Effects of statins on delirium following cardiac surgery – evidence from literature

Giovanni Mariscalco[1], Silvia Mariani[1], Fausto Biancari[2], Maciej Banach[3]

[1] Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, United Kingdom
[2] Division of Cardiac Surgery, University of Oulu, Oulu, Finland
[3] Department of Hypertension, Medical University of Lodz, Lodz, Poland

Summary

Delirium is a common complication after cardiac surgery, being associated with significant mortality and morbidity. The pathogenesis of postoperative delirium (POD) is complex and multifactorial, involving an interaction of multiple predisposing and precipitating factors. There are several hypotheses regarding the underlying mechanisms of POD, and the most recent emerging one involves neuroinflammation, which is exacerbated by the cardiopulmonary bypass-induced systemic inflammatory response. Experimental and clinical studies have recently documented improved perioperative central neural protection exerted by statins because of their anti-inflammatory, immunomodulatory, and antithrombotic properties. The present review will focused on the possible protective effect exerted by preoperative statin administration on delirium following cardiac surgery.

Key words: delirium, cardiac surgery, complications

Diagnosis and epidemiology

Despite refinements in surgical and anaesthesiological techniques, delirium remains a frequent complication following coronary artery bypass grafting (CABG) [1–10]. The incidence of postoperative delirium (POD) largely varies among studies, ranging from 1% to 50% [1–10]. Plausible explanations of this variation refer to the adopted definition, the mode of its detection and the clinical profile of patient populations [1–10]. Several definitions of POD have been proposed along with different diagnostic tools [10]. POD is generally defined as an acute deterioration of brain function characterised

by fluctuating mental status with inattention and disturbances in consciousness and presents clinically different subtypes, with or without accompanying agitation [11, 12]. Hyperactive delirium is characterised by active symptoms such as agitation and restlessness, characterised by excessive motor or verbal behaviour that interfere with patient care, patient or staff safety, and medical therapy [6, 11]. Conversely, hypoactive delirium is characterised by unresponsiveness and motionlessness [11]. However, POD is often confounded with postoperative cognition dysfunction [9, 13]. Patients affected by POD immediately report an impaired recent memory but an intact remote memory, while in patients affected by postoperative cognitive dysfunction it is not associated with a change in consciousness that requires sensitive test methods to be diagnosed [13]. Although there are several tools to diagnose and classify delirium, the most widely used tools in intensive care units (ICU) are the confusion assessment method-ICU (CAM-ICU) and the intensive care delirium screening checklist (ICDSC) [14, 15] (Table 1).

Pathogenesis of postoperative delirium

The pathogenesis of POD is complex and multifactorial, involving an interaction of multiple predisposing and precipitating factors [1–10] (Table 2). Among predisposing factors, older age, history of stroke and peripheral vascular disease are the most important ones, being mainly related to increased cerebral atherosclerosis, with a consequent inhibition of the cerebral blood flow, exacerbation of inhibition of flow, and increased cerebral embolisation risk [2, 4, 9, 16–18]. In addition, older age is associated with lack of cholinergic reserve, predisposing patient to delirium [2, 4–6, 19–21]. Earlier meta-analyses [10] showed that every one year increase of age was associated with an increase in the chance of POD by 8%. Several POD precipitating factors has also been reported, including duration of surgery, type of surgery, prolonged intubation, and red blood cell transfusion (RBC) [1–10].

Afonso et al. [22] evaluated 112 adult postoperative cardiac surgical patients, observing a 30% increase in delirium per 30 minutes of CPB (cardiopulmonary bypass). On the other hand, Kazmierski et al. [4] reported a fivefold increase of delirium when intubation was prolonged over 24 hours in a population of 846 consecutive cardiac surgery subjects. The same group observed a fourfold increase risk of POD in patients receiving more than 4 RBC units [4].

Table 1. **The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[a]**

Delirium is diagnosed when both features: 1 and 2 are positive, along with either feature 3 or 4.

Feature 1. Acute onset of mental status changes or fluctuating course
- Is there evidence of an acute change in mental status from the baseline?
- Did the (abnormal) behaviour fluctuate during the past 24 hrs, that is, tend to come and go or increase and decrease in severity?

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[a] Adapted from Ely EW et.al. Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001; 29:1370-1379.

Sources of information: Serial Glasgow Coma Scale or sedation score ratings over 24 hrs as well as readily available input from the patient's bedside critical care nurse or family.

Feature 2. *Inattention*
- Did the patient have difficulty focusing attention?
- Is there a reduced ability to maintain and shift attention?

    Sources of information: Attention screening examinations by using either picture recognition or Vigilance random letter test. Neither of these tests requires verbal response, and thus they are ideally suited for mechanically ventilated patients.

Feature 3. *Disorganised Thinking*
- Was the patient's thinking disorganised or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
- Was the patient able to follow questions and commands throughout the assessment?
1. "Are you having any unclear thinking?";
2. "Hold up this many fingers." (examiner holds two fingers in front of the patient);
3. "Now, do the same thing with the other hand." (not repeating the number of fingers).

Feature 4. *Altered Level of Consciousness*
- Any level of consciousness other than "alert";
- Alert – normal, spontaneously fully aware of environment and interacts appropriately;
- Vigilant – hyperalert;
- Lethargic – drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally;
- Stupor – difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly;
- Coma – unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer, so that the interview is difficult or impossible even with maximal prodding.

Table 2. **Predisposing and precipitating factors of delirium following cardiac surgery**

Predisposing factors	Precipitating factors
Age	Urgent surgery
Acute myocardial infarction	Intraoperative intra-aortic balloon pump (IABP)
Left ventricular ejection function	CPB duration
Preoperative atrial fibrillation	Aortic cross clamp time duration
Hypertension	Hypoperfusion
Diabetes	Anaemia
Renal function	Hypoxia
Peripheral vascular disease	Low cardiac output
Cognitive impairment	Valve surgery
Dementia	Red blood cells transfusion
Depression	Respiratory failure

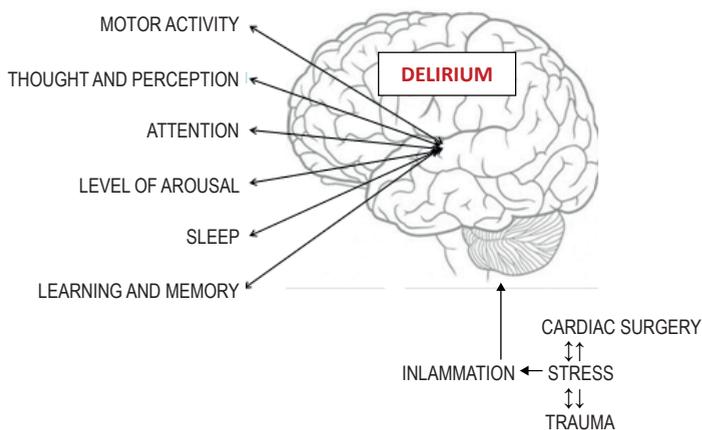| Prior delirium	Postoperative atrial fibrillation
Functional impairment	Postoperative acute kidney injury
Previous stroke	Infection/sepsis

Figure 1. **Simplified pathways of delirium following cardiac surgery (adapted from Hall et al. [23])**

Table 3. **Published studies with reference to the effect of statins on delirium after cardiac surgery**

	First Author	
	Mariscalco [1]	Katznelson [2]
Year of Study	2004–2011	2005–2006
Type of study	Retrospective (PM)	Retrospective
Number of Patients	4,079	1,059
Age (years)	67.8 ± 7.2	64%[a]
Female (%)	21%	29%
Elective (%)	92%	n.a.
Statins (%)	39%	64%
Type of surgery		
Isolated CABG (%)	75%	83%
CABG + Valve (%)	25%	17%
Hospital mortality (%)	2%	n.a.
POD incidence (%)	3%	11.5%

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POD assessment	CAM-ICU	CAM-ICU
POD predictors	CABG + Valve	RBC (> 5Units)
	Postop AKI	Intraop IABP
	LVEF	Preop depression
	Postop AF	Preop Creat > 150 µm
	Hypertension	Age ≥ 60 years
	Age	CABG + Valve
	COPD	Preop Statins
	History of CVA	
Statins effect on POD	None	Protective
	(OR 1.49, 95%CI, 0.97–2.29)	(OR0.54, 95%CI 0.35–0.84)

AF – atrial fibrillation; AKI – acute kidney injury; CABG – coronary artery bypass grafting; CAM – confusion assessment method; COPD – chronic obstructive pulmonary disease; CVA – cerebrovascular accident; IABP – intra-aortic balloon pump; ICU – intensive care unit; LVEF – left ventricular ejection fraction; PM – propensity matching score; POD – postoperative delirium; RBC – red blood cell; n.a. – not available

[a] percentage of patients ≥ 60 years

Inflammation and delirium

Although there are several hypotheses of the pathophysiology of POD, the most recent one involves neuroinflammation [23, 24]. This is caused by the hyper-responsiveness of brain immune cells to stimulation from peripheral inflammation, making the brain susceptible to the consequences of systemic inflammation [23, 24]. In a systematic review, Hall et al. [23] investigated the correlation between cerebrospinal fluid biomarkers and delirium, including 235 patients from 8 prospective studies. Delirium was associated with elevated levels of pro-inflammatory markers such as inteleukin-8 (IL-8), and neuronspecific enolase. Kazmierski et al. [25] conducted a prospective study enrolling 113 patients undergoing CABG surgery with CPB, investigating whether increased levels of IL-2 and TNF-α were associated with POD. An increased concentration of pro-inflammatory cytokines was independently associated with POD, and related to advancing age along with duration of CPB [25]. Peripheral cytokines can act directly through neurodegeneration, or indirectly through neurotransmission [26, 27]. Interleukins in human and animal models have been demonstrated to induce symptoms of delirium, also mediating exotoxic neurodegeneration [28–30]. Cytokine dysregulation possibly causes neuronal injury through altered neurotransmission, apoptosis, and activation of brain immune cells which leads to production of free radicals, complement factors, and nitric oxide [25]. Cytokine dysregulation has been observed to be related with aging as well as infection, trauma and (surgical) stress [26]. Therefore, the CPB-induced systemic inflammatory response should be considered as one of the

most relevant determinants of POD, leading to and exacerbating the afore-mentioned neuroinflammation [25]. Cardiac surgery with CPB is associated with a profound systemic inflammatory response due to surgical trauma, and the interaction between blood and artificial circuit surfaces, leading to blood barrier dysfunction, cerebral inflammation, and glial cell injury [31, 32]. The CPB-related inflammation may cause neuronal damage through microglia activation, oedema, microvascular thrombosis and alterations in local blood flow [33–35]. However, other mechanisms of delirium following cardiac surgery should be mentioned such as direct brain insults due to hypoxia, ischemia, and metabolic derangement [23, 24], which are not mutually exclusive with neuroinflammation [23, 24].

Impact of delirium on outcomes

POD is associated with increased morbidity and mortality, prolonging the ICU and hospital stay, at considerable expense of resources [1–8, 36]. In a cohort of 4,659 patients undergoing CABG, our group demonstrated that POD was associated with a ten-fold increased risk of hospital mortality, and with three-day increase in hospital stay [1]. POD is also accompanied by increased late mortality, as well as poorer cognitive and functional outcomes [19]. Koster et al. [19] by prospectively enrolling 112 patients undergoing cardiac surgery observed that POD patients had a higher rate of follow-up mortality (13% in patients with delirium versus 5% in patients without it), readmissions to the hospital (48% vs. 33%), dysfunction in memory (32% vs. 23%), concentration problems (37% vs. 20%), and sleep disturbance (47% vs. 24%). More importantly, POD severely contributes to the development of post-discharge cognitive decline [37].

Effects of statins on delirium

Due to the relevant prognostic impact of POD, its prevention is of utmost importance. Experimental and clinical studies have proved that statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have the potential to improve perioperative central neuronal protection [38–40]. Statins have important pleiotropic effects, including anti-inflammatory, immunomodulatory, and antithrombotic properties [38–40]. Wang et al. [41] demonstrated that statin treatment markedly reduced functional neurological deficits after traumatic brain injury in mice. In addition, histological reduction in degenerating hippocampal neurons and suppression of inflammatory cytokine mRNA expression in brain parenchyma was observed; Statin treatment also improved cerebral hemodynamics following the head injury [41]. Similarly, in a mouse model of cerebral ischemia, acute termination of statin administration resulted in a rapid loss of cerebral protection [42]. Statins prevent inflammation by interfering with multiple steps of leukocyte recruitment and migration into the central nervous system, including decreasing circulating monocyte expression of cytokines and inhibiting chemokine production in endothelial cells [43, 44]. Statins may also upregulate eNOS, leading to decreased leukocyte adhesion [45].

Statins and delirium following cardiac surgery

Based on these substantiations, it has been suggested that the administration of statins may represent a viable therapeutic and preventing strategy against POD. Aboyans et al. [46] recognised the protective effects exerted by statins on stroke as first in a prospective cohort of 810 patients undergoing CABG. Moreover, intensive cholesterol lowering with statins after CABG has been shown to decrease the long-term incidence of stroke [47]. However, data on the protective statin effects on stroke following cardiac surgery have not been subsequently confirmed [16, 48]. Conversely, statin administration in the critically ill patients has been shown to confer protection against delirium [49, 50]. Page et al. [49] conducted a prospective study on 470 consecutive critical care patients with 2,927 person/days follow-up. Statin administration in the previous evening was associated with a reduction in incidence of delirium (odds ratio (OR), 2.28; 95% confidence intervals (CIs), 1.01–5.13) [49]. Morandi et al. [50] performed a multicentre, prospective cohort study enrolling 763 patients with acute respiratory failure and shock, demonstrating that ICU statin users had a reduced incidence of delirium, especially in early stages of sepsis, while discontinuation of statins was associated with increased delirium. However, results of the statin effect on delirium occurrence after cardiac surgery are markedly controversial [1, 2, 16, 51] (Table 3). Only the observational study of Katznelson et al. [2], demonstrated that preoperative administration of statins was associated with a reduce risk of POD by analysing 1,059 patients undergoing cardiac surgery with CPB. In addition, the protective POD effect exerted by statins was more evident in patients with age ≥ 60 years [2]. Mathew et al. [51], retrospectively enrolling 440 patients undergoing CABG, investigated the effect of preoperative statin administration on cognitive dysfunction following CPB. They documented that cytokines (IL-1 and TNF-α) and C-reactive protein did not differ in patients affected by cognitive dysfunction independently of preoperative statin therapy [51]. Our data were also in consonance with those presented by Mathew et al. [1, 51]. In the largest study to date, we retrospectively examined 4,569 CABG patients, founding no association between POD and preoperative statin administration [1]. Interestingly, although cardiac surgery population accounted for 9.7% of the entire study population (9,272 out of 264,657 patients), Redelmeier et al. [16] retrospectively observed that the rate of POD was higher among patients taking statins than among those not taking them (OR: 1.28; 95% CI 1.12–1.46). Different plausible explanations for this controversial statin effect on POD have been advocated, especially with reference to the different and complex events that occur during cardiac surgery with CPB [1, 4, 6, 9, 48, 51]. Embolic events, postoperative cardiac output along with hypoperfusion and hypoxia phenomena, and prolonged ICU stay can overcome the protective statin effects on POD [1, 4, 6, 9, 48, 51]. In addition, the relevant pro-inflammatory effects of CPB, especially in complex and prolonged surgeries, may overwhelm the anti-inflammatory properties of statins [1, 51]. The sudden withdrawal of statins, especially in the first hours after surgery, may also reduce the protective statin effect [42]. Moreover, patient selection, statin type, and administered doses could explain the different effect of statins on POD, underlying the complex multifactorial pathophysiology of delirium

after cardiac surgery [1, 2, 16, 51]. Finally, possible effects of omega-3 polyunsaturated fatty acids on delirium after cardiac surgery have not been investigated yet.

Conclusions

Delirium is a common complication after cardiac surgery, correlating with an increased morbidity and mortality, at considerable expenses of resources [1–10, 48, 51]. Although several efforts have attempted to determine its exact pathogenesis, POD is the consequence of interplay of different pathophysiologic mechanisms [9–11]. Among these, neuroinflammation is one of the most emerging causative hypotheses related to POD occurrence [23, 24]. Experimental and clinical studies have documented neurological protective effect of statin administration because of their anti-inflammatory, immunomodulatory, and anti-thrombotic properties [38–40]. Although, statin administration has been associated with a reduction of POD in critically ill patients [49, 50], conflict results have been observed after cardiac surgery [1, 2, 16, 51]. The multifactorial and complex pathogenesis of POD may explain this discrepancy [51–58]. Therefore, no definitive conclusions on the protective effects of statins on POD can be determined in the cardiac surgery setting. Randomised trials are required to clarify the effect of preoperative statin administration and delirium following cardiac surgery.

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Address: Giovanni Mariscalco
Department of Cardiovascular Sciences
University of Leicester
Clinical Sciences Wing
Glenfield Hospital
Leicester, LE3 9QP United Kingdom