level was the same in both the control and intervention groups.5

The above mentioned proof-of-concept trials demonstrate that optimal intraoperative management of patients not only have an important role in reducing the incidence of POCD, particularly in elderly patients, but also may lead to an improvement in outcome generally following major surgery.6

It would be very unfortunate if such an excellent review left anaesthetists feeling that POCD was not really much of a problem and even if it was, there was nothing they could do about it. As our population ages, we can no longer be complacent about how our intraoperative management may affect postoperative outcome, and not only in POCD.

Declaration of interest

David Green has received monitoring equipment, travelling expenses, and honoraria from Covidien.

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Neurotoxicity of general anaesthesia is hypothetical

Reply from the authors

Editor—We thank Drs Green, Ballard, and Kunst for their interest in our review article and for their letter. We agree that one of the impressions which anaesthetists may gain from reading our review is that the choice of anaesthetic technique is unlikely to be a major component in the production of postoperative cognitive decline, and moreover, that the evidence for persistent cognitive decline attributable to either surgery or anaesthesia remains inconclusive and controversial.1

We certainly did not mean to suggest that ‘any old anaesthetic’ is acceptable for vulnerable older patients, who might be at risk for such complications as covert stroke, myocardial infarction, and acute tubular necrosis. Minimizing perioperative stress and preventing physiological perturbation is very likely to promote improved postoperative outcomes.2 However, it is not even established that regional anaesthesia is associated with improved cognitive outcomes compared with general anaesthesia,3 let alone that in the absence of physiological derangement slightly lighter general anaesthesia is superior in this regard to deeper anaesthesia. The notion that an isolated general anaesthetic is neurotoxic in older adults is currently speculative.4

Notably, a recent seminal 280 patient randomized controlled trial by Sauer and colleagues5 found that at 7.5 yr follow-up, patients who had undergone off-pump coronary artery bypass surgery had similar or even better cognitive performance than patients who had undergone percutaneous coronary intervention. In his editorial contextualizing this trial, Selnes6 stated, ‘This study by Sauer and associates adds to a long list of previous studies that by now have convincingly demonstrated that surgical interventions for coronary artery disease are not associated with a higher risk of late cognitive decline or Alzheimer’s disease than medical or nonsurgical interventions.’ The control group in this trial had neither heart surgery nor general anaesthesia, yet fared no better cognitively in the long term than those who were exposed to major surgery and lengthy general anaesthesia.

The proof-of-concept CODA trial7 and the trial conducted by Ballard and colleagues8 are certainly important and give pause for thought. The same is true for studies by Radtke and colleagues9 and Sieber and colleagues,10 which, like the CODA trial, found decreased postoperative delirium with lighter general anaesthesia. But all these studies are preliminary; they are hypothesis generating and require independent replication. The scientific literature is replete with initial positive trials that impacted the standard of care but were not replicated in subsequent studies.11 Although the CODA trial found an increase in delirium in the deep anaesthesia group, there was, surprisingly, also a non-significant decrease in postoperative mortality in the deep anaesthesia group.7 The nested, randomized controlled trial by Ballard and colleagues8 included only 81 patients (with 73 contributing to the data analysis), and could therefore not provide a precise estimate regarding a reduction in postoperative cognitive decline with bispectral index- and cerebral oximetry-guided anaesthesia.

We agree with Drs Green, Ballard, and Kunst that anaesthetists should not be complacent regarding the impact of perioperative management on postoperative outcomes, especially in relation to older, more vulnerable surgical patients. However, we also hope that the positive message in our article resonates with the readership of the British Journal of Anaesthesia; when surgery treats pain, decreases inflammation, and improves quality of life, postoperative cognitive improvement is a possible and desirable outcome.
However, this approach is difficult to perform in younger paediatric patients, who will barely tolerate pupillometry performance and will not bear any further manipulation of the surgical wound.

For this reason, we decided to use an approach similar to that of Bosselli and colleagues’ but with the pupillary pain index (PPI). The PPI consists in measuring the changes in pupillary dilation in response to a continuously increasing electric stimulus discharge until 13% of pupillary variation is reached. When a change >13% of the pupil size is detected, the stimulus stops and PPI is calculated by the device. Each electrical stimulation level lasts 1 s, and the increasing stimulus intensity varies from 10 to 60 mA in steps of 10 mA, assigning scores from 1 (when pupillary dilation is <5% despite maximal tetanic stimulation intensity) to 10 (when pupillary dilation rises above 13% with the 10 mA). The lower the score, the greater the impregnation of opioid receptors. This examination is not appropriate for awake children, so we decided to do it immediately before extubation, with minimal alveolar concentration values between 0.5 and 0.8, corresponding to a bispectral index >50. Our hypothesis was the same as that of Bosselli and colleagues, the score obtained would be predictive of the level of analgesia expected in the immediate postoperative period.

We performed a retrospective and observational study with data recorded after balanced (sevoflurane–fentanyl) anaesthesia. Ethical approval for this study (Ethical Committee HULP-Code PI-1217) was provided by the Ethical Committee of Clinical Research of Madrid La Paz University Hospital, Madrid, Spain.

An infrared portable pupillary algesimeter (Algiscan IDMed, Marseille, France) was used to obtain a PPI score immediately before tracheal extubation. Ten minutes after extubation, upon arrival in the postanaesthesia recovery unit, the VAS score (if the patient was co-operative) and/or a Spanish observational pain scale score (LLANTO scale) were assessed and recorded.

Twenty children were included. They were scheduled for several surgical procedures, including general, trauma and otorhinolaryngology surgery. The median age was 3.5 years. The average intraoperative fentanyl dose employed was 4 μg kg⁻¹. In this group of patients, PPI presented a statistically significant correlation (r=0.62, P=0.0038) with the LLANTO scale but not with VAS (r=0.05, P=1.5).

The PPI is a very simple way to measure the nociception/analgesia balance, and it can be employed even in very young children when they are still under residual anaesthesia. The PPI could be correlated only with the LLANTO scale, because VAS is a subjective scale influenced by many psychological factors, especially in children. An ANI monitor may be influenced by these psychological factors to a more important extent than pupillometry.

The measurement of PPI immediately before extubation after sevoflurane–fentanyl anaesthesia was significantly associated with the observational pain intensity measurement upon arrival in the postanaesthesia care unit. The measurement of PPI under these circumstances can be predictive for immediate postoperative pain in a simple and effective way.

**Immediate postoperative pain can also be predicted by pupillary pain index in children**

Editor—We have read with great interest the article by Bosselli and colleagues regarding the usefulness of a new analgesia/nociception index (ANI). The idea of effectively predicting late postoperative pain during the intraoperative period, when the anaesthetist can still manage analgesic drugs to avoid patients’ awakening in pain, is universally interesting. The article’s authors found an improved correlation between pre-extubation ANI and postoperative visual analogue scale (VAS) compared with the correlation between postextubation ANI and postoperative VAS that these authors had obtained in a previous work.

Pupillometry has been postulated as an alternative to ANI for the assessment of postoperative pain and assesses the pupillary dilation response to a stimulus in the operative site.

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**Declaration of interest**

None declared.

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