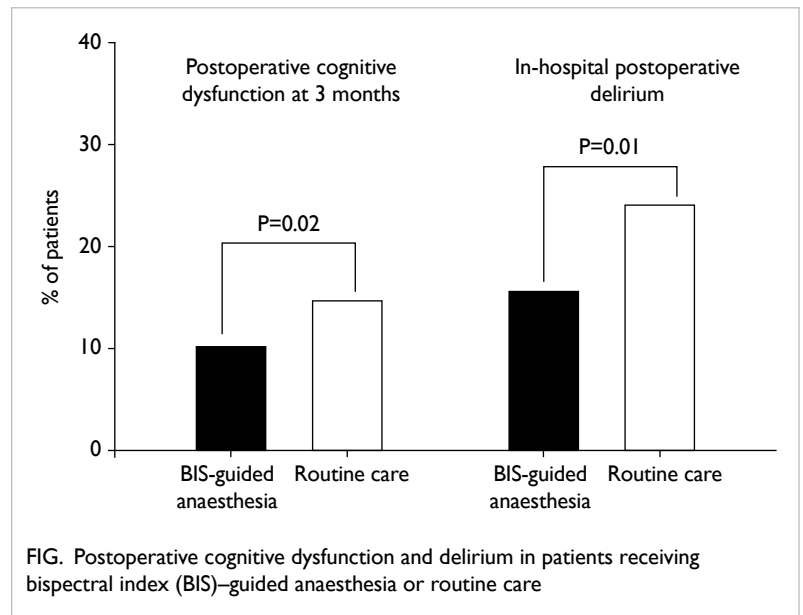


FIG. Postoperative cognitive dysfunction and delirium in patients receiving bispectral index (BIS)-guided anaesthesia or routine care