Postoperative cognitive dysfunction and dementia: what we need to know and do

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Abstract

Approximately 12% of apparently previously cognitively well patients undergoing anaesthesia and noncardiac surgery will develop symptoms of cognitive dysfunction after their procedure. Recent articles in this Journal have highlighted the difficulties of confirming any clear links between anaesthesia and cognitive dysfunction, in part because of the lack of consistency regarding definition and diagnosis. Postoperative cognitive dysfunction (POCD) is usually self-limiting and rarely persists in the longer term, although plausible biological mechanisms for an impact on brain protein deposition do exist. Clinical research studies are frequently confounded by a lack of agreed definitions and consistency of testing. Preoperative assessment of neurocognitive function and risk factor identification is imperative in order to ascertain the true extent of POCD and any causative link to anaesthesia and surgery. At present a multidisciplinary care bundle approach to risk factor stratification and reduction is the most attractive management plan based on evidence of slight benefit from individual interventions. As yet no individual anaesthetic technique, drug or mode of monitoring has been proved to reduce the incidence of POCD. Providing patients with appropriate and accurate information can be difficult because of conflicting evidence. The Royal College of Anaesthetists' patient liaison group has produced a useful patient information leaflet that is designed to provide guidance in discussions of individual risks whilst considerable uncertainties remain.

A proportion of apparently previously cognitively well patients undergoing surgery and anaesthesia will develop symptoms of cognitive dysfunction after their procedure. There is a suggestion that this is most marked in those over 65 yr of age, of which there are currently 10 million people in the UK and with a projected total of 19 million by 2050, representing significant numbers of people at potential risk.[1] Clearly any link of cognitive dysfunction with anaesthesia and surgery is of concern and anaesthetists should be aware of the current evidence base and make attempts both to

counsel patients appropriately and adopt techniques that minimize any further insults to high-risk patients. This review provides an overview of current clinical and research evidence regarding considerations for anaesthesia provision for patients considered to be at risk of postoperative cognitive dysfunction (POCD).

Several forms of cognitive dysfunction can occur in the perioperative period all of which are characterised by problems in thinking and perception. The earliest of these, delirium, occurs 24 to 96 h after a procedure and is manifest as an acute confusional state with disturbance in attention and reduced awareness of the environment. The National Institute for Health and Care Excellence (NICE) guidance on delirium, CG103, suggests pharmacological therapy if the patient is distressed by their symptoms or is a risk to others.[2] However there is considerable benefit in pro-active management of surgical patients at risk of delirium, for example reviewing the need for drugs with antimuscarinic actions that are known to be triggers for delirium such as ranitidine and digoxin, whilst being observant for the effects of nicotine and alcohol withdrawal. Delirium increases length of stay in hospital and associated costs such as use of critical care facilities, and has also been associated with increased mortality.[3–8] Patients over the age of 65 yr with a hip fracture or severe illness and already possessing a degree of cognitive impairment are particularly at risk, although multiple tools for assessing delirium risk are in use and their agreement as tools for risk stratification is poor.[3] Although delirium has not however been definitively linked to long-term cognitive impairment or dementia,[4] recent studies do implicate such a link.[5–7]

A persistent degree of cognitive impairment has been noted in up to 10% of elderly patients up to three months after a surgical procedure. When this persists beyond six–12 months it may be indicative of a more persistent state that some authors consider to be a form of long-term cognitive impairment.[8] For many people, any persistent degree of cognitive impairment would be of concern in itself, but there have been additional suggestions that the risks of developing dementia may be higher in older patients, particularly those who receive general anaesthesia.[9–11] Despite these concerns, recent articles in this journal have highlighted the difficulties of confirming any clear linkages in part because of the lack of consistency regarding definition and diagnosis.[12–14]

Definitions

Delirium is a recognisable acute confusional state representing symptoms that may or may not be linked to organic illness.[15] The Diagnostic and Statistical Manual of Mental Disorders (DSM) V recognises delirium and dementia as clearly defined disease entities.[16] In the most recent DSM V guidance, it is included within the category of major neurocognitive disorder and subclassified on its aetiology, for example Alzheimer’s disease.

The four diagnostic criteria for a major neurocognitive disorder are:

1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains
2. Interference with independence in daily activities
3. Not exclusively in the context of delirium
4. No other diagnosis better explains the symptoms

The diagnosis of a neurocognitive disorder requires both a history of cognitive decline and a documented substantial impairment in standardized neurocognitive testing.

Mild Cognitive Impairment (MCI) and specifically the amnestic subtype, is a common neuropsychiatric term encompassing a period between normal cognitive function and dementia (DSM-V: “mild neurocognitive disorder”) thus forming part of a declining cognitive trajectory.[17,18] Mild Cognitive Impairment converts to dementia at a rate of 10% per yr and has been linked with both delirium and POCD.[19] Detection of MCI can be difficult if patients are able to use compensatory mechanisms when in familiar circumstances such as home and family environments. These mechanisms have the potential to fail once the patient is placed in an unfamiliar hospital environment particularly alongside other risk factors for delirium and POCD.

The National Institute of Aging-Alzheimer’s Association 2011 definition of MCI is summarized in Table 1.[20]

Table 1

Definition of mild cognitive impairment (MCI)[20]

Characteristic	Source
A) Concern regarding a change in cognition	*Patient or Informant*
B) Impairment in one or more cognitive domains	*Neurocognitive Testing - e.g. Episodic Memory*
C) Preservation of Functional Independence	*Patient, Informant, Home assessment*
D) Absence of Dementia	*As per DSM-V definition*
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D) Absence of Dementia	*As per DSM-V definition*

Unlike delirium and dementia, no formal definition of postoperative cognitive dysfunction (POCD) has been codified. Neither the DSM nor International Classification of Diseases (ICD) recognises it as a distinct entity. While an international panel works towards a consensus definition and to refine its relation to other neurocognitive disorders, it remains a research construct.[13] At best it is possible to consider POCD as a mild neurocognitive disorder of unspecified aetiology within the confines of DSM V. Further uncertainty exists as to the relationship between POCD and both dementia and delirium. Some studies suggest delirium as a risk factor for both, but it is not clear whether POCD is part of a continuum that culminates in dementia or a distinct entity in its own right. Furthermore evidence suggests that POCD can occur in patients who did not first have delirium.[21] Resolving these relationships will allow better planning of postoperative testing and produce greater diagnostic certainty in future studies.

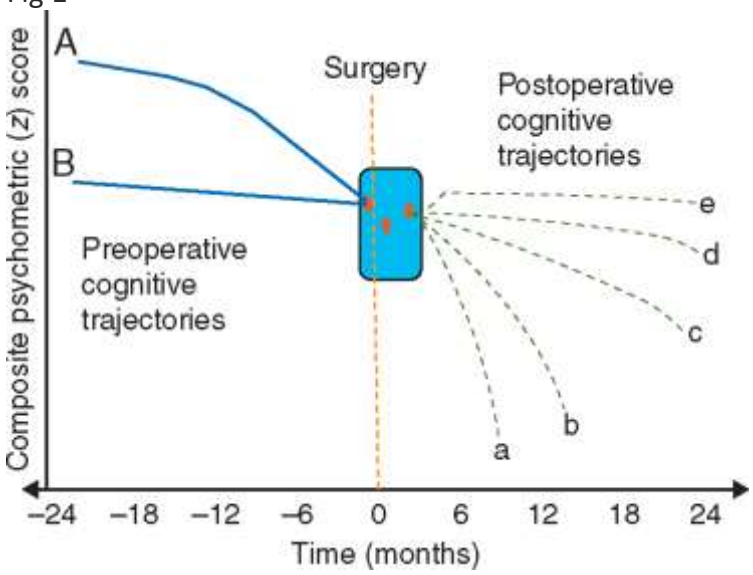
Diagnosis and cognitive testing

POCD is generally described as a form of cognitive dysfunction that begins between seven days and one year after surgery, but limited understanding of the condition to date precludes further categorisation. Given this, diagnosis has relied on administering batteries of neuropsychological tests to patients to observe any decline in function. While diagnosis using either biomarkers[22] or radiological investigations[23] remains under development, so far the cost and mixed results of small studies has prevented widespread adoption and resulted in a situation of relatively fluid descriptive terms. There is no consensus regimen for neuropsychological testing, and this is reflected in the literature. Systematic reviews of studies involving cardiac surgery[24] and non-cardiac surgery patients[25] both show marked differences in the type and number of neuropsychological tests used and the timing and interpretation of statistical significance of the results.

Despite the variation in testing regimens there is growing consensus as regards the best form of statistical analysis with the z-score emerging as the tool of choice.[24] The z-score or standard score is a measure of the number of standard deviations that an observation is from the mean. It is calculated by subtracting the mean (μ) from the observation (x) and dividing by the standard deviation (σ): $z=x - \mu/\sigma$. In assessing POCD it is the difference in preoperative and postoperative test scores that is of interest rather than a single result. To produce a population mean and standard deviation, a control group should be tested at the same intervals as the patient group and the mean difference calculated. Improvements resulting from performing the same test repeatedly are likely, and so the population mean is subtracted from the observed difference in the patients' test scores to control for this learning effect. For any chosen neuropsychological test, the difference in a single patient's preoperative and postoperative test score is subtracted from the mean difference from repeated testing on controls and divided by the control group standard deviation equals the z-score. To produce a dichotomous outcome, a z-score two standard deviations from the mean is considered to be abnormal and diagnostic of POCD.

An additional confounding factor is the point at which testing is performed, as this might give an incorrect impression of an individual's cognitive trajectory. Single point preoperative testing for cognitive impairment will not distinguish between an individual whose cognitive trajectory is worsened, unchanged or even improved by an intervention. For example, in a patient about to undergo total hip replacement, hip pain can impact cognition considerably such that postoperative reduction in pain and improved mobility can produce improvement in an individual's cognitive trajectory.[12]Figure 1 illustrates the difference in cognitive trajectories that can occur and how single point testing fails to adequately distinguish between them.

Fig 1



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Preoperative and postoperative cognitive trajectories. This illustrates possible preoperative and postoperative cognitive trajectories for a single patient. Curve (A) illustrates a patient experiencing cognitive decline before surgery whilst in contrast curve (B) represents a patient with relatively stable cognitive function. A number of postoperative trajectory curves (a-e are possible). In patient (A), curve (b) represents a continuation of the preoperative trend. Curve (a) would be an acceleration of cognitive decline and curve (c) would be a reduction in cognitive decline, or even cognitive improvement. Without knowing Patient A's cognitive trajectory in the pre-op period, curves (a–c) could all be interpreted as POCD. For patient (B), curve (c) shows POCD, curve (d) is no change from the preoperative course, and curve (e) represents a cognitive improvement. Of note curve c can be interpreted as relative cognitive *improvement* for patient (A) and relative cognitive *decline* for patient (B), hence the importance of knowing the preoperative cognitive trajectory for an individual. Reproduced with permission from.[12]

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Debate continues over the optimal timing of perioperative cognitive testing.[12] Test scores can be affected by anxiety, pain and acute medications, therefore testing on the day of surgery should ideally be avoided as a result of these confounding factors. Obtaining more than one episode of preoperative cognitive testing can be problematic[12,18] and potential solutions could include:

- Memory Clinics: either for the general ageing population or linked specifically to surgical specialties
- Primary Care Surgery Clinics: potentially nurse-led
- Separate assessments at Surgical Booking (i.e. at decision to proceed to surgery) and Anaesthetic Pre-assessment

Funding and time-constraints are clear barriers to these potential processes, however this topic is encompassed within the NHS England Commissioning for Quality and Innovation (CQUIN) guidance on Dementia/Delirium,[26] and thus could be considered as part of this nationally funded scheme.

Optimal postoperative cognitive testing has been suggested at one week and three months post procedure[27] depending on the clinical picture, absence of confounding factors and a robust follow-up pathway. Formal diagnosis of POCD is again impeded by a lack of definition and requirement for multimodal testing, but a decline in z-scores using one of the tests below should prompt consideration for referral to an appropriate specialist for further assessment (e.g. care of the elderly or psychiatric services).

Formal and appropriate testing of cognition is imperative in risk stratification for both delirium and POCD. Cognitive assessment tools such as the Abbreviated Mental Test (AMT) and Mini-mental state examination (MMSE) are widely used worldwide for screening and diagnosing dementia, however both lack the sensitivity and specificity to detect subtle cognitive impairment such as MCI.[17,28] There are numerous neurocognitive tests available for detecting MCI, however many are time consuming and lack either sensitivity or specificity.[17,28–30] Those that hold the most promise for use in a preoperative clinic environment include the Montreal Cognitive Assessment Tool (MoCA), Addenbrooke's Cognitive Exam (ACE-III) and the Quick MCI Screen (Qmci). These are summarized in Table 2, and further details are provided in Supplement Material S1.

Table 2

Summary of MoCA, ACE-III and Qmci test characteristics.[17,28–33] **Figures from original validation study*,[32,] *lower figures quote 48–68%*[29]

	MoCA (Version 8.1)	ACE-III	Qmci
Total Score	30	100	100
Cut Off Score for MCI	26	82–88	62
Average Time to Complete	10 mins	16 mins	5 mins

	MoCA (Version 8.1)	ACE-III	Qmci
Sensitivity %	90	84–93	90
Specificity %	87*	100	87
Limitations	Designed to suspect MCI rather than Dementia	Lack of discriminatory cut off scores between MCI & Dementia	Needs larger scale studies to validate use in detecting MCI
Available at	www.mocatest.org	*dementia.ie*	https://academic.oup.com/ageing
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	MoCA (Version 8.1)	ACE-III	Qmci
Available at	www.mocatest.org	*dementia.ie*	https://academic.oup.com/ageing

Both MoCA and ACE-III are used in many UK centres, particularly in stroke, care of the elderly and neuropsychiatry services. The Montreal Cognitive Assessment tool has been studied in vascular, neurosurgical, and emergency general surgery patient populations including assessment outcomes in carotid endarterectomy, traumatic brain injury and subarachnoid haemorrhage patients.[34–37] The ACE-III test is the most recent version of the examination with improved specificity for detecting dementia, but its use in surgical patients is not established.[33] The quick MCI screen was adapted from the AB Cognitive Screen 135 with evidence of improved ability to differentiate between normal cognition, mild cognitive impairment and dementia.[38] Large scale studies are ideally required to validate use of these cognitive tests in perioperative practice. The results of these tests should be matched against age, gender, education and cultural background of the individual being tested [12] and should be delivered by specifically trained staff with concomitant consultation with specialists in old age and neuropsychiatry for more formal assessments where concerns arise.

Prevalence and incidence

Dementia disease processes are estimated to double in incidence in the next 30 yr, and 48% of unplanned hospital admissions above 80 yr of age will have detectable disease.[39] Similarly the incidence of delirium varies depending on patient population and sampling methodologies.[40] Studies for vascular surgery patients quote incidences of 5–39%.[41,42] Numerous studies have been carried out to estimate the prevalence of POCD in the post-surgical population. Comparison of these reveals striking heterogeneity in the study populations, tests and follow-up period used; therefore a wide range of prevalence is quoted in the literature.[24,25]

In non-cardiac surgery a systematic review identified 19 studies and aggregated their results to give an incidence of 11.7% amongst the 6477 identified patients at three months of follow-up.[25] However, many of the studies included older patients undergoing higher risk surgery, and therefore the risk among an unselected UK hospital cohort is likely to be very different. For example the prevalence of POCD in patients undergoing elective hip surgery has been estimated to be 22%.[43] Amongst cardiac surgery patients the rate of POCD may be as high as 60%. However, a systematic review that analysed 62 studies of POCD after cardiac surgery found a 10-fold variation in quoted incidence as a result of differences in study populations and the protocols used

to detect POCD.[24] Further work is required but all indications are that a significant number of people will be affected by POCD after surgery.

Another focus of ongoing study has been the follow up of patients with POCD to establish whether the condition is self-limiting or progressive. A subgroup of participants in the original international multicentre study on long-term postoperative cognitive dysfunction (ISPOCD 1) study were followed up between one and two years after surgery and compared with non-surgical controls.[44] The incidence of test results indicative of POCD was 10.4% and 10.2%, respectively, with only 0.9% of patients consistently showing cognitive impairment at all three time points (one week, three months and one to two years). A longer term follow up of the same cohort 10 yr after the initial study found no association between a subsequent diagnosis of dementia and a prior diagnosis of POCD at either one week or three months post-surgery.[45] This study suggests that POCD developing in the postoperative period can largely be reversible and rarely persists in the longer term.

Risk factors

Risk stratification to enable identification of those at high risk of developing delirium and POCD does not yet exist in a robust form in most UK surgical centres. Thus preoperative counselling and any potential optimisation processes cannot be targeted to any reasonable degree of accuracy. Identification of risk factors has been beset by methodological problems but a number of case-control, retrospective and prospective studies have tried to characterise the risk factors for developing POCD. Paredes and colleagues[25] found that increasing age was the most common risk factor and was identified in seven of the 24 studies analysed. Other risk factors identified in multiple studies were fewer years of education, postoperative delirium and the use of sedative drugs.[13,27,46] Multiple additional risk factors were noted in single studies namely; depression, previous stroke, postoperative infection, postoperative pulmonary complications, lacunae on brain imaging and total time spent with Bispectral Index (BIS) readings lower than 40 as summarized in Table 3.[25,46]

Table 3

Comparison of perioperative risk factors for delirium and POCD

Delirium[46–48]	**POCD**[13,25,27,46]
Age >65 y	Increasing age

Delirium[46–48]	**POCD**[13,25,27,46]
Visual/Hearing Impairment	Poor education (shorter time in school education)
Acute Admission/Emergency Surgery	History of cerebrovascular disease with no residual impairment
Alcoholism/Substance Misuse	Duration and Type of Surgery (Cardiac, Orthopaedics and Vascular)
Pre-existing Cognitive Impairment	Pre-existing Cognitive Impairment
Abnormal Electrolytes/chronic kidney disease	Poor functional status
Poor nutrition/Poor functional status	Postoperative respiratory complications
APACHE 2 scores >16	Postoperative infections
Type of Surgery (e.g. Major Vascular/Cardiac)	Time spent with BIS<40 (inconclusive)
Polypharmacy	
Frailty	
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Frailty	

Screening tools for those at risk of delirium already exist but are not universally used. Marcantonio and colleagues[47,48] developed and validated prediction models for delirium in both non-cardiac[47] and cardiac[48] surgical patients. The former uses seven risk factors including age>70 yr, pre-existing cognitive impairment, poor functional status, self-reported alcohol abuse, electrolyte disturbances and major vascular surgery.[47] Scores are graded into low, moderate and high risk for delirium. The American Geriatric Society consensus statement on delirium suggests that two or more of the factors in Table 3 should prompt prevention measures.[49]

Formal risk stratification for POCD is not currently possible because of the lack of definition and identification as discussed above. However use of the above named risk factors could be used to trigger referral for more formal cognitive testing and consideration of any preventative measures. Type of surgery may potentially play a role with one single centre cohort study of 1064 patients showing increased risk of early (but not late) POCD with major thoracic, intra-abdominal and orthopaedic procedures.[50]

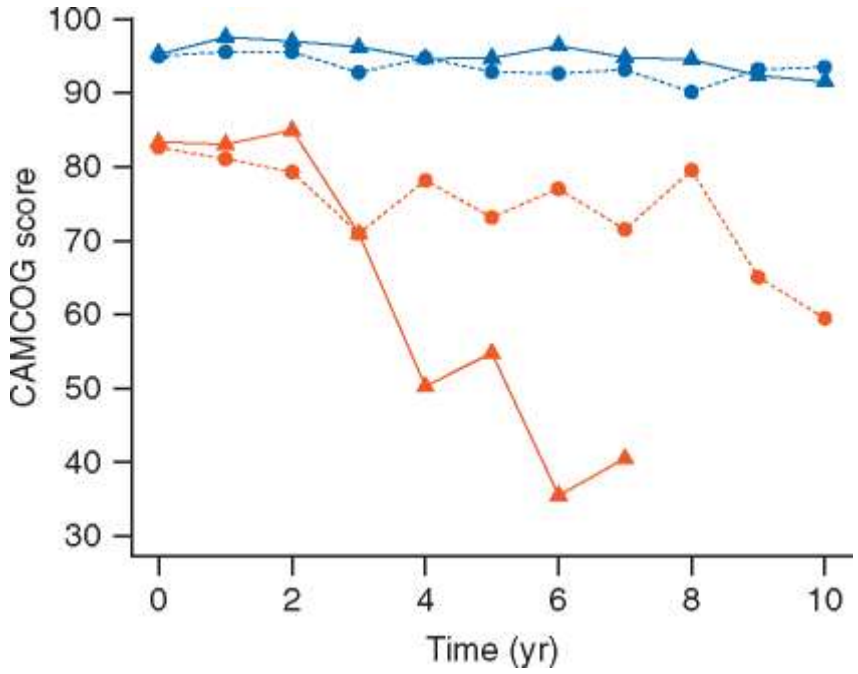
Anaesthesia and dementia

Whether or not anaesthesia can lead to dementia is of increasing interest. It has been the subject of case-control, cohort and prospective studies which have yet to yield a conclusive answer. A 2011 meta-analysis of 15 case-control studies failed to find any association between general anaesthesia and subsequent Alzheimer's dementia (AD).[51] Encompassed within the meta-analysis, two studies investigated an association between regional anaesthesia and AD, but again none was found. Supporting this conclusion, a cross-sectional study of over 600 elderly patients in Vienna failed to show a dose-dependent link between number of anaesthetics received and cognitive dysfunction.[52] Subsequent published work has produced mixed results. In Taiwan a recent large case control study of 135 000 records from a national database gave a statistically significant

hazard ratio of 1.99 for dementia associated with anaesthesia.[53] However it was also noted that the anaesthetic cohort was older and burdened to a greater extent by depression and cardiovascular co-morbidities as potential confounding factors. The Taiwan database review conflicts with the results of a large prospective cohort study.[54] Amongst 4000 patients in the ACT (Adult Changes in Thought) cohort, there was no increased risk of dementia in patients who had undergone an anaesthetic and even amongst a group whose surgery was deemed high risk.[54]

Analysis of patients enrolled in the Oxford Project to Investigate Memory and Ageing (OPTIMA) study suggests a more nuanced picture (Fig. 2).[55] Elderly people were recruited into this prospective study as either controls or with MCI, and 394 subsequently underwent moderate or major surgery. Mixed effects modelling of their Cambridge Cognition Examination (CAMCOG) showed that whilst surgery did not precede cognitive decline in cognitively normal patients, in those with a degree of existing cognitive impairment there followed a worsening of function. Criticism of this study remains that there is risk of bias and confounding that casts doubt on any clear link however biologically plausible.[56]

Fig 2



Cognitive trajectories of patients with no existing cognitive impairment (blue) and existing cognitive impairment (orange) who underwent surgery (solid lines) or no surgery (dashed lines). Over 10 yr the cognitive decline of people with existing cognitive impairment was seemingly accelerated by surgery. A cut off of 79 in the CAMCOG is traditionally used to diagnose dementia. Reproduced with permission from.[55]

Biological mechanisms of POCD

While the pathophysiology underlying dementia is the subject of intense and ongoing study, little is yet known about the mechanism by which POCD occurs. Translational research so far has focused on the interaction between anaesthetic agents and the pathological processes of Alzheimer's disease. Histologically Alzheimer's disease is characterised by intraneuronal neurofibrillary tangles, composed of hyperphosphorylated tau protein arranged in paired helical filaments, and extracellular amyloid plaques, composed of Aβ40 and Aβ42 peptides that are the result of aberrant processing of the amyloid precursor protein (APP).[57] The pathological effects of these changes are an increase in neuronal death and loss of synapses, principally of cholinergic neurones of the basal forebrain region. The central cholinergic system is important in the formation and regulation of consciousness, learning and memory, and therefore its degradation by amyloid plaques and neurofibrillary tangles contributes to the observed clinical picture of a global decline in memory, reasoning, judgment and orientation.[57]

Studies involving clinically relevant concentrations of isoflurane, sevoflurane and desflurane all show potentiation of the pathophysiological processes associated with Alzheimer's disease that lead to neuronal death. For example mice exposed to 2.1% sevoflurane for six h showed an increase in caspase-3 activation (a marker of apoptosis) in brain.[58] When exposed to 3% sevoflurane they also found increased levels of APP processing and increased levels of Aβ peptides. Transgenic Alzheimer's disease mice were also found to be more susceptible to sevoflurane induced neurotoxicity when given the same dose and duration of sevoflurane. Whether this work done in cell culture and animal models is clinically relevant requires further study, but evidence of *in vitro* biological change does provide a plausible mechanism whereby general anaesthetic agents could lead to cognitive dysfunction in the postoperative period.[59]

Additional work has been done to investigate putative roles for the processes of neuroinflammation and cerebral microemboli. In rat models both isoflurane and sevoflurane increase permeability of the blood-brain barrier by damaging brain vascular endothelial cells, and this process is more pronounced in older animals.[60] This could allow cytokines and other pro-inflammatory mediators to access the brain and the resulting cellular dysfunction might cause POCD. Cardiac surgery models provide additional hypothetical contributory mechanisms. Micro-emboli formed either from the surgical site or the cardiopulmonary bypass circuit could cause cerebral infarctions leading to POCD. While in population studies small lesions present on diffusion weighted imaging magnetic resonance imaging (MRI) scans are associated with cognitive dysfunction, their role in POCD remains unclear. Several perioperative studies of patients undergoing cardiac surgery demonstrated new postoperative lesions, but proving a temporal relationship with POCD is difficult. From 13 studies identified in a recent review, no firm

conclusions of a causal link could be drawn, in part because of the variable timings of the MRI scans and neuropsychological tests.[18]

While potentially anaesthetic-related modifiable factors such as hypotension, hypoxia and altered cerebral perfusion have been postulated as contributing to POCD, the evidence to support this is weak. The ISPOCD cohort study prospectively recruited 1218 patients aged over 60 yr of age in 13 countries who were undergoing major noncardiac surgery. It failed to show an association between either hypotension or hypoxia and POCD.[27] However there is some suggestion that during cardiac surgery maintaining mean arterial pressures of 80–90 mm Hg may reduce the incidence of both postoperative delirium and cognitive dysfunction. This together with studies showing suggested associations between reduced cerebral oxygenation, as measured by near infrared spectroscopy (NIRS), and POCD, does suggest that cerebral hypoperfusion or hypoxia could be a contributing factor to changes in cognition.[61] It appears therefore that current levels of knowledge regarding the impact of anaesthesia and surgery on POCD are at best patchy and incomplete, and there is considerable need for focus on areas where we can identify and support patients at risk in the perioperative period.

Preparation and optimisation

To date there are no specific treatments available for POCD, but the condition is of concern to some elderly patients, and it is important that anaesthetists and surgeons consider ways to reduce its incidence and engage in discussion of the risks with patients preoperatively. As POCD is likely to be multifactorial, the approach to prevention should be multidisciplinary and include consultation with care of the elderly specialists where appropriate. The Canadian PREHAB study, a randomized controlled trial examining the impact on clinical outcomes of providing preoperative rehabilitation for frail elderly patients before cardiac surgery, is ongoing.[62] It may provide information about the benefits of a pre-optimisation approach as cognitive function will be examined as part of the assessment process.

Preoperative orientation programs in paediatric surgery already exist and have been shown to potentially reduce anxiety levels and improve patient satisfaction.[63,64] Studies into similar processes in adults suggest improvements in postoperative pain, negative emotion and a small reduction in length of stay, but are too heterogeneous to reach a confident conclusion.[65] The orientation process can involve both verbal and written methods including group sessions and hospital tours and ideally would involve a close family member or caregiver.

Chronic disease management

Perioperative medicine is increasingly recognized as a multidisciplinary specialty in its own right, particularly for elderly and frail patients undergoing major surgery.[66] Involvement of care of the elderly specialists is well established for hip fracture patients with good results,[67] but this is less common in other surgical specialties. The Royal College of Anaesthetists 2017 guidelines for provision of preoperative assessment services recommends that older, frail patients have access to a consultant geriatrician, and that joint surgical, geriatric and anaesthetic clinics should be considered.[68] The cost burden of such an assessment process is obvious, but financial savings and improved quality of life could be anticipated as a result of the impact on delirium and POCD and a considerably improved care pathway. There is a need to consider health economic analyses of these type of approaches when planning intervention studies.

Vascular risk factors such as hypertension, obesity, diabetes mellitus and smoking are linked with cognitive decline in the general population.[12,27] It is therefore logical that optimisation of these features would assist in lowering the risk of POCD and dementia. These are also risk factors for postoperative complications such as wound infections and respiratory deterioration that are also linked to delirium and POCD.

Alcohol excess is strongly linked with delirium and long-term cognitive impairment and dementia via cerebral atrophy and vitamin B1 deficiency.[69] There is some evidence that chronic alcohol excess is also a risk factor for POCD particularly in those over 55 yr old.[69,70] Use of benzodiazepines is the most common form of treatment in such cases but confers potential additional risks including delirium itself. Thus preoperative counselling should include a strong emphasis on the cognitive benefit of controlled reduction and if possible cessation of alcohol consumption.

Pre-assessment should also include evaluation and documentation of visual and/or hearing impairments with an emphasis on ensuring access to aids throughout the perioperative period. Preoperative improvement of general health may yield indirect benefits, for example correction of anaemia and electrolyte abnormalities although not directly linked to cognitive dysfunction. Anaemia in isolation is associated with increased postoperative mortality and wound infections. Oral iron therapy in the elderly can be problematic as a result of poor compliance and gastrointestinal absorption, but evidence is building for use of i.v. iron preoperatively,[71] although results from the PREVENTT trial are still pending.[72] Magnesium levels are intrinsically linked to cognitive function with chronic deficiency causing memory impairment alongside muscle weakness and lethargy. Dietary replacement of magnesium has been shown to help in a subset of dementia patients particularly those with Alzheimer's Disease.[73,74] Oral organic magnesium salts such as magnesium citrate have good bioavailability and replacement should aim for an intake of 4–6 mg kg^{-1} day^{-1}.[74] Reduction in fasting times for clear fluids should be considered for those at risk

of POCD and delirium, with the aim to help prevent dehydration and electrolyte disturbances and aid patient comfort.

Polypharmacy in the elderly is associated with postoperative delirium, but the link with POCD is less robust.[30,49] Evidence from the ISPOCD study showed an association between preoperative benzodiazepines and a reduced incidence of cognitive decline postoperatively, however this study did not stipulate the duration or dosage of benzodiazepines, which have themselves been previously linked to delirium.[27] Other studies have failed to show similar results or any link to POCD[75,76] such that benzodiazepine use cannot be recommended in the perioperative period. Continuation of chronic psychoactive medications such as anticholinesterase therapy is important as withdrawal of drugs such as donepezil has been shown to double the risk of nursing home placement in severe Alzheimer's dementia.[77] Medication reviews as part of a comprehensive geriatric assessment in the frail elderly are recommended by the British Geriatrics Society; a meta-analysis of 22 trials using such an assessment approach showing increased likelihood of improved cognition after emergency admission to hospital.[78]

Patient counselling and surgical options

Surgical consent processes do not yet regularly include a discussion regarding the cognitive burden of surgery and anaesthesia, although there is increasing public awareness of the issue.[79] Despite the additional concern this will inevitably place on the patient and family members, POCD is a material inherent risk[25] that alongside other surgical complications deserves discussion. It is generally considered appropriate in English law to inform patients of "a significant risk which would affect the judgement of a reasonable individual," and this concept is engrained into the General Medical Council (GMC) guidance on consent.[80,81] However after recent case law including the case of *Chester v Afshar* (2004) whereby the House of Lords held that a patient was not informed of a risk inherent to the surgery, despite a low probability of occurrence, the Department of Health now advises that healthcare practitioners provide information about all possible serious adverse events and ensure documentation of such a discussion.[80] An individualised approach to the process of consent should take place, taking into account known risk factors, type and urgency of surgery, and the patient's wishes. It may be entirely appropriate to discuss the risks of POCD with a high-risk patient who is concerned about the condition, even if there are no definitive methods to prevent its occurrence.

Moreover the decision to proceed with surgery can be based on the physical burden of disease that can in itself impact on the patient's cognitive function. For example, there is evidence that cardiac surgery, by improving oxygen delivery, reducing pain and symptoms of breathlessness, can actually lead to cognitive improvement[81] (see Fig. 1). However, for patients with milder disease

symptoms who are at high risk for developing delirium, POCD or dementia conservative management of their disease may be more a prudent decision at an individual time point.

Intraoperative prevention

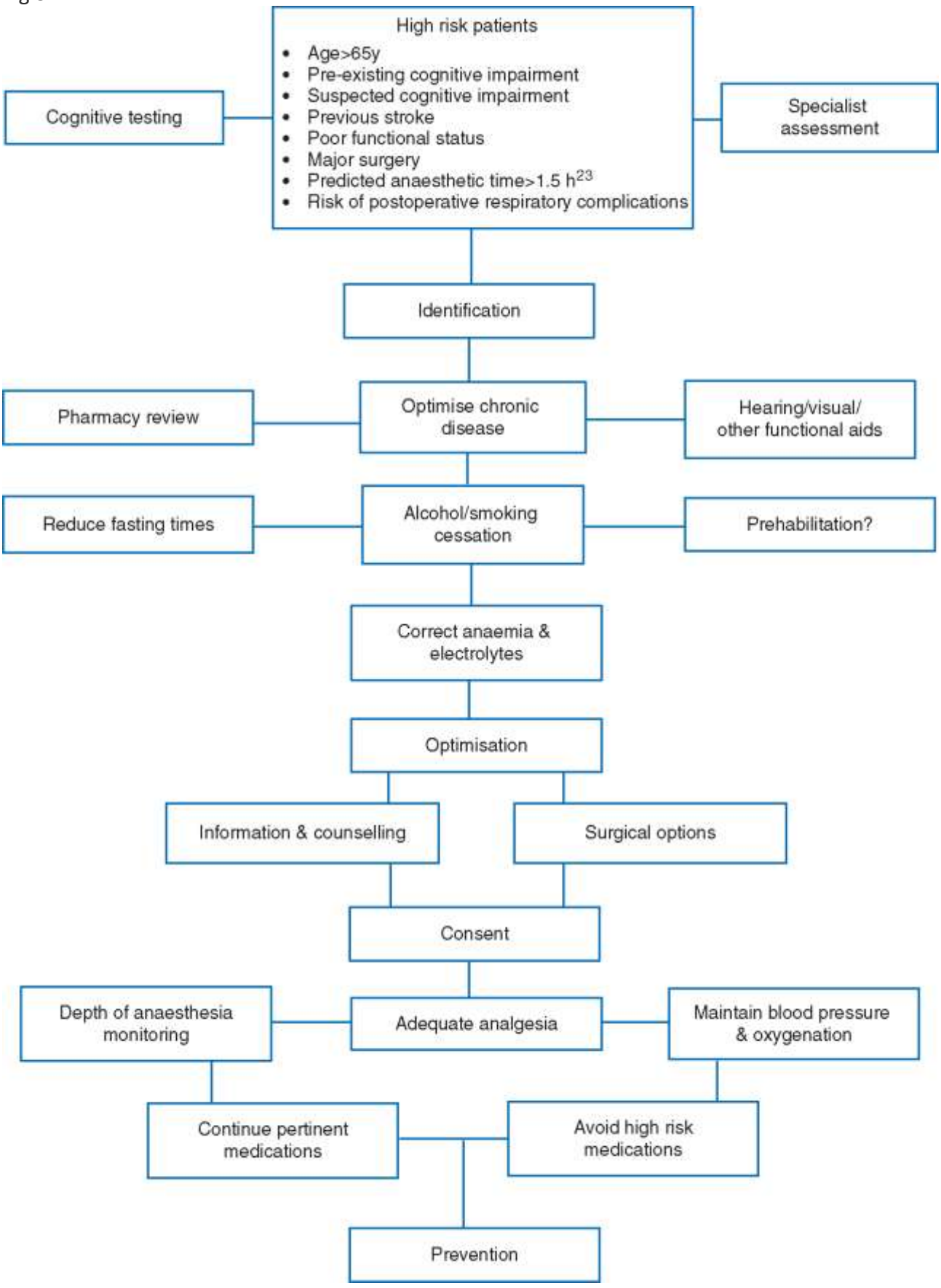
Studies using processed electroencephalogram (pEEG) monitoring to minimize the cumulative time at low BIS levels have given mixed results, but there is growing evidence that pEEG monitoring reduces the incidence of POCD and delirium.[82,83,84] In the largest randomized study of POCD and pEEG, 921 elderly patients undergoing major non-cardiac surgery were randomized to receive BIS-guided anaesthesia with a target of 40 to 60 or standard care.[85] Amongst those in the BIS group there was a statistically significant reduction in POCD from 14.7% to 10.2% at three months postoperatively. Those in the BIS group spent significantly less time with BIS<40 and received lower end-tidal anaesthetic concentrations than the usual care group. The authors estimate that if their study protocol was used more widely, BIS-guided anaesthesia would prevent 23 cases of POCD in every 1000 elderly patients undergoing major surgery. The use of near infrared spectroscopy (NIRS) in cardiac surgery to avoid low cerebral oxygen saturation might also be useful although observational studies have produced inconsistent results.[13,86,87] Conversely the ISPOCD study[27] failed to find any association between hypoxia and POCD in non-cardiac patients.

There is no good clinical evidence that any individual anaesthetic agent reduces the probability of POCD, and in particular no consistent evidence that i.v. anaesthetic techniques offer any advantages. A study by Schoen and colleagues[88] of 128 patients undergoing on-pump cardiac surgery, found significantly less POCD in the first week postoperatively when sevoflurane was compared with propofol for maintenance of general anaesthesia. The opposite was found in 180 patients undergoing lumbar spine surgery; at two years of follow-up the group randomized to sevoflurane showed significant progression in MCI compared with a control group, and there was no significant decline in the propofol group.[89] While it would seem intuitive that regional anaesthesia would confer cognitive protection, once again evidence is lacking, and the heterogeneous nature of trials makes comparisons difficult.[90] Similarly a trial of intraoperative remifentanil in elderly patients undergoing major abdominal surgery failed to show any benefit for its use over fentanyl boluses.[91]

Other developments have included a small randomized controlled trial suggesting the benefits of remote ischaemic preconditioning in patients undergoing cardiac surgery.[92] Another area of ongoing research is the use of antioxidants, and a randomized controlled trial using N-acetylcysteine is underway.[93] With such a limited evidence base, one strategy for managing patients at risk or concerned about developing POCD would be to extrapolate from efforts to reduce the incidence of postoperative delirium. Guidelines[2,94] already exist for this, and would be

expected to yield some benefit for the earlier stages of POCD. Beyond this further research is required and it may be that care bundles can be developed to pool together some of the above interventions. Figure 3 illustrates the authors' suggested approach to managing patients at high risk of POCD who are being considered for surgery.

Fig 3



Suggested flow diagram for the perioperative process of patients at high risk of POCD. Developed by C. Webb, M. Needham, D. Bryden.

Conclusions

Decline in cognitive function after a surgical event and associated anaesthesia is recognized in the elderly population, however providing patients with appropriate and accurate information can be difficult because of many uncertainties. The RCOA patient liaison group has produced a useful patient information leaflet that is designed to provide guidance in discussions of individual risks.[95] Considerable uncertainties remain. Agreed definitions for cognitive dysfunction and identification of appropriate assessment tools are needed in order to ensure appropriate funding and consistency of research approaches. Improved perioperative patient pathways to include involvement of care of the elderly specialists, along with increased training of staff involved in the perioperative patient pathway, are required to help address the increasing numbers of patients anticipated to present to hospital with evidence of, or at risk of, developing cognitive decline in the perioperative period.

Authors' contributions

Study design/planning: D.C.B. Study conduct: Data analysis: Writing paper: all authors Revising paper: all authors

DCB contributed to the design, planning and writing. CEW and MJN contributed to the writing and reviewing of the article.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

D.C.B. is a member of the editorial board of *BJA Education*, and a member of HTA Emergency and Elective Specialist Care Research Panel. M.J.N. and C.E.W.: none declared.

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