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Review Article

Internal Medicine Section

A Review of Clinical Evaluation and Management of Delirium

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ABSTRACT

Delirium is a syndrome characterised by the acute onset, fluctuating course of disturbed consciousness and cognitive impairment. It is an important medical condition with poor outcomes. Delirium is still under-recognised problem in intensive care unit. This is our endeavor to review the diagnosis and management of delirium based on the published literature. Two reviewer independently searched Electronic databases MEDLINE/PubMed, Google Scholar, Cochrane library and Scopemed with Mesh (Medical Subject Headings) terms "delirium", "diagnosis", and "management" from earliest possible date to January 31st, 2018. Articles in any language especially those published in recent years were given preference. Delirium is categorised into hypoactive, hyperactive and mixed type. The Confusional assessment method is an effective, easy and user-friendly tool to diagnose delirium. The non-pharmacological management like reorientation, mobilisation, and termination of the reversible cause is the initial step of delirium management. Haloperidol is a drug choice for delirium; however, newer antipsychotics are showing promising results.

Keywords: Antipsychotic, Diagnostic tool, Outcomes, Pathophysiology, Risk factors

INTRODUCTION

Delirium (sometimes called acute confusional state) is a syndrome characterised by acute onset, fluctuating course of disturbed consciousness and cognitive impairment [1]. The point prevalence of delirium was 10-15% which was even higher if we consider only elderly population [2]. It is a serious medical condition with poor outcomes. Every 48-hours of delirium increases mortality by 11% [3]. Delirium is widely considered as a marker of the quality of hospital care [4]. The misdiagnosis of delirium in the medical and surgical ward was up to 46% [5]. Delirium is still an under-recognised problem in intensive care unit [6]. The delirium is generating considerable interest in a patient care in the developed world; however, it is still neglected in developing countries. In this review, we aim to analyse the diagnosis and management of delirium based on published literatures of delirium.

PATHOPHYSIOLOGY

The pathophysiology of delirium is a complex process and not clearly understood yet. Among the various theories hypothesised, the most widely accepted theory is neurotransmitter theory and neuroinflammation theory. The neurotransmitter hypothesis states that delirium is a result of decreased cholinergic activity and increased dopamine, noradrenaline, and glutamate activity in the brain. It occurs due to the reduced oxidative metabolism of neurotransmitter [7]. This theory is supported by the improvement of delirium with the use of cholinesterase inhibitor and a dopamine antagonist.

Neuroinflammation theory states that delirium is due to release of different cytokines, which leads to brain dysfunction. In a delirious patient, there was an elevation in Interleukin-6 and Interleukin-8 [8]. This theory gives explanation to the toxic and septic delirium. The other proposed theories of delirium are: neuronal aging, oxidative stress, neuroendocrine, diurnal dysregulation, and network disconnectivity [9]. To explain all the theory of delirium is out of the scope of this review.

RISK FACTORS

The risk factors for a delirium are categorised into predisposing and precipitating factors as mentioned in [Table/Fig-1] [10]. Predisposing factors are an inherent characteristic of individuals to have delirium whereas precipitating factors are often modifiable factors associated with delirium.

Predisposing factors	Precipitating factors
Dementia	Infection
Advanced age	Benzodiazepines use
Visual impairment	Alcohol withdrawal
High co-morbid burden	Brain insult
History of alcohol abuse	Acute kidney injury
Malnutrition	Liver failure
Past history of stroke	Heart failure
Hearing loss	Catheterisation
	Physical restraint
	Polypharmacy

[Table/Fig-1]: Risk factors for delirium.

CLINICAL FEATURES

Delirium is characterised by a global disturbance in a cognition, attention, and consciousness. It is usually of an acute onset. The severity of delirium fluctuates with time. It shows sun-downing phenomenon. Caregivers often need to take history from the patient attendant and nursing staff. The heterogeneity in the symptoms of delirium led to under recognition of this condition. The diagnosis is often confused with other condition like catatonic depression and dementia [5]. The clinical features of delirium vary according to its type. Delirium is classified into three motor subtypes- 'Hypoactive', 'Hyperactive' and 'Mixed type' [11]. Hypoactive delirium is characterised by drowsiness and inactivity whereas hyperactive delirium is dominated by restlessness and agitation. The mixed type has the features of both agitation and drowsiness [12]. The prevalence of hyperactive, hypoactive and mixed type delirium was 50.15%, 19.93%, and 24.6% respectively [13]. Even though most of the delirium is precipitated by the benign conditions, sometimes it may be a manifestation of life threatening condition. The red flag sign for delirium is illustrated in [Table/Fig-2] [14].

CLINICAL EXAMINATION

There are numerous causes of delirium. We should examine the patient thoroughly to identify the etiological diagnosis of delirium. The summary of the examination is illustrated in [Table/Fig-3]. We should perform complete blood count, electrolyte panel, random

1	Altered level of consciousness
2	Age <65 years
3	Head trauma
4	Neurological sign
5	Severe headache
6	Delirium tremens
7	Vomiting
8	Presence of co-morbidities

[Table/Fig-2]: Red flags for delirium.

blood sugar, renal function, hepatic function analysis and arterial blood gas analysis. Chest X-ray may show evidence of pneumonia. Computed tomography of the head should be done if delirium associated with the focal neurological deficit. Toxicological profile may be required if history is suggestive of toxin intake [15].

General physical examination	Assess dehydration, temperature, icterus
Central system examination	Sensorium, focal neurological sign, meningeal sign, pupillary reaction
Gastrointestinal system	Look for abdominal distension
Respiratory system	Assess for pneumonia and chronic respiratory disease
Cardiovascular system	Look for evidence of heart failure
Genitourinary system	Asses for urinary bladder distension
Musculoskeletal system	Asses for musculoskeletal injuries

[Table/Fig-3]: Clinical examination to look for delirium.

DIAGNOSIS TOOL

In the assessment of delirium, there are various tools and criteria like Confusion Assessment Method (CAM) tool, Diagnostic Statistical Method-V (DSM-V) criteria and Delirium Rating Scale (DRS). Among the various methods, CAM is an easy, reliable and user-friendly tool. It can be done within five minutes [16]. The confusional assessment method had a sensitivity of 94% and specificity of 89% to diagnose the delirium [17]. Adamis D et al., in his study reported that the there was an agreement between CAM, DSM-IV, DSM-V and delirium rating scale-R98 in diagnosing the delirium [18]. The questionnaire of CAM is shown in [Table/Fig-4]. In intensive cares setting, a well validated a CAM-ICU tool can be applied to screen delirium in a critical ill patients. Similarly, memorial delirium assessment scale is reliable, easy and a time-saving tool to assess the severity of delirium [19].

1	Acute onset and fluctuating course
2	Impaired attention
3	Disorganised thinking
4	Altered level of consciousness
For diagnosis of delirium 1 and 2 plus either 3 or 4 is required	

[Table/Fig-4]: Confusional assesment method.

TREATMENT

Non-pharmacological Treatment

The management of delirium begins with the counseling to the caregiver regarding the symptoms, prognosis, and mode of management of delirium as soon as the diagnosis of the delirium established. Adequate hydration and nutrition therapy is an important component of the management of delirium. We should correct the identifiable reversible cause as soon as possible. The multi-component nonpharmacological interventions should be offered to patients with delirium. It includes promoting mobilisation, avoiding bed changes, limiting medical monitoring, reorienting patients and promoting sound sleep [15].

Physical Restraining

Physical restraining is a commonly practiced method for managing the delirium. Physical restraining was associated with increased mortality and morbidity [20]. The most common indication for physical restraint was the prevention of disruption of therapy [21]. Physical restraint of the delirious patient should be discouraged unless the patient combativeness hampered their or other patient's therapy. Physical restraining should be time-limited. Caregiver should re-evaluate the indications, side-effects, and effectiveness of physical restraining frequently while managing the patients with delirium [22].

PHARMACOLOGICAL THERAPY

Haloperidol

Haloperidol is the most frequently prescribed typical antipsychotic drugs for delirium due to its lesser anticholinergic and sedative side-effects. Devanand DP et al., in their study demonstrated that standard dose haloperidol (2 to 3 mg/day) was significantly more effective than low dose haloperidol (0.5-0.75 mg/day) and placebo to reduce the psychomotor agitation in a patient of Alzheimer's disease with delirium [23]. Haloperidol was equally effective to risperidone, olanzapine and aripiprazole to reduce the delirium but the extra pyramidal side effects were more than other antipsychotic drugs [24].

Risperidone

Risperidone is a second line atypical antipsychotic with predominant action on 5HT2 and dopamine-2 receptor [25]. Risperidone is recently advocated by many clinicians for its use in delirium due to its decreased extra-pyramidal side-effects. Han CS and Kim YK, in their study demonstrated that 'Risperidone' and 'Haloperidol' had comparable efficacy and side-effects profile; however, the sample was smaller in the study and need of study with larger sample size was recommended [26]. The low dose of risperidone (2.6±1.7 mg/day) was effective and safe in delirium in the medically ill patient [27]. The side effects of risperidone are tremor and rigidity [28].

Quetiapine

Quetiapine is an atypical antipsychotic with little extra-pyramidal and antimuscarinic side effects [29]. Srisurapanont M, in their open-label study on delirium demonstrated that quetiapine at a dose of 25-100 mg/day is well tolerated and significantly reduces its severity [30]. It is comparable to haloperidol in efficacy and safety for the management of behavioural disturbances in the delirious patient [31]. The extra-pyramidal side-effects and QT_C prolongation of quatiapine are lesser than haloperidol. The major side-effects of quetiapine are somnolence, dizziness, and postural hypotension [32].

Olanzapine

Olanzapine is a atypically antipsychotics action with antagonist action on D2 receptor and 5HT2 receptor. Olanzapine has a poorer response in the elderly population above 75 years of age [24]. Olanzapine was comparable to haloperidol for resolving the delirium [33,34]. Olanzapine was also effective in reducing the episode of delirium if given prophylactically to elderly patients undergoing joint replacement surgery [35]. The extra-pyramidal side-effects of olanzapine were negligible; however, sedation is a major issues in in about 30% of patient treated with olanzapine [36].

Dexmedetomidine

Dexmedetomidine is a selective alpha-2 agonist. It shows sedative, anxiolytic and analgesic effect. It was more effective than haloperidol in reducing the ICU length stay, duration of intubation and need of sedation in a patient who was under mechanical ventilation [37]. Phandharipande P et al., reported in their study that 'Dexmedetomidine' was better than 'lorazepam' to achieve the targeted level of sedation in a mechanically ventilated patient with fewer days in delirium [38]. Among mechanically ventilated patient, dexmedetomidine treated patient had a lesser risk for delirium than

midazolam with the same level of sedation. The added advantage of dexmedetomidine in a mechanically ventilated patient is not causing respiratory depression. Common side effects of dexmedetomidine are nausea, hypotension, and bradycardia [39].

Aripiprazole

Aripiprazole is a partial D2 partial agonist, 5-HTA1 agonist, and 5-HTA2 antagonist [40]. Boettger S and Breitbart W, reported in their study that 'Aripiprazole' is effective in managing the hypoactive as well as hyperactive delirium in the hospitalised cancer patient [41]. Aripiprazole is preferred in a patient with the cardiovascular disease and diabetes due to its minimal effect on QT_C interval, weight gain, lipid profile, and glucose profile [42]. The starting dose of aripiprazole is 1 mg BD [43].

Benzodiazepine

Benzodiazepine is commonly used to control the agitation in the hospitalised patient. In the meta-analysis done by Mayo-smith MF et al., demonstrated that benzodiazepines were more effective than a neuroleptic agent to reduce the alcohol withdrawal related delirium [44]. Lorazepam is an important a risk factor to cause delirium in the mechanically ventilated patient [38]. Benzodiazepines cannot be recommended for the management of delirium other than alcohol withdrawal delirium due to limited evidence [31]. The side effects of benzodiazepines use is respiratory depression and somnolence.

PREVENTION

The prevalence of preventable delirium was 30-40% in a hospital setting [45]. As the delirium has a huge impact on mortality, morbidity and health care costs, we should take utmost care to prevent the delirium in a hospitalised patients. Inouye SK et al., reported that early intervention of the cognitive impairment, vision problems, hearing difficulty, immobility, sleep deprivation and dehydration were effective to prevent the delirium in a high-risk population than usual group [46]. Serafim RB et al., in their study demonstrated that the use of antipsychotic in surgical ICU as the preventive strategies may be effective to decrease the prevalence of delirium; however, Neufeld KJ et al., in the systemic review and meta-analysis of 19 studies demonstrated that antipsychotics was not effective for prevention and treatment of delirium [47,48]. Sleep protocol including back rub, warm drink, and relaxation tape reduced the use of sleep hypnotic drugs in a hospitalised elderly patient which prevent the onset of delirium [49]. Brummel NE and Girard TD, in their review reported that delirium can be prevented by pain management, early mobilisation and improving sleep in ICU patient with multiples risk factors [50]. Hence, non pharmacological intervention like pain management, sound sleep, early mobilisation, reduced used of hypnotics, addition of sensory aids should be encouraged and practiced by to prevent the delirium in hospitalised patients.

STRENGTH

The simplified approach to a case of delirium and reviews of current medication of delirium.

LIMITATION

We didn't conduct meta-analysis. Despite the present maximal effort, there might be a selection bias of studies and recent important studies have been missed out.

CONCLUSION

Delirium is a common problem in a clinical practice. The clinical feature of delirium is based on its type. CAM is an effective and easy method to diagnose delirium. We should advocate for a nonpharmacological method like termination of reversible causes, reorientation, and ealry mobilisation of the hospitalised patient. Use of physical and chemical restraint should be minimised. The preventive methods of delirium in should be practiced in day to day care of the high risk population. Use of antipsychotics should be minimised and restricted to hyperactive delirium.

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