Postoperative cognitive deficits: more questions than answers

Advancements in surgical and anaesthetic techniques have improved overall morbidity and mortality in patients undergoing major general and cardiac surgery. However postoperative cognitive deficits remain as significant complications, particularly in elderly patients [1,2]. Postoperative cognitive deficits result in prolonged hospitalization, increased morbidity and mortality, increased costs and have an adverse impact on quality of life [3]. Postoperative cognitive deficits are generally characterized as limitations of attention, cognition, recognition, orientation, memory and learning. While numerous synonyms such as acute brain syndrome, mental dysfunction and acute confusional state exist, it is important to discriminate between an early and mostly short-term postoperative delirium and the longer lasting postoperative cognitive dysfunction (POCD).

Delirium, defined in the International Statistical Classification of Diseases and Related Health Problems (ICD-10, World Health Organization), describes a nonspecific organic brain syndrome that is characterized as simultaneously occurring disturbances of consciousness, cognition, memory, emotion and psychomotor function as well as the sleep-wake cycle [4]. Postoperative delirium usually develops acutely with a peak onset on the second postoperative day and has a fluctuating clinical course [5]. The incidence of postoperative delirium varies with patient age, type of surgery, preoperative patient cognitive performance and level of education, coexisting disease as well as the method of diagnosis [6]. In a large review of 80 primary data-collection studies on postoperative delirium, the authors reported an average incidence of 36.8% while a range anywhere from 10 to 70% can be found in the literature [6,7]. Potential but unproven aetiologies of postoperative delirium include disturbances of central cholinergic and glutaminergic neurotransmission, electrolyte or fluid deficits and withdrawal symptoms [8]. As postoperative delirium often has one or more causes that can be identified and treated, good assessment and documentation leading to an immediate and correct diagnosis are essential [9]. It appears that a multifactorial and interdisciplinary approach, including assessment and treatment of underlying causes backed by excellent nursing care are key elements for successful prevention and treatment of postoperative delirium [10,11]. This is important as untreated postoperative delirium is a risk factor for POCD [12].

Postoperative cognitive dysfunction is more subtle and therefore neuropsychometric tests are needed to detect and quantify it. Similar to postoperative delirium, the incidence depends on the type of surgery, patient age, method of detection, preoperative level of education, coexisting disease and preoperative patient cognitive performance. Following cardiac surgery employing cardiopulmonary bypass, POCD can be detected in hospital in up to 80% of patients and is still present in as many as 42% 3–5 yr later [2,13,14]. The aetiology of such POCD is most likely multifactorial, including the effects of emboli and generalized cerebral hypoperfusion during cardiopulmonary bypass. In addition, other potential contributors to POCD include systemic inflammation [15–17], genetic predisposition [18] and rapid cerebral rewarming or hyperthermia after cardiopulmonary bypass [19,20].

The incidence of POCD after non cardiac surgery appears to be much lower. Following a large international multicentre trial investigating long-term POCD after general surgery in the elderly, the short-term incidence (1 week) was reported to be 25.8% while the longer-term incidence was 9.9% at 3 months and 1% at 2 yr [1,21]. Possible but unproven aetiologies following non-cardiac surgery include hypotension, cerebral hypoxaemia, the effects of long-acting sedatives or anaesthetics and metabolic disturbances as well as cerebral embolization, e.g. during hip replacement surgery or carotid artery surgery [1,22,23]. The hypothesis that regional anaesthesia might reduce the long-term incidence of POCD following major non-cardiac surgery has not been substantiated by large randomized studies of elderly patients [24–26].

As the incidence of POCD is very much higher in the cardiac surgery population compared to patients undergoing major non-cardiac surgery, it is tempting
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potential of this study is twofold: first, it points to
the postoperative period as an important and thus
far understudied phase to investigate in non-cardiac
surgery as well. Further, a simple but yet unproven
intervention such as the prevention of postoperative
fever could alter cognitive outcome. As a second exam-
ple, it has recently been demonstrated that atrial fibr-
illation is associated with poorer cognitive function
6 weeks after coronary artery bypass surgery [29].
Although the mechanism of this association has yet to
determined, the prevention or treatment of peri-
operative atrial fibrillation may result in improved
neurocognitive function especially as 30% of peri-
operative strokes in non-cardiac surgery patients are
associated with atrial fibrillation. Further evidence for
an association between atrial fibrillation and poor
cognitive function independent of stroke, high blood
pressure and diabetes was also documented in a non-
surgical population of elderly men [30].

It is likely that certain genotypes are more vulner-
able to perioperative cognitive dysfunction. Again,
there is evidence from the cardiac literature that cer-
tain genotypes might function as indicators of increased
susceptibility to POCD. In a small clinical study by
Tardiff and colleagues the presence of the apolipo-
protein E e-4 allele was shown to alter neurocogni-
tive function following coronary artery bypass graft
surgery [31]. Interestingly, this preliminary study has
not been followed by a larger trial which might be
due to the fact that numerous genetic covariates such
as single nucleotide polymorphisms may have an effect
on neurocognitive outcome. The latter emphasizes why
large patient populations need to be enrolled when
an association between a genetic marker or poly-
morphism and clinical outcomes is to be tested [32].

Despite the above examples, extreme caution is
advised with any extrapolation from the cardiac sce-
nario as the role of cardiac surgery-related idiosyn-
rasies such as the cardiopulmonary bypass circuit
and surgical techniques (e.g. aortic cross-clamping,
cardiac manipulation) as contributors to POCD remain
under active investigation. The ‘cardiac model’ may
be a quicker way to test hypotheses about POCD but
ultimately both positive and negative results have to
be tested in more general populations before apply-
ing the results to non cardiac patients.

What are some of the characteristics of ‘ideal’ stud-
ies and what topics are most promising for future
investigation? First, it is important to prospectively
study large multicentre patient populations with ran-
domized, placebo-controlled, double-blind methods
and having control groups that are both hospitalized
and not. This is essential to monitor for a practice
effect, variability related to specific neuropsychologi-
cal tests, and other unknown effects of hospitaliza-
tion [33]. Second, clinical endpoints and outcomes
need to be internationally accepted and reproducible.
Computer-based systems will facilitate the applica-
tion of neuropsychological test batteries and question-
naires but these require appropriate validation for
multicultural and multi-linguistic use [34]. A (sim-
ple) bedside test for early detection would obviously
be invaluable. Third, although difficult to quantitate,
the impact of POCD on quality of life needs to be fur-
ther evaluated [3]. Fourth, genetic markers or poly-
morphism, or both, should be studied as they may also
help to identify the underlying pathophysiology and
potential new targets for prophylaxis and treatment
[35,36]. Fifth, biochemical markers such as the inflam-
matory serum markers haptoglobin and C-reactive pro-
tein that have lately been shown to be indicators for
impaired cognitive performance in a 6 yr follow-up
study in a healthy aging population appear as poten-
tially important components of future studies [37].
Other factors that have not been sufficiently investi-
gated include the effects of the primary disease, e.g.
cancer and chronic diseases, and hospitalization on
POCD and postoperative delirium.

In conclusion, continuous investigation of post-
operative delirium and POCD is warranted. This is
important as the aged population presenting for major
non-cardiac and cardiac surgery steadily grows and the
social and economic impact of these complications
increases. The need for simple, reproducible, standard-
ized and quantifiable tests, both for research as well as
for day to day clinical use is evident. The utilization of
cardiac surgery as a disease model of POCD for major
non-cardiac surgery should be employed with great
caution and, at best, for hypothesis generation only.

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References


