REVIEW ARTICLE

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Postoperative Delirium in Cardiac Surgery: An Unavoidable Menace?

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DELIRIUM IS DEFINED as a "mental disturbance" marked by disorientation and confused thinking in which the patient incorrectly interprets his/her surroundings. The Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria[1] include "disturbance of consciousness such as reduced clarity or awareness of the environment with reduced ability to focus, sustain, or shift attention; a change in cognition or the development of a perceptual disturbance that is not better accounted by a preexisting, established, or evolving dementia; development of the disturbance over a short period of time (usually hours to days) with a tendency to fluctuate during the course of the day; and evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition."[1] Corresponding to Encyclopedia Britannica, "the delirious person is drowsy, restless, and fearful of imaginary disasters. They may suffer from hallucinations (eg, imagine terrifying creatures or think that the building is on fire). Maniacal excitement may follow."[2]

Identified decades ago, delirium usually develops within 72 hours after surgery. Fifty years ago, cardiac surgery patients already had been perceived as a high-risk group. Half a century later, postoperative delirium in cardiac surgery is still a frequent and relevant problem. It is well documented that after cardiac surgery delirium is associated with increased mortality (13.5% *v* 2%), more hospital readmissions,[3] prolonged length of ICU and hospital stay,[4] and a reduced quality of life.[3,5] It is also associated independently with functional decline after 1 month and a trend towards such an association at 12 months,[6] thus, complicating long-term outcome.[5] Furthermore, in the general ICU population (excluding cardiac surgery patients), it has been shown that the duration of delirium is associated with worse long-term cognitive function.[7] Several studies also have revealed delirium as a predictor of sepsis, respiratory failure, sternal instability, and reoperation.[8,9] In view of the fact that postoperative delirium often is underdiagnosed or not even recognized, particularly because there is a predominance of the hypoactive form, the impact of delirium on an unfavorable outcome even may be underestimated.

A PubMed search in July and October 2013 with the search terms, "delirium and cardiac surgery" for papers published between 1964 and 2014 revealed 196 publications; 132 of these are cited in this review. Most studies were prospective studies (95 in total, including 13 prospective cohort studies, 78 prospective observational studies, 2 prospective descriptive studies, and 2 prospective blinded multicenter studies) followed by review articles (42 in total, including 32 narrative, 8 systematic, 1 combined systematic and meta-analysis, and 1 meta-analysis). A smaller group of 10 studies consisted of retrospective data (cohort, chart review, post hoc analysis). Ten studies were randomized, controlled clinical trials. The remaining manuscripts were comments, case presentations, meta-analyses, preliminary reports, case-control studies, and historic perspectives. The number of detected preoperative, intraoperative, and postoperative risk factors seems unlimited, and no unequivocal treatment or preventive measure has been established so far. At present, despite a negative recommendation in the latest American guidelines for sedation, analgesia and delirium (Reference: CCM Guidelines sedation, analgesia and delirium[10]), haloperidol is the first-line agent used worldwide for the treatment of delirium in general.[11]

EPIDEMIOLOGY

The incidence of postoperative delirium among cardiac surgery patients seems to be associated strongly with the type of cardiac intervention. Although disputed, most studies measured a significantly lower rate of delirium in exclusive aortocoronary bypass grafting ("closed surgery") compared to valve and aneurysm repair with or without additional bypass ("open surgery").[12] Among elderly patients, an incidence of 25% generally is assumed.[13] However, values in the literature vary greatly, ranging from 10% to 80%.[14,15]

PUBLISHED RISK FACTORS FOR POSTCARDIOTOMY DELIRIUM

In the 196 papers reviewed, a total of 123 risk factors for postoperative delirium after cardiac surgery could be found. Eighteen were questioned or rejected in the same study. Only 2 definitely were excluded, and 25 were considered modifiable

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in the period between diagnosis and intervention. Age was the only consistently reported risk factor.

Among these 123 risk factors, 8 were mentioned in at least 10 studies (age, cardiac status, personality traits, cerebrovascular or peripheral vascular disease, metabolic syndrome [diabetes, BMI], preoperative cognitive impairment, type of surgery, and duration of surgery) (Table 1).[16–109]

A restricted plan of action is evident after considering the documented modifiable risk factors in Table 1. Many predisposing factors have been found, but the associated level of evidence often is low. For example, one observational study and one systematic review declared low albumin level as a risk factor or a biomarker for identifying patients at high risk for delirium,[17,110] as it is also the case with electrolyte disturbances or blood glucose levels. In addition to the limited evidence of predisposition, coincidence cannot be ruled out for many factors (eg, atrial fibrillation and delirium could both be signs of severe surgical or inflammatory injury without any causative interaction).

Reasonable intraoperative anesthetic and surgical management of blood pressure and volume load are of importance. However, there is no conclusive evidence that a specific intraoperative strategy will reduce the incidence of delirium and the role of the type of anesthesia as a factor contributing to delirium could not be determined to date.

Patients undergoing coronary artery bypass graft (CABG) and/or valvular surgery usually spend at least 1 night in the ICU. For initial analgesia and sedation, they depend on various drugs with anticholinergic side effects (eg, opioids, benzodiazepines, and barbiturates), which often persist long after extubation. These might work as precipitating factors superimposed on the anticholinergic medication risk factor when administered intraoperatively (eg, sevoflurane, desflurane, propofol, ketamine, and atropine). Ketamine, however, has been shown to lower the incidence of postoperative delirium.[111] The threshold for transfusion of blood and blood products or administration of other fluids has to be evaluated with respect to the patient's comorbidities and intraoperative and postoperative development. The role of immobilizing therapies such as sedatives, IABP, or other ventricular support devices is unclear. However, early and consequent physiotherapy may, to some extent, antagonize the consequences of these mostly unavoidable treatment procedures on cognitive impairment. Further research is warranted in this field.[24,54,91]

Reflecting on the proverb from the Tenth Satire of Juvenal, which states, "mens sana in corpore sano" (a healthy mind in a healthy body), 1 study specifically suggested preoperative and postoperative psychiatrist visits that focus on the patient's will to live, his/her expectations, and anxiety about the surgery as a patient's condition postoperatively potentially will influence his/her physical status.[112] Nevertheless, no consistent psychologic etiology has been found,[45] and the results remain inconclusive.[20]

BASIC PATHOPHYSIOLOGY

Many pathophysiologic mechanisms for the development of delirium have been described in various studies. There is at least one consensus reported in the literature: The pathogenesis is not entirely or is even poorly understood and is assumed to be a complex interplay of preexisting predisposing and perioperative precipitating factors.[75,113]

Possible pathophysiologic explanations may stem from neurotransmitter disturbances (neurotransmitter hypothesis). These include dysfunction of cholinergic, serotonergic, noradrenergic, dopaminergic, or GABA-ergic transmission or potential stress-related disruptions in serum cortisol levels. These may be present with or without a combination of psychiatric factors (see Table 1, outlining personality traits), such as depression or type-D personality ("D" standing for "distress," describing a general tendency towards adverse emotional sensation, such as irritability and negativism, accompanied by low self-esteem and unsociability),[90] in addition to socioeconomic status,[77] impaired cognitive performance,[21,22,41] and educational and occupational level.[77]

Physical stress caused by surgical trauma leads to increased activity of the limbic-hypothalamic-pituitary-adrenal axis and low T3 syndrome. The degree of imbalance of thyroid hormones depends on the severity of the disease or trauma. Increased corticosteroid levels may disrupt the limbic and the immune systems, thus influencing brain, immune, and thyroid function and possibly eventually provoking delirium.[84]

Inflammatory parameters (CRP, IL-6, procalcitonin) are significantly higher postoperatively as a result of surgical trauma.[12,73-75] Microglial cells are activated by peripheral inflammatory responses and are able to produce neuroactive cytokines and other neuroactive signals, thus contributing to profound neuropsychiatric changes after surgery.[18] It is very likely that the interplay between cholinergic transmission and neuroinflammation plays a key role in the development of delirium.[114] Those factors making cardiac surgery a special case are of particular interest.

CARDIAC SURGERY PATIENTS AS A HIGH-RISK POPULATION

The type of cardiac surgery (ie, cardiac surgery with or without cardiopulmonary bypass) may play an important role. Cardiopulmonary bypass leads to an increased rate of thromboembolic events and consecutive cerebral embolism,[12] whereby the number[21,60,95] but not the size[14] of the emboli has been found to be relevant. Embolic events lead to neuron-specific enolase (NSE) release,[21] a parameter that was found to be elevated in patients suffering from delirium.[21,22,115,116] Furthermore, fat-contaminated pericardial suction blood seems to markedly impair capillary perfusion (flow properties of blood) and lead to small artery emboli in the brain after cardiac surgery,[72] thus aggravating the mechanism. Nevertheless, the roles of emboli and ischemia recently have been revisited.[117]

In the context of hypoxia and microembolic stroke, it is hypothesized that excitatory amino acids binding to glutamate receptors can cause prolonged calcium-dependent depolarization and eventual neuronal degeneration. Furthermore, acetylcholine synthesis is very vulnerable to hypoxia, which could be a further contributing factor supporting the role of cholinergic transmission in the development of delirium.