REVIEWS

Predicting the onset of delirium in the post-operative patient

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Abstract

The number of people over 65 is increasing and those over 65 requiring surgery will likewise increase. Post-operative delirium (POD) affects up to 47% of patients undergoing surgery and is more prevalent in older people. Importantly, POD is associated with increased morbidity, mortality, length of stay and care home placement. There is evidence that specialist geriatrician input reduces POD but to be cost effective, needs to target patients with increased risk for POD. Many factors have been associated with increased risk of POD, including age, cognitive impairment, gender, depression, alcohol, drug use, smoking, co-morbidity, functional status, ASA score and pre-operative biochemical and haematological abnormalities. This article reviews the literature associated with the above factors, considers frailty as a factor and also suggests that POD may be associated with rapidity of onset and severity of the insult to the patient.

Keywords: elderly, predicting, delirium, confused, surgery

Introduction

The number of people over 65 years is increasing dramatically and will continue to do so over the next 10–15 years. Those requiring surgery will proportionally increase in number. Delirium, defined as a multi-factorial neuro-psychiatric disorder with well-defined predisposing and precipitating factors, is a common outcome in the hospitalised older person. Although estimates vary substantially, the Royal College of Physicians (2006) has estimated that up to 30% of hospitalised older people suffer with delirium [1]. Surgical studies have quoted post-operative delirium (POD) in as many as 47% of patients [2, 3, 4, 5]. Importantly, POD is associated with increased morbidity, mortality, length of stay and care home placement [6–12, 13, 14–19]. As a consequence, it adds substantially to the health care cost per patient episode [20].

Few randomised controlled trials have been sufficiently powered to show benefit of any intervention, although Marcantonio demonstrated that geriatrician input starting pre-operatively and continuing post-operatively significantly reduced POD in orthopaedic patients [21]. Evidence points to introducing a range of measures to prevent POD including educating staff members to improve detection of POD [19, 22, 23–27]. However, providing a multi-disciplinary specialist-led service for every post-operative patient would be too time consuming. Additionally, although preventing POD decreases length of stay, multi-disciplinary intervention has to be carefully targeted to make it cost effective [28].

A literature search was conducted in Ovid, Medline, EMBASE and Pubmed between 1980 and September 2008 using the keywords ‘predicting delirium’, ‘elderly surgery’, ‘post-operative delirium’ and ‘post-operative confusion’. Those articles were selected that assessed the predictive value of variables to cause POD.

Can we predict who will develop POD?

Predicting POD is difficult as its pathogenesis remains poorly understood [29]. Numerous studies have identified risk factors predicting POD. Many predisposing factors have been reported with varying levels of evidence [30, 31, 32]. Predisposing factors can be divided into those present at admission which can be identified pre-operatively, and those introduced iatrogenically, e.g. use of more than three medications and urinary catheterisation [33, 34].

Inouye et al. (1993) created a validated prediction model for delirium in hospitalised, elderly medical patients [33]. Four criteria each allocated one point were assessed for on
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admission. These included severe illness, visual impairment, cognitive impairment and elevated serum urea nitrogen to creatinine ratio. Only 9% of patients with no risk factors developed delirium compared with 83% with three to four factors. When the rule was tested in patients admitted for elective and emergency hip surgery [35], an increased incidence of POD was recorded in the group scoring 3–4. Independently though, elevated urea to creatinine ratio was not a significant predictive factor whilst including older age and emergency admission significantly increased the tool’s predictive value for that single-centre population.

Another predictive tool based on a mixed surgical cohort, the Brigham and Women’s Hospital Delirium (BWD) risk assessment system [36], looks at patients’ pre-operative use of medications, alcohol and smoking habits, history of acute or chronic illness, evidence of psychological or neurological disease or evidence of previous delirium. The BWD scores from 0 to 8. When validated in a cohort of 500 patients consisting mostly of elective orthopaedic and neurosurgical patients, a score of ≥2 produced sensitivity of 62% and specificity of 83%. However, positive predictive value was only 26% [3].

The Delirium Elderly At-Risk (DEAR) instrument, a pre-operative questionnaire is based on risk factors previously documented to increase POD. It measures age, activities of daily living (ADLs), cognitive impairment, sensory impairment and substance abuse. A score of ≥2 significantly correlated with delirium [37]. However, this score awaits wider application.

The prediction models described highlight the problems with attempting to generalise a predictive risk model. Each study carried out assessing risk factors for POD is unique and therefore introduces significant heterogeneity. Nevertheless, a picture starts to form of which predisposing factors lead to increased risk of POD.

Three key variables

The key to predicting who is going to develop POD whether medical or surgical hinges on three variables. The first is rapidity of onset of the insult; second the severity of the insult and third pre-procedural patient health.

The first variable, rapidity of onset of insult is illustrated by orthopaedic trauma. Various studies show that in comparison with patients having elective procedures for joint replacement, patients requiring surgery for fractured neck of femur are at significantly higher risk of POD [35, 38, 39].

It could be argued that fracture patients are not optimally prepared. Additionally, patients sustaining fracture will usually have underlying reasons for falling, e.g. increased frailty, cardiac disease, sensory abnormalities and multiple medication [31, 40]. However, of over 1,000 patients observed, emergency surgery results in a significantly greater incidence of POD.

The second variable, severity of insult, is also independently important. Vascular procedures for example can be crudely divided into aortic and non-aortic. One study found that more patients undergoing aortic surgery were diagnosed with POD compared with those undergoing other vascular procedures [41]. Similarly, another study found that neurosurgery was an independent risk factor for POD; the study comprised mostly orthopaedic and neurosurgical patients [3].

Whilst impact of individual procedures can be weighed up to determine severity of insult on the body, there is evidence that longer procedures also predispose to POD [42, 43]. However, whether there is a particular cutoff in terms of procedure length influencing POD remains to be established.

Certain procedures already utilise scores which help predict morbidity and mortality, e.g. Euroscore and POSSUM [44–46]. There may be scope to adapt these to predict POD per individual procedure. Norkiene et al. have already shown that in patients’ undergoing coronary artery bypass graft (CABG) surgery, a high Euroscore correlated with increased incidence of POD [47].

The patient

The third variable is the patient. The challenge is perhaps not to identify the cognitively impaired, institutionalised dependent adult as being at increased risk of POD but recognising the apparently independent patient as well. Various predisposing risk factors have been investigated.

Age

Prevalence of delirium increases with age. Despite regression analysis to control for confounders, many studies have found age a significant predictive factor for POD. The older the patient, the greater probability of finding associated co-morbidity, prescription of multiple medications and cognitive impairment. Therefore, age is also a guide to the likely presence of other problems.

Also true however is the increased prevalence of frailty as one ages [48]. Frailty does not necessarily imply illness but rather lowers functional reserve explaining why older people are more likely to develop POD. In studies looking at delirium, it is noticeable that in surgical cohorts POD has been observed in those over 60 [49], 65 [41, 47] and 70 [3, 35, 36, 50–53]. Medical admissions however which hypothetically are less stressful and physiologically demanding report typical ages of 75 [54] or 80 [55, 56] as being associated with delirium. Contrast this with a study that found that after severe trauma, those over 45 years were more likely to become delirious [57] and another study that found that the average age of patients with delirium post-haematopoietic stem cell transplantation was 43 versus 39 in the non-delirious group [58].

Cognitive impairment

Cognitive impairment is common. A recent study concluded that up to one-third of the U.S. population over 71 years
has cognitive impairment [59]. In a recent systematic review of risk factors for POD in patients undergoing non-cardiac surgery, Dasgupta and Dumbrell (2006) found that pre-existing cognitive impairment was one of the only two significant risk factors [32]. More generally, many observational studies have noted an increased incidence of POD in patients with cognitive impairment [3, 36, 50, 51, 60–66, 67, 68, 69–72].

Importantly, in many studies, cognitive impairment does not necessarily imply dementia. Whilst an Mini-Mental State Examination (MMSE) [73] of <24/30 is associated with a greater risk of POD [35, 39, 41, 67, 74, 75], one study found that a fall in the MMSE from 28.27 (control group) to 26.69 (study group) resulted in a significantly increased risk of POD despite the MMSE in both groups falling in what is considered the normal range [41].

A ‘normal’ MMSE would therefore not appear to adequately predict POD. More recently, the short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score was found to be a significant predictor of POD in patients undergoing elective orthopaedic surgery [76]. Unlike the MMSE, the IQCODE controls for education and culture [77]. Of 101 patients assessed whose average MMSE was 26, an IQCODE score of >50 (ranges from 16 to 80) was found to be significantly associated with POD.

Poor pre-operative performances on other neuropsychological tests are also associated with POD [41, 78]. Fisher and Flowerdew in a study including 80 patients found that the 14 patients who developed POD had lower pre-operative clock-drawing scores [79]. In another prospective observational study of 80 patients undergoing cardiac surgery, Rudolph et al. found that measures of memory function were not significantly related to POD [80]. Of the executive function measures however, verbal fluency, category fluency, Hopkins Verbal Learning Test learning and backward recounting of days and months were all significantly related to POD, and in a large cohort of 1,161 patients, the Visual Verbal Learning Test Learning Score and Stroop Colour Word Test were independently associated with POD [78]. Finally, in a prospective study looking at 100 consecutive elective admissions for orthopaedic surgery, pre-operative attention deficits were closely associated with POD [81].

Leung et al. measured the 15-point Geriatric Depression Score (GDS) [85] in 219 patients undergoing major non-cardiac surgery [86]. A total of 100 were diagnosed with POD using the Confusion Assessment Method (CAM) [87]. A pre-operative GDS score of 6+ was associated with POD but the result did not reach significance. This may be due to the authors pooling scores on the GDS of 6 (mild depression) together with higher scores. Therefore, the impact of more severe depression cannot be assessed independently. Further studies are therefore required.

Gender

Six studies have linked male sex with increased risk of delirium. Two small prospective studies looking at orthopaedic patients [38, 79] found a positive association. In a study of 1,161 patients in eight countries undergoing non-cardiac surgery [78], male sex was associated with POD. Finally, three prospective cohort studies looking at medical admissions [16, 55, 88] linked male sex with increased risk of delirium. In contrast, other studies demonstrated no link between gender and POD [30, 89].

There is no clear explanation why men should have an increased risk of delirium. Men have an increased risk of cardiovascular disease which may be a factor. Rudolph et al. (2007) proposed that vascular risk factors leading to accelerated atherosclerosis formation increases the risk of POD [78]. They demonstrated that an increased atherosclerotic burden calculated by looking for plaque formation in the aorta (assessed by transoesophageal echocardiography), coronary vessels (requiring bypass surgery) and carotid arteries (assessed by Duplex ultrasound) was associated with an increased incidence of POD in a small cohort of post-CABG patients [90].

Smoking

Smoking plays a role in atherosclerosis and also in increasing arterial wall stiffness [91, 92]. Therefore, smokers’ brains may be poorly equipped to deal with stressful situations. Studies looking at outcomes in cardiac, vascular and other types of surgery have noted an increased risk of POD in smokers [52, 68, 78, 93].

Co-morbidity

Older people undergoing surgical treatment often have co-morbidity. Several studies have identified that having a number of unspecified co-morbid problems, including a previous episode of delirium, increases the risk of POD [3, 54, 60, 67, 94].

Interestingly, conditions which either increase vascular risk or indicate vascular damage are shown to increase risk of POD. These include hypertension [66, 93, 95, 96], diabetes mellitus [43], myocardial infarction [78], stroke [74, 97], atrial
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fibrillation [71, 93, 98], peripheral vascular disease [47, 51, 71], heart failure [99, 100] and previous amputation [72].

Drug use

Goldenberg, in a small elderly population hospitalised with hip fracture, found that prescription of more than three medications increased risk of POD [101]. Other studies have found that centrally acting drugs increase risk of POD [3, 39, 64, 68, 74, 83].

Kudoh et al. recruited 328 patients aged 65–80 undergoing orthopaedic surgery [102]. POD incidence increased in those taking benzodiazepines pre-operatively compared with benzodiazepine-naïve patients. The incidence of POD was also higher in those taking benzodiazepines for >1 year. However, their study excluded patients taking antipsychotic, anti-depressant and anti-cholinergic medications, heavy drinkers (>25 g/day of alcohol) and those with cerebrovascular disease or heart failure. Therefore, generalising these findings is difficult. Böhner et al. found no increased risk of POD when using benzodiazepines in the pre-operative period [41].

A small observational study conducted on ITU found that 9 patients who developed delirium had higher serum levels of anti-cholinergics than the other 16 patients [103]. Certain medications have higher anti-cholinergic potential. A recently validated Anti-cholinergic Risk Scale showed that the more potent the drug’s anti-cholinergic potential the greater likelihood of adverse events in the elderly including delirium [104].

Finally, two studies have found conflicting results regarding statins and risk of POD [105, 106]. This requires further study.

Alcohol

Several studies have looked at pre-operative self-reported alcohol abuse and the risk of POD. In two large studies [3, 36], alcohol excess was a significant predictor of POD. A number of smaller studies also found an association with alcohol and increased incidence of POD [4, 50, 60, 69, 107]. Böhner et al. however found no increased risk of POD with prior heavy alcohol use [41].

Functional status

Several studies report that inability to complete one or more ADLs increases the risk of POD [3, 36, 50, 108, 109]. Nursing home residency also increases likelihood of POD [39]. More studies might have shown this association but most excluded patients unable to communicate because of aphasia or dementia. Visual and hearing impairment have also been shown to increase risk of POD [39, 74].

Patient assessment

American Society of Anaesthesiologists (ASA) Score

Several studies found that an ASA score of ≥3 (patient with severe systemic disease) increased the likelihood of POD [50, 110, 111]. Böhner et al. found no increased risk but this is likely due to little variation in ASA classification between their delirious and non-delirious patients (2.8 versus 2.9) [41].

Haematological abnormalities

Anaemia may result in reduced perfusion of vital organs during surgery. Böhner et al. did not find that pre-operative haemoglobin was linked to POD [41]. However, in their cohort the delirious groups’ haemoglobin was 14.3 versus 13.7 g/l in the non-delirious cohort. In contrast, Joostens et al. found that pre-operative haemoglobin in men <11.1 g/l substantially increased risk of POD [88]. In women, they found no relationship. Finally, Goldenberg found that a haematocrit of <33% was associated with an increased incidence of POD [101].

An elevated white blood cell count usually indicates stress or infection. Two small studies with <50 delirious patients combined have found that pre-operative leucocytosis is associated with an increased risk of POD [39, 50].

Biochemical abnormalities

Low pre-operative albumin may indicate poor nutritional status which has been associated with POD [51, 101, 108]. Low albumin may also imply worsening disease or other comorbidity [52].

Other biochemistry associated with increased risk of POD includes markedly abnormal sodium [36, 39, 50, 110], potassium [36, 50], glucose [36, 50], hypermagnesaemia [58] and increased urea nitrogen to creatinine ratio [58, 61, 93]. Finally, one study found that elevated C-reactive protein showed a trend towards increased risk of POD [41], a finding not backed by a smaller study [112].

What can we deduce from these findings?

Most studies seeking to determine predisposing predictive factors used prospective observational studies. They selected risk factors, measured them pre-surgery and then analysed whether prevalence was increased in the delirious group. Using this methodology, many risk factors have been identified. Extrapolation however remains difficult for the following reasons:

- Different studies measure different parameters and risk factors. Whilst some factors are found to be significant, the measurement of other parameters thought to be significant is not used in comparison. Therefore, it remains unclear which will be the strongest predictors.
- Different rating scales have been used to collect data, e.g. when measuring cognitive impairment and depression. Inter-scale reliability may be a problem.
• Studies quoted have cohorts of varying sizes and are often multi-national and multi-ethnic with often a small number of delirious patients from whom risk factors are identified. Extrapolation is therefore difficult.
• Most studies excluded patients where communication was difficult including those with aphasia, coma and dementia severe enough to prevent the gathering of data.
• Results from studies published less recently and studies recruiting patients over many years, might have been confounded by the use of less modern surgical techniques. Ultimately, surgical skill, procedure complexity and peri-operative care play a role in the onset of POD. Additionally, methods to detect delirium have improved. Extrapolation therefore will never be completely ideal.

Is a measure of frailty the best predictor?
Although some factors are more significantly associated with POD than others, true risk can currently only be ascertained by completing the equivalent of a comprehensive geriatric assessment. Whereas the questionnaires discussed provide a faster method, their external validity and positive predictive value remain questionable. Measuring frailty may predict outcome better.

Frailty has been poorly defined until recently which has prevented research into how it predicts outcomes [113]. Recently, general agreement has defined frailty as ‘a biological syndrome of decreased reserve and resistance to stressors resulting from cumulative declines across multiple physiologic systems and associated with adverse outcomes’ [114].

Frailty affects 7% of those aged over 65 and 25–40% aged over 80 [115]. Of the frail elderly, 7% have no illness and 25% have only one co-morbid diagnosis [116]. Therefore, these patients could be missed in pre-admission clinic. However, frail elderly are at an increased risk of dependency, long-term care and death compared with the non-frail, and this may be triggered by an inadequately prepared surgical patient [115, 117–119, 120].

The most commonly used frailty measure is the five-point score proposed by Fried (2001) [112]. A score of 3–5 correlates with the increased incidence of hospitalisation, falls, worsening disability and death. This measure however is time consuming and other frailty measures have been devised [121, 122]. Frailty remains to be researched as a marker of POD.

Conclusion
POD is an important and often unrecognised complication which has important consequences for the individual and health care organisations. Multi-factorial specialist-led interventions decrease incidence of POD but may only be cost effective when targeted at high-risk patients.

Of the three variables discussed, rapidity of onset of the insult and to some extent an understanding of insult severity will help identify those at highest risk of POD. The third variable, pre-procedural patient health, involves multiple predictive factors and more work is required to develop sensitive, specific and easy-to-use prediction tools with good inter-rater reliability.

Key points
• Post-operative delirium is common in older people.
• It leads to increased morbidity, mortality, length of stay and care home placement.
• Rapidity of onset of the insult, severity of the insult and pre-procedural patient health determine risk of post-operative delirium.
• Measuring frailty may be a more sensitive marker of determining post-operative delirium.

Conflicts of interest
There are no conflicts of interest to declare.

Supplementary data
Supplementary data are available at Age and Ageing online.

References
(The long list of references supporting this review has meant that only the most important are listed here and are represented by bold text throughout the review. The full list of references is available at Age and Ageing online.)

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