Revista Mexicana de Anestesiología

CONFERENCIAS MAGISTRALES
Vol. 35. Supl. 1 Abril-Junio 2012
pp S330-S332

Postoperative delirium

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(Parts of the presentation have been previously published as Deiner, S and Silverstein J Postoperative Delirium and Cognitive Dysfunction Br. J Anesth 2009 103 Suppl 1)

DEFINITIONS

Delirium is well defined and is described in the *Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSSM IV TR)*. The key characteristics are a change in mental status characterized by a reduced awareness of the environment and a disturbance in attention. This may be accompanied by other, more florid, perceptual symptoms (hallucinations) or cognitive symptoms including disorientation or temporary memory dysfunction. The patient may express hypoactive, hyperactive or mixed psychomotor behaviors. Several tests have been developed and validated for use in diagnosis and grading of delirium. These include the Confusion Assessment Method (CAM), the Delirium Rating Scale Revised-98, and the Delirium Symptom Interview[1,2]. A recent study from Japan found that the NEECHAM Confusion Scale and the Estimation of Physiologic Ability and Surgical Stress (E-PASS) are useful in diagnosis as well.[3] Severity may vary, can be graded, and may have prognostic value[4]. By definition, although the disorder develops acutely, the condition will wax and wane during the course of a day. These symptoms are not exclusive to delirium. Patients who have baseline dementia, psychosis, or anxiety/depressive disorder may present diagnostic challenges.

There are many subtypes of delirium including those attributable to an underlying medical condition (*delirium due to a general medical condition*), medications (*substance-induced delirium, substance intoxication delirium*), or withdrawal from medications (*substance withdrawal delirium*). Sometimes delirium may be multifactorial (*delirium due to multiple etiologies*) or of unclear etiology (*delirium not otherwise specified - NOS*). Emergence agitation or delirium might be thought of as a subset of subset of *substance-induced* delirium. It has predominance in pediatric patients, has been correlated with general anesthesia, and provided the patient is guarded from harming themselves, usually resolves without sequelae[5]. Emergence delirium in the pediatric population has been demonstrated to be associated with preoperative anxiety and responds to behavioral preparation and preoperative sedation. For the purpose of this review, we are interested in delirium that occurs after a relatively normal emergence and that occurs at some interval following surgery and anesthesia. This entity, which is more closely associated with older age is referred to as postoperative (interval) delirium.

Postoperative delirium is not temporally related to emergence from anesthesia. By definition patients with postoperative delirium do not have an identifiable etiology, though there may be other contributing factors. These patients often emerge smoothly, and may be lucid in the post-anesthesia care unit. However, after this initial lucid interval the patients develop the classic fluctuating mental status, most commonly between postoperative day 1 and 3. Some postoperative patients may reside in the ICU; however the term *ICU delirium* (previously known as *ICU psychosis*) may include both medical and surgical patients. POD may differ from delirium in medical patients because the admission characteristics of the two groups may be different. By definition patients hospitalized for medical indications are either acutely ill or have exacerbations of chronic diseases. Most surgical operations are elective and patients have been managed to ensure optimal physical status before entering the hospital. Surgery and the associated anesthetics and analgesics are generally absent in medical patients, but may contribute to POD. An important reason to distinguish postoperative delirium from delirium seen in medical patients is the report by Brauer suggesting that patients with postoperative delirium may be more likely to result

in initial complete recovery than other forms of delirium[6]. However, postoperative delirium is far from benign. In several recent two year-plus cohort studies of elderly patients hip fracture patients who develop POD are more likely to die, be diagnosed with dementia or mild cognitive impairment, and require institutionalization[7].

PATHOPHYSIOLOGY AND ETIOLOGY

Delirium as a behavioral manifestation of cortical dysfunction is associated with characteristic signs. The electroencephalogram may show diffuse slowing of background activity. A wide variety of disturbances in neurotransmitter systems has been described. Serum anticholinergic activity has been associated with delirium and may be especially important, as well as other mediators: melatonin, norepinephrine, and lymphokines[8]. Delirium has been hypothesized to occur as a result of the inflammatory response associated with the stress of surgery. Interestingly, elevated preoperative inflammatory markers including C-reactive protein, interleukin 6, insulin growth factor 1 (IGF-1) have not been found to be associated with the development of postoperative delirium[9,10]. However, postoperative chemokines have been found to be more elevated in patients who became delirious than in matched controls. This difference was non-significant by postoperative day four and other inflammatory cytokines were not found to be different in the two groups at any time point. This would point to a mechanism for delirium which might include initial leukocyte migration into the central nervous system and potentially a breakdown of the blood-brain barrier[9].

Although the mechanism of delirium has not been elucidated, there has been significant description of associated patient risk factors. Some of these may be considered preexisting- i.e. existing vulnerabilities, and others precipitating- i.e. noxious injuries. Age > 70, preexisting cognitive impairment, preoperative use of narcotics or benzodiazepines, previous history of postoperative delirium, self reported health impairment from alcohol are all closely associated with the development of postoperative delirium[11]. Other predisposing risk factors include vision impairment, severe illness, cognitive impairment, serum urea nitrogen: creatinine ratio of 18 or greater[18]. Vascular risk factors have also been strongly associated with development of delirium (tobacco use, vascular surgery), although it is unclear whether the increased risk is due to atherosclerotic burden or the surgical procedure itself[12]. Decreased cerebral perfusion as a risk factor for POD is supported by a recent study which associated low preoperative regional oxygen saturation as measured by a cerebral oximeter[13]. Low preoperative executive scores and depressive symptoms, as measured by the several different instruments have been found to identify patients at risk of postoperative delirium[14]. Postoperative delirium is also associated with preexisting attentional deficits in non-demented patients. Precipitating factors include: use of physical restraints, malnutrition, more than 3 medications added 24-48 h before the onset of delirium, use of a urinary bladder catheter and iatrogenic events including electrolyte and fluid abnormalities[14]. Specific perioperative risk factors include greater intraoperative blood loss, more postoperative transfusions, postoperative hematocrit of less than 30%[15]. Severe acute pain regardless of the method of analgesia (opiod type, method, dose) is associated with POD[16]. While it is tempting to speculate mechanism from these observations, association may not infer causality. Certain types of injury, particularly hip fractures, and serious illness requiring intensive care are also associated with high incidences of delirium.

TREATMENT AND PREVENTION

POD is preventable in some patients, and delirium prevention/intervention programs have met with some success. A proactive geriatric consult alone has been shown to significantly decrease the incidence of POD[17]. Successful intervention programs include the Hospital Elder Life Program. This program focused on protocol driven management of six risk factors for delirium: visual and hearing impairment, cognitive impairment, sleep deprivation, immobility, and dehydration. The study patients had significant reduction in the number and duration of episodes of delirium.[18] Specific interventions include prominent presentation of orienting information e.g. Date, time, name of hospital personnel, cognitive stimulation activities, exercise, feeding and fluid assistance, and nonpharmacologic sleep aids (e.g. relaxing music, massage). Attempts at pharmacologic prophylaxis have met with mixed results. Though we have excluded cardiac surgery patients from our discussion, it is interesting to note that single dose ketamine (0.5 mg/kg) given upon induction was associated with a lower serum levels of C-reactive protein and lower incidence of delirium in this population. Authors postulate that ketamine's neuroprotective effects-prevention of excitotoxic injury and apoptosis, and suppression of CNS inflammatory response may be responsible[19]. It should be noted that a single dose of ketamine has been reported to have a profound, two week impact on patients with refractory depression. Another study of cardiac surgery patients targeted the reduced cholinergic transmission associated with delirium with rivastigmine, a cholinesterase inhibitor. This study did not find that prophylaxis was associated with a decreased incidence of delirium, though the study found an overall lower rate of delirium than expected and was therefore underpowered for their primary outcome. A study of haloperidol prophylaxis in combination with nonpharmacologic delirium prevention strategies had similar methodologic difficulties, and showed no difference in the incidence of delirium. However patients who received

delirium prophylaxis with haloperidol did have a significant reduction in delirium severity and duration with an associated decrease in hospital length of stay[20].

Treatment of postoperative delirium has remained constant-identification of underlying medical issues, optimization of environment and pain control, and pharmacologic treatment for refractory cases. It is important to stress that pharmacologic treatment is not first line. However it may be necessary when agitation puts the patient and caregivers at risk of harm or prevents normal postoperative care. The drug of choice remains haloperidol. It is an antipsychotic dopaminergic agonist and is administered at a dose of 0.5 mg-1 mg intravenously every 10-15 minutes until the behavior is controlled. Intramuscular dosing is possible as well, but much less desirable. The dosage is 2-10mg and interval for titration is 60-90 minutes. Careful titration is important to avoid oversedation and prolonged effects secondary to its long (up to 72 hour) half life. Newer antipsychotics have been shown to be effective in acute agitation when administered as intramuscular injections, but have not been tested in medical and surgical patients. Physical restraints are undesirable except in the most severe cases and then only as a temporary measure while pharmacologic and other interventions have failed.

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