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Postoperative cognitive dysfunction

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The target organ for anaesthetic drugs is the brain. For many years, it has been assumed that their effects do not outlast their pharmacological action, that the target organ is restored to its previous state once the agent is eliminated. There is increasing evidence that this is not true, that long term or even permanent neuronal and neurological change can follow administration of anaesthetic drugs. The brain appears to be particularly vulnerable at the beginning and end of its life. Animal studies have suggested that permanent changes may be induced in developing brains,[11 12 23] but this review will concentrate on changes which may occur in the ageing brain. The earliest manifestation of neuronal damage in the brain is a decline in the higher cortical functions of storage and recall of memory and cognitive processing.

The increasingly aged population has stimulated research into premature cognitive decline from all causes. A number of studies have investigated postoperative cognitive dysfunction (POCD), predominantly in the elderly, and these will be discussed together with theories on causation and the limited animal work available thus far.

One of the difficulties of human research in this area is that anaesthesia is hardly ever administered as a sole procedure but is almost invariably given to facilitate surgery. As will be discussed below, the stress response to surgery has been suggested as a possible mechanism for POCD. Thus, in all human studies, the term 'operation' should be understood to include both anaesthesia and surgery.

Definition and measurement

Cognition is defined as the mental processes of perception, memory, and information processing, which allows the individual to acquire knowledge, solve problems, and plan for the future. It comprises the mental processes required for everyday living and should not be confused with intelligence. Cognitive dysfunction is thus impairment of these processes.[34] It is usually expressed by patients in terms of failure to perform simple cognitive tasks, for example to move to another room and, on arrival, to have forgotten the reason for the move, or to be unable to complete mental tasks, such as crosswords, that were previously easily attainable. Such subjective lapses are often characterized as 'senior moments' and have been measured with instruments such as the Cognitive Failures Questionnaire[8] but, being subjective, they are not necessarily the best method for assessing cognitive decline and objective tests of executive and psychomotor function have generally been preferred. The requirements for such tests have been fully reviewed.[35] Space does not permit a full review of all the tests which have been used in studies of POCD, but not all of them have been suitable for the purpose. Many studies have failed to use a normal control group to allow for practice effects; have adopted tests with low sensitivity or those with floor and ceiling effects; or have used tests without validated parallel versions. An example of a test which has been commonly misused in this situation is the Mini-Mental State Examination (MMSE),[17] which was designed as a screening tool in the clinical examination of patients with dementia. Most normal adult subjects of any age score at, or very close to, the maximum with ease. Minor degrees of cognitive decline will therefore not be detected because of a ceiling effect. In addition, it has no parallel versions and consequently the same questions are administered with each application. This permits learning effects in subjects who score just less than the maximum but retain sufficient mental capacity to learn, but not in those who score either very low or the maximum. It is best used in studies of POCD to exclude subjects with a significant degree of pre-existing cognitive dysfunction, as it is difficult to construct tests without ceiling or floor effects, which can be successfully used in subjects with a wide variation in intelligence, education, and cognitive abilities.

The degree of change in a test deemed to constitute POCD has varied widely between studies ranging from a deterioration of 1 SD in one or more tests in a battery to the more rigorous *z*-score.[10] Mean changes in control group scores from baseline to 1 week and baseline to 3 months provide measures of average learning effects, which are subtracted from changes in individual patient's scores from baseline to postoperative test. Each result is divided by the standard deviation of the change in control group scores to give a *z*-score for individual patients in each subtest. Composite

Table 1 Incidence of POCD after 1 week, 3 months, and 1–2 yr (POCD1, POCD2, and POCD3, respectively) and POCI after 1 week and 3 months (POCI1 and POCI2, respectively). Number (%) [95% confidence interval]. Modified from reference[37] by kind permission of the Editor, *Acta Anaesthesiologica Scandinavica*

Group	1 week			3 months			1–2 yr[1]
	POCD1	POCI1	POCD1/POCD2	POCI2	OCD2/POCD3	POCI1	POCI2
Patients ⩾60 yr major surgery GA[26]	266/1031 (25.8) [23.1–28.5]	43/1031 (4.2) [3.0–5.6]	6.2	94/947 (9.9) [8.1–12.0]	58/947 (6.1) [4.7–7.8]	1.6	35/336 (10.4) [7.2–13.7]
Controls ⩾60 yr[26]	6/176 (3.4) [1.3–7.3]	6/176 (3.4) [1.3–7.3]	1.0	4/170 (2.4) [0.6–5.9]	4/170 (2.4) [0.6–5.9]	1.0	5/47 (10.6) [1.8–19.4]
Patients 40–59 yr major surgery GA[24]	89/463 (19.2) [15.7–23.1]	22/463 (4.8) [3.0–7.1]	4.5	26/422 (6.2) [4.1–8.9]	33/422 (7.8) [5.4–10.8]	0.79	
Controls 40–59 yr[24]	7/176 (4.0) [1.6–8.0]	8/176 (4.5) [2.0–8.8]	0.88	7/169 (4.1) [1.7–8.4]	9/169 (5.3) [2.5–9.9]	0.78	
Patients ⩾60 yr minor surgery GA[9]	22/323 (6.8) [4.3–10.1]	28/323 (8.7) [5.8–12.3]	0.79	20/303 (6.6) [4.1–10.0]	22/303 (7.3) [4.6–10.8]	0.91	
Patients ⩾60 yr major surgery GA or RA[36]	59/364 (16.2) [12.6–20.4]	18/364 (4.9) [3.0–7.7]	3.3	48/340 (14.1) [10.6–18.3]	17/340 (5.0) [2.9–7.9]	2.8	

scores are averaged from the individual test scores of the battery. A value of more than/equal to 2 in two or more tests or a composite score more than/equal to 2 from all tests has been used in the International Studies of PostOperative Cognitive Dysfunction (ISPOCD)[1 9 24 26 36] to define POCD.

Test–retest reliability

Test–retest reliability of neuropsychological tests is important in determining whether a true change in cognitive dysfunction has occurred. Random variation will result in an equal proportion of subjects showing 'improvement' or 'deterioration', even if no true change has occurred. If test–retest reliability is poor and only data from subjects showing a reducing score are analysed, a large apparent decline in cognitive function will be claimed even if there has been no true change in cognitive function. Rasmussen has recently reanalysed the data from 2536 patients and 359 control subjects studied in the four published ISPOCD studies,[37] and calculated the ratio of subjects showing improvement to those showing a decline (Table 1). Using this analysis, statistically significant differences between the incidence of POCD and PostOperative Cognitive 'Improvement' (POCI) were present only 1 week after operation in elderly (⩾60 yr) patients undergoing major surgery. The POCD/POCI ratio ranged from 3.3 to 6.2 at the 1-week test in these patients and from 1.6 to 2.8 at the 3-month time point. Test–retest reliability ranged from 0.9 for Letter-Digit Coding to 0.2 for the error score of Part C of the Concept Shifting test.

One explanation for poor test–retest reliability for those tests which have both a time and error component, such as the Stroop and Concept Shifting tests, is a change in patient strategy, trading speed for accuracy, between test periods. Patients who are aware of a 'poor' performance at initial testing may opt for a strategy of reduced speed in completing the task in order to improve accuracy. If time is taken as the measure of cognitive ability then deterioration will be inferred, whereas if accuracy is taken then improvement will be concluded even though no true change in cognitive function has occurred. Clearly, analysis in these circumstances should take account of both factors.

Objective tests do not always agree with the patient's assessment of his or her cognitive status.[15] A university educated, middle-aged, professional man was a normal control subject studied in our centre as part of the ISPOCD 2 programme.[24] Subsequently, he underwent urgent major abdominal surgery followed by early re-operation. In the late postoperative period, he complained of poor cognitive function to a degree where he was forced to take early retirement. We retested his cognitive function using the ISPOCD test battery, which he had completed previously. There were no significant changes from the values obtained previously. It is clear that there is still room for development in cognitive test batteries for the detection of POCD.

Risk of POCD

Before discussing risk factors, it is appropriate to ask if POCD exists or whether it is a consequence of inadequate or misinterpreted neuropsychological test batteries. A recent editorial in the *British Medical Journal*[46] reviewed much of the ISPOCD data and suggested that there was insufficient evidence at present to be sure. It is appropriate also to discuss when POCD can be deemed to have started. Many studies purporting to have been directed at POCD have only studied patients immediately after surgery or within 1–2 days thereafter. Clearly, patients who are still under the influence of anaesthetic or analgesic drugs may have impaired cognitive performance. This is of significance if they are expected to remember instructions or carry out complex tasks, such as driving a motor vehicle but, in the author's view, this does not constitute POCD. The earliest test point should be about 1 week after surgery once centrally acting analgesics are no longer required and any active metabolites have been eliminated.

Motivation may be a problem also in the early postoperative period. In a subjective account reported by Pockett,[33] a patient describes how she felt after consciousness returned: 'The thing was, I felt actually rather good in general, but nothing seemed to *matter* . . . Thus when a nurse came to see if I was awake, although I was actually very much awake and feeling quite pleasant and well disposed towards this solicitous person, it seemed to be just too much trouble to answer the questions. She went away convinced I was still asleep'. False negatives were encountered in a study of mid latency auditory evoked responses to awareness with patients who heard the command (and thus were aware) but could not be bothered to respond.[28]

Post-cardiac surgery

The greatest incidence of POCD and the greatest number of studies is in patients undergoing cardiopulmonary bypass surgery (CPB) (for example see[22 34 45]). Many of the studies do not meet the stringent criteria set out by Rasmussen,[36] but there are sufficient large scale studies using appropriate test batteries and control groups to be sure that POCD, both early and late, does occur in these patients and is common. The potential for brain injury in these patients, including hypoperfusion and micro-emboli, is self-evident and POCD is thus not surprising. However, two studies used the same test battery and methodology in both cardiac and major abdominal surgical patients and reported a similar or greater incidence of POCD in the non-cardiac group.[40 50]

Before the 1990s, most reports of POCD in non-cardiac surgery were anecdotal and were generally felt to be a response to some perioperative catastrophe, which may or may not have been noted by the medical attendants. The advent of pulse oximetry in the early 1980s and its subsequent widespread adoption into anaesthetic practice resulted in a large number of studies of oxygenation throughout the perioperative period. A number of studies demonstrated marked hypoxaemia at night which was at its worst on the second to the fourth night after surgery.[16 41] Other studies showed that this was a result of rebound of slow wave and rapid eye movement sleep on those nights, following their suppression on the first postoperative night coupled with the parallel decline in lung function. This previously unreported hypoxaemia seemed to be the obvious cause of several postoperative complications including myocardial ischaemia and infarction and cognitive dysfunction. Möller, having conducted a major study of the benefits of pulse oximetry in anaesthetic practice,[25] co-ordinated an international group of investigators (ISPOCD) to test the hypotheses that POCD existed, that it was more likely in the elderly and that it was because of postoperative hypoxaemia and/or hypotension. 1218 patients, aged over 60 yr, were studied with a brief neuropsychological test battery and continuous physiological monitoring before and 1 week and 3 months after major surgery. A subgroup of 336 patients was studied again 1–2 yr later. Forty-seven normal subjects were studied with the same test battery at the same time intervals. POCD was defined as a z-score of more than 2.0 as described above. The results are shown in Table 1.[1 26] The investigators concluded that POCD existed and age was a major risk factor. Neither hypoxaemia nor hypotension nor the combination, were risk factors for POCD. The same group went on, in a second multicentre collaborative programme of research (ISPOCD2) using very similar methodology and the same test battery, to investigate further whether POCD followed minor surgery in the elderly and major surgery in the middle aged. They concluded that POCD was present to a very small degree in the elderly after in-patient minor surgery after 1 week but not at 3 months.[9] The same was true for the middle aged undergoing major surgery (Table 1).[24]

While there are a number of other studies of POCD in non-cardiac patients,[3] they have generally been small and the differences in methodology and criteria for the definition of POCD have been such that a meta-analysis is not appropriate. The ISPOCD studies remain the largest and best controlled of the studies conducted to date although it could properly be questioned whether the psychometric test battery was sufficiently sensitive and robust. As noted above, Rasmussen[37] has re-analysed data from all patients who participated in the ISPOCD studies to examine the effects of test–retest variability. He concluded that by comparing the ratio of POCD with POCI, he could be confident of cognitive decline only in elderly patients 1 week after major surgery. Only 30–48% of patients with POCD at 3 months also had POCD at 1 week. POCD may be progressive and only become apparent several months after surgery. Similar results have been found after cardiac[44] and carotid artery surgery.[19]

The evidence for POCD following cardiopulmonary bypass (CPB) is much stronger, not least because the incidence is generally greater. Newman[27] found an incidence of 53% at discharge from hospital and an incidence of 36, 24, and 42% 6 weeks, 6 months, and 5 yr, respectively, after surgery. Early decline predicted late decline. Similar findings have been reported by Stygall and colleagues.[47] However, neither study used a rigorous definition of POCD nor a control group to control for learning effects. Such studies raise the possibility that operation is a risk factor for early cognitive decline, including in Alzheimer's disease (AD). Further evidence comes from recent studies by Bednar and colleagues (B. Wolozin, personal communication, 2004). The development of AD 5–6 yr after surgery was determined in 5216 patients who had undergone coronary artery bypass grafting (CABG) and compared with 3954 patients who had undergone percutaneous transluminal coronary angioplasty (PTCA). The adjusted risk of CABG *vs* PTCA was 1.71 (95% CI, 1.02–2.87, P=0.04). However, in a further study, the same group compared the incidence of AD patients who had undergone either a prostatectomy or a herniorraphy under general (GA) or loco-regional anaesthesia (LA). After controlling for age, duration of hospitalization, co-morbidity, and number of procedures in a Cox

proportional hazard model, the adjusted risk of GA *vs* LA was 0.65 (0.43–0.98) and 0.71 (0.49–1.04) for herniorraphy and prostatectomy, respectively. The authors suggest that this may indicate that GA may delay the onset of AD. As the patients were not randomly allocated to LA or GA however, it may indicate also that frailer patients had their operations under LA. (Abstracts of these papers (S1-03-06 and P3-437) may be found at: http://www.elan.com/icadrd/.)

Loss of olfactory function has been shown to be an early marker of cognitive decline, often preceding clinical symptoms by up to 2 yr.[14] Using the same protocol and test battery as in the ISPOCD studies, odour identification ability was measured in a pilot study, before and after major surgery in the elderly, to examine whether any perioperative change in olfactory function correlated with development of POCD, or whether preoperative odour identification deficit predicted POCD.[38] Neither hypothesis was supported by the results.

Some circumstantial support for a link between POCD and early cognitive decline comes from the work of Houx and colleagues on biological life events (BLE).[20,21] Subjects were subjected to a battery of cognitive function tests and then, blindly, divided into those who had suffered BLE, which included minor closed head injury, self poisoning and operations lasting more than 2 h, and those who had not. Older patients without BLE had better preservation of cognitive function.

Causation of POCD

If it is accepted that POCD exists, it implies an effect on the brain which outlives the action of the drugs associated with anaesthesia, but, as the brain is their target organ, it does not exclude the possibility that the drugs might be responsible. Additional tasks of the ISPOCD2 studies have tested several hypotheses of the causation of POCD. The role of anaesthesia *per se* was examined in a randomized comparison of 364 elderly patients undergoing major, predominantly orthopaedic surgery, under either GA or regional anaesthesia (RA).[36] There was no difference in the frequency of POCD between the groups receiving GA and those receiving RA, suggesting that anaesthesia is not a risk factor. However, as most patients in the RA group received a sedative infusion of propofol, this conclusion may be questioned.

Animal studies

Hanning and colleagues[18] investigated the effects, in rats, of repeated anaesthesia throughout life with pentobarbital, compared with a control group. Central cholinergic function was estimated by radiolabelled α-bungarotoxin and epibatidine binding in the cortex, striatum and hippocampus when the rats were 26 months old. There was a highly significant reduction in a bungarotoxin binding in the superior cortex and in the molecular cortex. α-Bungarotoxin binds to the α7 subunit of the nicotinic receptor, which is also one of the sites for anaesthetic binding,[4] and is often most reduced in patients with AD.[5,13,31] This was a small study with an agent no longer used in human anaesthetic practice and the results should be treated with caution. There is however, some support for an effect of long-term administration of cholinergic drugs on cognitive function from other fields. For example, patients with Parkinson's disease treated with anti-muscarinic drugs are more likely to show Alzheimer pathology at post-mortem examination;[32] nicotine has been shown to be protective of nicotinic cholinergic receptors;[6,49] and low level exposure to organophosphorus esters may cause neurotoxicity.[22]

Greater impulsivity in behavioural task performance was noted between the elderly rats that had been subject to repeated anaesthesia throughout life and the control animals mentioned above.[7] Culley and colleagues have reported long-term effects of anaesthesia on cognitive function in rats with agents commonly used in human practice.[11,12]

Genotypes

Subjects with the apolipoprotein ε4 allele are known to have worse cognitive and neurological outcomes after brain injury and stroke,[48] and to be at greater risk of AD.[43] The role of APOE genotype was investigated in 976 patients undergoing major surgery in the ISPOCD2 studies,[2] and in the smaller odour identification study mentioned above.[38] In neither study was the ε4 allele a risk factor for POCD. This does not rule out the possibility of a genetic propensity for POCD but suggests that other candidate genes should be sought.

Cortisol

Hypercortisolaemia has been known for some time to impair cognitive function.[30,42] It was hypothesized that hypothalamic cell loss in the elderly impaired the normal mechanisms that damp down the increased cortisol secretion that follows stress and that the normal hypercortisolaemia of surgery would be enhanced and prolonged. Morning and afternoon salivary cortisol concentrations were measured in patients receiving a general anaesthetic in the randomized study of major surgery in the elderly, which formed part of the ISPOCD2 studies.[36] Other stress markers such as IL-6 were measured also. There was no evidence of greater or prolonged cortisol release in subjects with POCD although there was a loss of circadian effect in those patients (L. S. Rasmussen, personal communication, 2004). The significance of these findings remains to be elucidated.

Conclusions

Do patients undergoing anaesthesia and surgery have long-term or permanent decline in cognitive function? While there is little doubt that this is true for CPB, it is not so clear for non-cardiac surgery, at least after the first week in elderly patients. There is a strong body of evidence

suggesting that long-term POCD does occur in these patients but definitive proof is presently lacking. Further research will require more sensitive test instruments with high test–retest reliability. Study of patients with AD and other causes of premature cognitive decline to determine whether previous operation is a risk factor would be helpful also, as will the development of animal models of POCD.

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