Review Article

Postoperative delirium in elderly citizens and current practice

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Abstract

Postoperative delirium (POD) represents an acute brain dysfunction in the postsurgical period. Perioperative physicians caring for the older adults are familiar with the care of dysfunction of organs such as lungs, heart, liver, or kidney in the perioperative setting, but they are less familiar with management of brain dysfunction. As early detection and prompt treatment of inciting factors are utmost important to prevent or minimize the deleterious outcomes of delirium. The purpose of this review is to prepare perioperative physicians with a set of current clinical practice recommendations to provide optimal perioperative care of older adults, with a special focus on specific perioperative interventions that have been shown to prevent POD. On literature search in EMBASE, CINAHL, and PUBMED between January 2000 and September 2015 using search words delirium, POD, acute postoperative confusion, and brain dysfunction resulted in 9710 articles. Among them, 73 articles were chosen for review, in addition, National Institute for Health and Clinical Excellence guidelines, American Geriatric Society guidelines, hospital elderly life program-confusion assessment method training manual, New York geriatric nursing protocols, World Health Organization's International Classification of Diseases, 10th Revision classification of mental disorders, Food and Drug Administration requests boxed warnings on older class of antipsychotic drugs 2008 and delirium in Miller's text book of anesthesia were reviewed and relevant information presented in this article.

Keywords: Current practice, elderly citizens, postoperative delirium, prevention

Introduction

Postoperative delirium (POD) is an acute disorder of cognition and attention, exhibits fluctuating symptoms of inattention, cognitive dysfunction, associated with disorganized thinking, and altered level of consciousness.[1] Other features of this syndrome include disorientation, impaired memory, perceptual instability, altered psychomotor activity, and altered sleep-wake cycles.[2] POD is one of the most unexpected and perplexing complications encountered following surgery. POD is associated with longer duration of hospital stays, more frequent discharge to long-term care amenities leading to greater cost with additional complications of poor recovery and increased mortality.[3] Even though POD is reversible in character, because of its long lasting sequelae in the form of cognitive deficits remaining for up to months, it can become chronic particularly in the elderly citizens following surgery.[4] In older patients, delirium can be a key factor in initiating a cascade of events that may lead to a, loss of independence, decline of executive function, institutionalization, and ultimately, death.[5]

The capability to predict patients at high risk for POD has enabled the physicians to do proactive interventions to prevent or to reduce the rate and severity of POD. Thus, a cornerstone in the management of POD is the detection and treatment of any underlying inciting factor. Therefore to familiarize the clinician in the management of POD a targeted literature search was performed, in EMBASE, CINAHL, and PUBMED between January 2000 and September 2015 using the keywords "delirium," "postoperative delirium" "acute postoperative confusion" and "brain dysfunction"

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resulted in 9710 articles, among them 73 articles were chosen for review. In addition National Institute for Health and Clinical Excellence guidelines, American Geriatric Society Guidelines, Hospital elderly life program-confusion assessment method (CAM) training manual, New York geriatric nursing protocols, World Health Organization's International Classification of Diseases, 10th Revision (WHO ICD-10) classification of mental disorders, Food and Drug Administration requests boxed warnings on older class of antipsychotic drugs 2008 and delirium in Miller's text book of anesthesia were reviewed.

Articles published in English language, describing precipitating, predisposing factors, pathophysiology, clinical features, diagnosis, preventive strategies, treatment regimens and outcomes of POD particularly in elderly, were analyzed and relevant information presented in this article. Excluded topics were delirium biomarkers, predictive models, prognostic methods, tools of assessment, alcohol or substance abuse, withdrawal, nonelderly populations (e.g., pediatric), dementia (e.g., Alzheimer disease), psychosis (e.g., schizophrenia), terminal illness (e.g., acute stroke), brain surgery, and traumatic brain injury.

The Epidemiology

The overall incidence of delirium is just 1%–2%, in the society, but in the hospital setting after admission this increases to 14%–24%.[5] The rate of delirium occurring during a hospital stay increase from 6% to 56%, and this number is still higher in those admitted in the Postanesthesia Care Unit, Intensive Care Unit (ICU) and palliative-care settings.[6-8] POD complicates in 15%–53% of surgical patients aged above 65 years,[9] and among these patients admitted to ICU the occurrence of POD can reach as high as 70%–87%.[10]

Risk Factors for Development of Postoperative Delirium

Development of POD depends on a compound interaction of multiple risk factors. A few of these risk factors are modifiable and are possible targets for delirium prevention. Health-care workers caring for elderly surgical patients should conduct a preoperative assessment for delirium risk factors, including age older than 65 years, dementia or chronic cognitive decline, poor vision, impaired hearing, severe illness, existence of infection, and any other risk factor as shown Table 1.[5,9,11-13] Patients with two or more risk factors should have greater risk for POD than patients with no or single risk factor. The risk for POD, in general, is greater in the emergency situation in comparison with the elective setting.

Pathophysiology

Many possible pathophysiologic mechanisms were postulated for the development of delirium. The widely

Table 1: Risk factors for development of postoperative delirium

Modifiable risk factors	Nonmodifiable risk factors
Preoperative predisposing factors	
Immobilization or limited mobility	Age >65 years
Hearing or vision impairment	Male gender
Presence of infection or shock	ASA physical status ≥III
Inadequately controlled pain, use of opioid analgesic commonly mepridene	History of delirium, stroke, neurological disease, falls, or gait disorder
Depression	Current hip fracture
Alcohol abuse or smoking	Dementia or cognitive impairment
Anemia and hypoalbuminemia	Functional impairment
Decreased oral intake and malnutrition	Renal or hepatic insufficiency
Intra-operative precipitating factors	
Hypoxia or hypercarbia	Aortic procedures
Dehydration-oliguria	Multiple co-morbidities burden
Use of psychotropic medications (antipsychotics, benzodiazepines, anticholinergics, antihistamines, meperidine)	Surgery: Emergency surgery, vascular surgery, orthopedic surgery
Electrolyte abnormalities (hyper- or hypo-natremia)	
Poly-pharmacy: More than 5 drugs at a time	
Postoperative precipitating factors	
Risk of urinary retention or constipation	Environment (e.g., admission to ICU)
Presence of urinary catheter	Prolonged hospital stay (chronic illness)
Pain, emotional distress	Advanced oncological disease
Sustained sleep deprivation	

ASA = American Society of Anesthesiologists, ICU = Intensive Care Unit

suggested mechanisms include alterations in one of several neurotransmitter systems,[14] inflammatory mediators, physiological stress,[9] metabolic disorders, and electrolyte disturbances. An extensive evidence supports an imbalance between dopaminergic and cholinergic neurotransmitters as a key factor in the genesis of delirium.[15] In fact, drugs with anticholinergic properties can incite delirium,[16] and therapy with cholinesterase inhibitors such as physostigmine can effectively reverse delirium in some occasions.[9] The antipsychotics, which block dopamine receptors are successful in the treatment of delirium.[15] Thus, a reduced cholinergic reserve and relative excess of dopaminergic transmission in certain regions of the brain were related to the development of delirium.[16] Pro-inflammatory mediators, such as interferon α or β, interleukin (IL)-1β, IL-6, IL-8, IL-10 and tumor necrosis factor-alpha, may contribute to the genesis of delirium by increasing the blood brain barrier permeability, thereby altering neurotransmission.[17] In addition, biological stressor response from anesthesia and surgery is known to incite sympathetic over activity to liberate glucocorticoids which may play a key role in the genesis of delirium.[18]

Although the basic pathophysiologic mechanisms of delirium are not yet completely understand, in the geriatrics prototype, delirium characterizes an atypical presentation of disease,[19] in which acute disease is manifested through weakest link of the most susceptible organ system, in this case, it is brain, results in delirium. This hypothesis explains that the normal course of aging can be characterized as homeostenosis, the progressive shrinkage and constriction of homeostatic reserve in every organ system's ability to respond to stress.[19,20] In addition, the aging brain is more prone to be affected by drugs and that cloud the sensorium of brain. The sum of all these effects leads some older adults to be teetering on the edge of neurodysfunction. If these elderly people are subjected to the stressor, is now beyond the reserve limits as a result of homeostenosis of aging. In this case, it is brain centered, decompensation occurs, because compensatory mechanisms are over whelmed, results in delirium.[19]

Clinical Features

All health-care workers need familiarity with the symptoms and signs of delirium. POD can develop from the 1st to 3rd postoperative day.[21] The clinical manifestations of delirium vary and can often be vague. On the basis of psychomotor behavior Robinson *et al.*,[22] using validated instruments measured and broadly classified delirium into three subtypes.

- The hypoactive type, in which patients are withdrawn and quiet, unaware, with prominent lethargy or apathy, decreased alertness, staring, psychomotor slowing, slowed movements, sparse, or slow speech
- The hyperactive type, featuring prominent agitation, hyperarousal, hypervigilance, irritability, restlessness, combativeness, fast or loud speech, singing, swearing, laughing, fast motor responses, hallucinations, impatience, anger, uncooperative, wandering, easy startling tangentiality, distractibility, nightmares, or persistent thoughts, often associated with life-endangering autonomic instability
- The last mixed type in which patients frequently fall somewhere along a spectrum between the hyperactive and hypoactive extremes, sometimes swinging from one to the other type within minutes.[19,23]

In most cases, the clinical features of delirium have a tendency to fluctuate both in severity and type, with a lucid interval in between them. It has been implicated that each subtype of delirium can result from a different pathological mechanism, and that each one might carry a varied prognosis.[24,25]

Delirium Screening Tools

A range of bedside screening devices are available to help the clinician in the recognition of delirium. Many screening instruments have been narrated in the published articles,[26,27] among them 11 tools were identified for the evaluation of delirium.[27,28] The CAM[29] was reported as the best validated and most accurate of the tools reviewed. The CAM operates on the Diagnostic and Statistical Manual, 4th edition (DSM-IV) criteria, increased reliability is demonstrated when health-care professionals trained in the use of a screening tool evaluated the patients for delirium. CAM is used by many as a screening instrument (short form) and diagnostic tool (long form with algorithm).[26-29] The CAM is a bedside rating scale developed to assist clinicians not trained in psychiatry for rapid and accurate diagnosis of delirium in clinical settings, can be administered by any health-care worker and may also be administered by trained lay interviewers. The sensitivity of the CAM is 94%–100%, with specificity 90%–95% against the gold standard of psychiatric diagnosis.[19] Other validated instruments commonly used for screening delirium are delirium symptom interview and nursing delirium screening scale.[30] The CAM-ICU[31] and Intensive Care Delirium Screening Check List[32] has been adapted for measuring delirium of ventilated patients in the ICU. For elective surgery, patients should have their preanesthetic cognitive testing to record their baseline level.[33,34]

Diagnosis of Delirium

Early diagnosis and treatment of POD are crucial components for precise surgical care of older adults. The most important step

to establish the diagnosis of delirium is obtaining history from an observer (e.g., caregiver or family member), doing a brief cognitive assessment (e.g., level of arousal for verbal stimulus, low arousal states of acute onset, disorientation to time place and changes in language indicate cognitive deficit. Attention can easily be assessed by simple bedside tests such as digit span or telling the months of the year backwards) and review of medical records. For laboratory investigations, targeted testing is the best strategy. Table 2[11,35] summarizes the recommended work-up and diagnostic assessments (e.g., laboratory testing or neuroimaging) on the basis of the patient's history and physical examination.[35]

A high degree of clinical suspicion is the mainstay to discern delirium in older patients after surgery.[36] The hallmark of delirium is acute fluctuating cognition from baseline, inattention is the cardinal feature of delirium, associated with either disorganized thinking or an altered level of consciousness are diagnostic of delirium. Use of a cognitive test is required for accurate diagnosis, a formal delirium diagnostic tool such as the DSM-V,[37,38] the WHO ICD-10,[39] or CAM diagnostic algorithm[29] used by a competent health care professionals will make the diagnosis of delirium more accurately.

Prevention

Prevention is the most effective strategy to minimize the detrimental outcomes of delirium, and an estimated 30%–40% of cases of POD can be preventable by early treatment of predisposing factors.[5] Although the evidence is weaker for prevention of delirium, several moderate to high quality studies demonstrated benefit from non-pharmacologic measures [Box 1].[9,40-44] Implementing and monitoring these interventions by an interdisciplinary team, may successfully

Table 2: Approach to a patient for evaluation of delirium

Approach
An organic cause should be ruled out first by detailed history, physical examination, laboratory investigations, or other diagnostic tests
Any risk-associated medications, doses may be minimized or stopped temporarily
History
Baseline cognitive function, attention and acute changes in mental status (history from staff or surrogates) can be assessed while taking history from the patient
Recent changes in condition, new diagnoses
Review all current drugs (including herbal preparations and over-the-counter purchases); pay special attention to new drugs and drug interactions
Review sleep disturbances, sedative and alcohol use
Assess discomfort and pain (e.g., thirst, urinary retention and constipation)
Physical examination
Vital signs, record postural vital signs as required
Measure core body temperature, oxygen saturation
Thorough physical examination and review of all systems
The neurologic examination requires a careful assessment of mental status
Search for signs of systemic infection, dehydration, deep vein thrombosis, acute abdominal pain and other acute illness
Look for sensory impairments e.g., visual and hearing
Investigate for meningitis signs and focal neurological changes
Explore for evidence for nonconvulsive status epilepticus
Laboratory investigations (selected tests based on history and physical)*
Consider complete hemogram; urinalysis; measurement of concentrations of serum glucose, electrolytes and calcium
Tests for renal, liver, pulmonary, and thyroid function
Send urine, blood and sputum for cultures
Measure serum concentrations of drugs, cortisol, ammonia, and vitamin B12
Arterial blood gas analysis
Do ECG
Lumbar puncture should be reserved for evaluation of fever with headache and meningitis signs or suspicion of encephalitis
Targeted imaging (in selected patients)
X-ray, chest and abdomen
Electroencephalography (in selected patients of suspected encephalitis and head trauma)
Computed tomography brain (stroke can present as delirium)
Review all medical records including nursing notes
Differentiate other psychiatric disorder from delirium

**Conducting all these tests in all patients is not necessary; rather, specific tests should be performed guided by history, physical examination, and previous results. ECG = Electrocardiography*

Box 1: Non-pharmacologic strategies for prevention of delirium

- Sensory improvement by providing visual and hearing aids for patients with visual and hearing impairments
- Maintain safe early mobility (at least twice a day ambulation if possible)
- Reorientation to surroundings and remedial activities
- Adequate pain control with nonopioid analgesics (generally acetaminophen if suitable)
- Cognitive stimulation (if feasible, modified to the interests and mental status of patient)
- Regular communication and approaches to de-escalation of behaviors
- Nutrition and fluid (meeting the nutritional needs and hydration)
- Nighttime routine sleep enhancement (discourage daytime sleep, nonpharmacologic approach for sleep and relaxation)
- Review of current medications and optimal management (use of lower effective dose)
- Daily, interdisciplinary team clinical rounds to reinforce the intervention

reduce the rate of POD about 30%–40% in the postsurgical period.[42,44]

Perioperative Preventive Measures

Although several intra-operative issues were studied for their effect on POD, however there is inadequate information on the topics studied earlier, which including regional anesthesia versus general anesthesia (GA), specific anesthesia agents, intra-operative blood transfusion, systemic arterial pressure monitoring and use of medications such as statins or dexamethasone. Previous studies have found deep sedation was associated with increased rates of POD and lighter planes of anesthesia will reduce POD in comparison with deeper sedation.[45] A Randomized use of Bispectral Index by anesthesia providers to guide anesthesia depth during GA have reduced the incidence of POD in older patients when compared with those who received regular care. Monitoring anesthetic depth during intravenous sedation or GA for older patients using processed electroencephalographic (EEG) monitors may reduce POD. The idea is that by EEG monitoring and providing a lighter depth of anesthesia by administering lower doses or fewer anesthetic agents will reduce POD in comparison with deeper sedation.[46,47]

Inadequate postoperative analgesia contributes to development of POD. Postoperative pain control is paramount to curtail the frequency of delirium.[48,49] A magnitude of evidence suggests that nonopioid analgesics diminish POD in comparison with opioid-only analgesic regimes.[50,51] The use of regional anesthesia has been found to reduce POD in two studies.[52,53] Current practice guidelines to improve the safety of medication use in older adults advocated avoidance of drugs prone to enhance the severity or risk of delirium [Table 3].[54,55]

Poly-pharmacy use of 5 or more medicines has been associated with an increased risk of delirium, likely due to the psychoactive properties of one or more of the medications in the patient's regimen.[56]

Prescribing antipsychotic medications to prevent POD has limited, conflicting, and contradictory support in the literature. Several studies found decreased incidence of delirium with prophylactic antipsychotics,[57-59] and a few did not.[60-62] Potential tribulations of this class of medication are considerable; therefore, antipsychotics are not recommended to thwart delirium.[63-66] Prophylactic administration of newly approved cholinesterase inhibitors are not effective in reducing POD,[67-69] and may cause increased harm including mortality;[70] hence, no prophylaxis is currently recommended with these agents in the current practice guidelines.

Treatment of Delirium

Even though, the quality of evidence is low for recognizing and treating the underlying inciting factors of a patient's delirium, health-care professionals are strongly recommended to carry out a medical evaluation, make environmental and medication adjustments, and perform appropriate investigations to identify and treat underlying contributors for development of POD. Neuroimaging is generally limited to patients with recent head trauma or falls, focal neurologic signs, use of anticoagulation and fever of unknown explanation [Table 2].[11,35] Thus, the treatment of POD consists of treating the underlying cause, correcting fluid, electrolyte imbalance, hypoxia, and removing catheters if present. The next step consists of initiating the nonpharmacological measures, which are similar to preventive measures [Box 1][9,40-44] but also include regimens for de-escalation of agitation, education of nurses, physicians, and proactive geriatric consultation, the last step is treating the patients who are restless, aggressive, agitating and harm to self or others with antipsychotics [Table 4].[39,55,71,72]

Current practice guidelines recommended lowest effective dose and shortest duration of antipsychotics to treat patients who are severely violent or aggressive, and are threatening sizeable harm to others or self. In all patients, management with antipsychotics should be started only if behavioral procedures have failed or are not possible, and continuing use should be assessed daily with physical examination of patients. Antipsychotic or benzodiazepines [Table 4][39,55,71,72] are not prescribed for treatment of POD in older adults who are not agitated or distressed.[25] No current evidence supports the routine use of benzodiazepines in the delirium treatment. There

Table 3: Drugs prone to increase the risk of postoperative delirium

Low risk medications	High risk medications
Anticonvulsants Carbamazepine, phenytoin, valproate	Sedative-hypnotics Benzodiazepines: Alprazolam, diazepam, lorazepam, midazolam, others: Zolpidem, zaleplon, alcohol, propofol
Antiarrhythmics Beta-blockers, clonidine, digoxin	Dopamine agonists Amantadine, levodopa, bromocriptine pergolide, ropinirole, pramipexole
Antimicrobials Acyclovir, amphotericin B, linezolid, aminoglycosides, cephalosporins, fluoroquinolones, macrolides, penicillin, sulfonamides	Corticosteroids Hydrocortisone, prednisone, methylprednisone, dexamethasone
Gastrointestinal agents Histamine2-receptor antagonists Antiemetics-promethazine	Antispasmodics Atropine, benztropine, diphenhydramine, scopolamine
Skeletal muscle relaxants Baclofen, cyclobenzaprine, tizanidine	Analgesics Opioids - meperidine, NSAIDs
Antipsychotics First-generation-chlorpromazine, thioridazine Second-generation-olanzapine	Antidepressants Mirtazapine, selective serotonin reuptake inhibitors Tricyclic antidepressants-amitriptyline, doxepin, imipramine
Other drugs with anticholinergic properties Antihistamines: Cyproheptadine, hydroxyzine diphenhydramine Antimuscarinics: Oxybutynin, tolterodine	
Poly-pharmacy – using ≥5 medications increases risk of delirium	

NSAIDs = Nonsteroidal anti-inflammatory drugs

Table 4: Most commonly used drugs in the treatment of delirium

Class and drug name	Dosage	Side effect	Scientific evidence
Antipsychotics			
Haloperidol	0.25-1 mg oral, IM or IV (with ECG) can be repeated 4th hourly, maximum dose 4.5 mg/day	Extra-pyramidal syndrome, prolonged QT interval	Used in hyperactive types of delirium. Paucity of scientific evidence
Atypical antipsychotics			
Risperidone	Oral 0.25-0.5 mg twice a day, maximum 4 mg/day	Extra-pyramidal syndrome, dizziness, excessive sedation, prolonged QT interval, hypotension	Indicated for agitation and behavioral symptoms. Scanty data from clinical studies
Olanzapine	Oral 1.25-2.5, IM 2.5 mg 4th hourly maximum 10 mg/day	”	”
Quetiapine	6.25-12.5 mg twice a day, maximum 150 mg/day	”	”
Benzodiazepines			
Lorazepam	0.5-1 mg oral; can be repeated every 4th hourly	Paradoxical excitation, confusion, excessive sedation, respiratory depression	Indicated in delirium due to alcohol or drug withdrawal. Evidence significant
Midazolum	1-5 mg		
Cholinesterase inhibitors			
Donepezil	5 mg 6th hourly	Nausea, vomiting, diarrhea	Used in delirium due to anticholinergic agents. Little scientific evidence

IM = Intramuscular, IV = Intravenous, ECG = Electrocardiography

is a significant evidence that benzodiazepines promote delirium.[73] Conversely, benzodiazepines remains the suggested therapy for treatment of alcohol and drug withdrawal induced delirium.[74]

Outcome

POD, which results from dissimilar multiple etiologies, can contribute to poor patient outcome, irrespective of the

underlying cause. It has been reported that POD is associated with poor outcomes even after controlling basic patient personality and etiological factors,[75] and the more severe the occurrence of POD, the poorer will be the outcome.[76] Some patients (33%) never get back to their baseline state of cognitive function following an attack of delirium and show persistent functional and cognitive deficits. Patients with dementia who subsequently develop delirium, besides demonstrating worst outcomes, have higher rates (33%) of institutionalization, hospitalization and death than those who do not suffer from this condition.[77-80]

Conclusion

POD is a serious cause and complication of hospitalized elderly patients. Irrespective of the specific etiology, POD has the potential to distinctly affect the overall outcome and prognosis of severely ill patients, as well as significantly increasing health-care costs. Nonpharmacologic prevention strategies have shown to be effective at diminishing the incidence of delirium; as pharmacological prevention strategies have no trial-based support. Assessing and recognizing delirium risk preoperatively, implementing delirium prevention strategies, and applying standardized treatment protocols when it occurs are essential components of optimal perioperative care for elderly citizens.

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CONFERENCE CALENDAR July-September 2017

Name of conference	Dates	Venue	Name of organising Secretary with contact details
27th Annual Conference Research Society of Anaesthesiology Clinical Pharmacology (Rsacpcon 2017)	September, 14th - 17th, 2017	Status Club, Kanpur	Dr Anil Kumar Verma Prof & Head, Deptt of Anaesthesiology, Critical Care & Pain Medicine, GSVM Medical College, Kanpur, Uttar Pradesh 9336107410, 7408945150, E-mail: anil_16021976@rediffmail.com; www.rsacpcon2017kanpur.in
10th National Conference of Association of Obstetric Anaesthesiologists. AOACON 2017. at	September 30th - October 2nd 2017	Hotel Clarks Exotica, Bengaluru	Dr. Murali Chakravarthy Organizing Chairman Dr. Anitha Prashanth Organizing Secretary E-mail: aoa2017blr@gmail.com, www.aoabengaluru.in
65th Annual National Conference of the Indian Society of Anaesthesiologists	November, 25th - 29th, 2017	Biswa Bangla Convention Center, Newtown, Rajarhat, Kolkatta	Dr. Sumanta Dasgupta Organizing Chairman Dr. Subhendu Sarkar Organising Secretary Mobile: 9831171162 Indian Society of Anaesthesiologists (West Bengal State Branch) 41 D, Palm Avenue, Kolkata - 700019 http://isacon2017kolkata.com
TMC National Conference on "The Difficult Airway" (TMC-DAC 2017)	December 1st - 3rd, 2017	Tata Memorial Hospital, Mumbai	Dr. Sheila Nainan Myatra Organizing Secretary TMC-DAC 2017 Clinical Research Secretariat, 3rd Floor, Main Building, Tata Memorial Hospital, Parel, Mumbai - 400 012 Phone No: (+91 22) 24177000 Ext: 4254 (9.30 am to 5.30 pm) E-mail: tmcdifficultairwayconference@gmail.com