Research article

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Assessment of risk factors and precipitating factors of delirium in patients admitted to intensive care unit of a tertiary care hospital

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Abstract

Background and Aim: Delirium is defined as disturbance in attention and awareness. Delirium is a common complication in patients admiited to intensive care unit. The focus of the researchers has shifted from treatment to prevention of the syndrome. There is a need to study risk factors for prevention of delirium. Data on delirium in intensive care unit is scarce in the Indian subcontinent. Hence, the present study was done to assess risk factors and precipitating factors of delirium in patients admitted to medical intensive care unit of a tertiary care hospital.

Materials and Methods: This is an observational study done over a period of 1 year. Patients admitted to medical ICU were screened for presence of delirium within first 72 hours of admission using RASS and CAM-ICU. Comatose patients, with RASS score of -4 or -5, were excluded from the study. Risk Factors and precipitating factors associated with delirium were assessed. Independent t-sample test or the Pearson Chi-square test were used to calculate differences between delirious and non-delirious subjects. Odds ratios (OR) was calculated for all factors using univariate binary logistic regression.

Results: Percentage of patients developing delirium within the first 72 hours of admission was 25.7% (406/1582). 52% of patients had hypoactive delirium, 48% of them had hyperactive delirium. Alcohol (OR 6.54), sedatives usage at the time of admission (OR 2.48), visual disturbances (OR 2.22), bowel and bladder disturbances (OR 1.67) were significant modifiable risk factors contributing to delirium. Previous psychiatric illness (OR 3.73), previous cognition impairment (OR 2.73) were significant non-modifiable risk factors contributing to delirium. Predominant precipitating factors among delirious subjects were uremia (25.1%), hepatic encephalopathy (22.7%), hyponatremia (19.5%).

Conclusion: Delirium is common in intensive care unit patients. Major risk factor contributing to delirium was alcohol consumption. Most common precipitating factors resulting in delirium were deranged metabolic parameters. All ICUs should implement both RASS and CAM-ICU for early detection of delirium.

Keywords: CAM-ICU, hypoactive and hyperactive delirium, RASS

Abbreviations: CAM-ICU= Confusion Assessment Method for ICU, ICU = Intensive Care Unit, RASS= Richmond Agitation-Sedation Scale, OR = Odds ratio

Introduction:

According to DSM V, delirium is defined as disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). This disturbance develops over a short period of time and it represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.

The focus of the researchers has shifted from treatment to prevention of the syndrome. There is a need to study risk factors for prevention of delirium[1]. Data on delirium in the intensive care unit is scarce in the Indian subcontinent[2].

A multicenter study indicated risk factors significantly contributing to delirium were related to patient characteristics (smoking, daily use of more than 3 units of alcohol, living alone at home), chronic pathology (pre-existing cognitive impairment), acute illness (use of drains, tubes, catheters, use of psychoactive medication, a preceding period of sedation, coma, mechanical ventilation) and the environment (isolation, absence of visit, absence of visible daylight, transfer from another ward, use of physical restraints)[1]. Psychoactive medications can provoke a delirious state. Lorazepam has an independent and dose related temporal association with delirium[3].

Each additional day spent in delirium is associated with 20% increased risk of prolonged hospitalisation and 10% increased risk of death[4].

Hence, the present study was done to assess risk factors and precipitating factors of delirium in a medical intensive care unit of a tertiary care hospital.

Materials and methods:

This is an observational study done over a period of 1 year in a tertiary care medical college hospital located in southern part of India. Ethical committee approval for the study was obtained from the institutional ethical committee.

All patients admitted to medical intensive care unit in our tertiary care hospital, were screened for presence of delirium during the first 72 hours of admission using Richmond Agitation Sedation Scale (RASS) and Confusion Assessment Method for ICU (CAM-ICU). Patients with delirium were classified as delirious and the remaining as non-delirious patients. Comatose patients (RASS score -4 or -5) were excluded from the study.

Patients were initially screened with Richmond Agitation Sedation Scale (RASS). It is a 10-point scale, with 4 levels of agitation (+1 to +4) and 5 levels of sedation (-1 to -5). Level zero indicates calm and alert patient. Patients with RASS score of -4 or -5 (deep sedation and unarousable patients) were excluded from the study. Patients with RASS score of +4 to -3 were then screened for presence of delirium using Confusion Assessment Method for ICU (CAM-ICU). CAM–ICU has 4 criteria:

- 1) Acute onset and fluctuating course of delirium
- 2) Inattention
- 3) Disorganized thinking
- 4) Altered level of consciousness

The diagnosis of delirium requires the presence of criteria 1 and 2 and of either criterion 3 or 4.

Risk factors for developing delirium were assessed in the study population. Risk factors are those proven factors which may also be present before patient's admission to intensive care unit, and which predispose the patient to develop delirium. Risk factors were compared between delirious and non-delirious patients. Risk factors which were assessed were history of diabetes and hypertension, history of previous stroke, history of previous cognition impairment, history of previous psychiatric illness, history of previous trauma, history of previous episodes of delirium, history of bowel and bladder disturbances prior to admission (such as constipation and urinary retention respectively), history of alcohol abuse (consumption of more than 2 units of alcohol), history of smoking (more than 10 cigarettes per day), history of consumption of substances other than cigarettes and alcohol (such as cannabis, cocaine etc.), history of uncorrected visual or hearing disturbances before admission, history of usage of barbiturates (such as phenobarbital), benzodiazepines (such as alprazolam, chlordiazepoxide, clobazam, clonazepam) & opioids (such as morphine) before admission, history of usage of sedatives (such as haloperidol, midazolam, fentanyl) and pain killers (such as morphine, tramadol) at the time of admission. Metabolic risk factors which were compared between delirious and non-delirious subjects were uraemia, hyponatremia, hyperbilirubinemia, metabolic and respiratory acidosis.

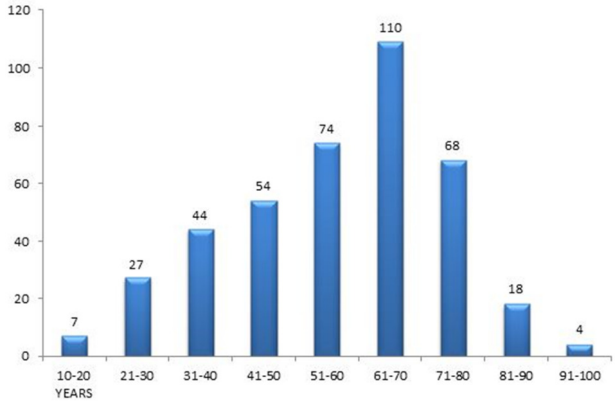
Precipitating factors weredefined as factors that were the likely causes of delirium in delirious patients. Precipitating factors for delirium which were looked into were exposure to toxins (alcohol/drugs), deranged metabolic parameters, infections and central nervous system causes.

SPSS21 software was used to calculate statistics. Independent t-sample test and the Pearson Chi-square test were used to calculate differences between delirious and non-delirious subjects. Odds ratios (OR) was calculated for all factors using univariate binary logistic regression.

Results:

Total number of patients enrolled in the study was 1582, of which 406 were diagnosed with delirium. Percentage of patients developing delirium within first 72 hours of admission was 25.7%. Hypoactive delirium was present in 52% and hyperactive delirium in 48% of patients. Patients who experienced delirium (57.5 $\pm$ 17 years) were older compared to their non-delirious (53.3 $\pm$ 18.1 years) counterparts (p value <0.0001). Among delirious subjects, majority were in the age group of 61-70 years (Figure 1).

Figure 1- Age distribution among delirious patients



38.2% of delirious patients and 39.3% of non-delirious patients were females. 61.8% of delirious patients and 60.7% of non-delirious patients were males.

Alcohol consumption [OR = 6.54 (95% CI 3.76-11.4, p = 0.0001)], previous psychiatric illness [OR = 3.73 (95% CI 1.712-8.159, p = 0.033)], previous cognition impairment [OR = 2.739 (95% CI 1.509-4.972, p = 0.001)], sedatives usage at the time of admission [OR = 2.488 (95% CI; 1.452-4.264), p = 0.001)], visual disturbances [OR = 2.227 (95% CI; 1.328-3.733, p = 0.002)], bowel and bladder disturbances [OR = 1.677 (95% CI 1.044-2.693, p = 0.032)] were significant risk factors contributing to delirium after univariate analysis (Table 1). Metabolic acidosis [OR = 1.996 (95% CI 1.469-2.711, p = 0.0001)] and hyperbilirubinemia [OR = 1.448 (95% CI 1.111-1.886, p = 0.006)] were significant metabolic parameters contributing to delirium after univariate analysis (Table 2).

Precipitating factors (Table 3) for delirium are those factors that were considered the most likely causes of delirium among the delirious patients. Precipitating factors for delirium were classified into toxins, deranged metabolic parameters, infections and central nervous system causes, of which metabolic parameters were most common. Among metabolic parameters, uraemia (25.1%), hepatic encephalopathy (22.7%) and hyponatremia (19.5%) contributed to the majority of cases with delirium.

Table 1 – Univariate analysis of risk factors of delirium

		NO DELIRIUM		DELIRIUM			
		COUNT	%	COUNT	%	P	UNIVARIATE
Diabetes	**No**	**729**	**62**	**226**	**55.7**	**.025**	**1.3(1.1-1.6)**
	Yes	**447**	**38**	**180**	**44.3**		
Hypertension	No	684	58.2	239	58.9	.8	.97(0.8-1.2)
	Yes	492	41.8	167	41.1		
History of Stroke	No	1107	94.1	379	93.3	.6	1.14(0.7-1.8)
	Yes	69	5.9	27	6.7		
Previous memory disturbances	**No**	**1149**	**97.7**	**264**	**89.7**	**<.0001**	**4.9(2.9-8)**
	Yes	**27**	**2.3**	**42**	**10.3**		
Previous psychiatric illness	**No**	**1161**	**98.7**	**386**	**95.1**	**<.0001**	**4(2-7.9)**
	Yes	**15**	**1.3**	**20**	**4.9**		
Trauma	No	1137	96.7	396	97.8	.3	0.6(0.3-1.3)
	Yes	39	3.3	9	2.2		
Previous episodes of delirium	No	1155	98.2	402	99	.3	0.55(0.2-1.6)
	Yes	21	1.8	4	1.0		
Bowel & bladder disturbances	**No**	**1107**	**94.1**	**350**	**86.2**	**<.0001**	**2.6(1.8-3.7)**
	Yes	**69**	**5.9**	**56**	**13.8**		
Alcohol	**No**	**1089**	**92.6**	**336**	**82.8**	**<.0001**	**2.6(1.8-3.7)**
	Yes	**87**	**7.4**	**70**	**17.2**		
Smoking	No	981	83.4	354	87.2	.07	0.7(0.5-1.03)
	Yes	195	16.6	52	12.8		
Other substance abuse (apart from cigarettes and alcohol)	No	1071	91.1	391	96.3	.001	0.4(0.22-0.6)
	Yes	105	8.9	15	3.7		
Visual disturbances	**No**	**1062**	**90.3**	**298**	**73.4**	**<.0001**	**3.4(2.5-4.5)**
	Yes	**114**	**9.7**	**108**	**26.6**		
Hearing disturbances	**No**	**1104**	**93.9**	**338**	**83.3**	**<.0001**	**3.1(2.2-4.4)**
	Yes	**72**	**6.1**	**68**	**16.7**		
Barbiturates	No	1155	98.2	401	98.8	.5	0.7(0.3-1.8)
	Yes	21	1.8	5	1.2		
Benzodiazepines	No	1155	98.2	400	98.5	.7	0.8(0.3-2.1)
	Yes	21	1.8	6	1.5		
Opioids	No	1176	100	405	99.8	.9	4.7(0-IN)
	Yes	0	.0	1	.2		
Sedatives usage in present admission	**No**	**1143**	**97.2**	**369**	**90.9**	**<.0001**	**3.5(2.1-5.6)**
	Yes	**33**	**2.8**	**37**	**9.1**		
Pain killers usage in present admission	No	1080	91.8	400	98.5	<.0001	0.17(0.07-0.39)
	Yes	96	8.2	6	1.5		

Table 2- Univariate analysis of metabolic parameters

		NO DELIRIUM		DELIRIUM			
		COUNT	%	COUNT	%	P	UNIVARIATE
Uraemia	**NO**	**648**	**55.1**	**186**	**45.8**	**0.001**	**1.45(1.2-1.8)**
	YES	**528**	**44.9**	**220**	**54.2**		
Hyponatremia	NO	645	54.8	202	49.8	0.08	1.2(0.98-1.5)
	YES	531	45.2	204	50.2		
Hyperbilirubinemia	**NO**	**837**	**71.2**	**246**	**60.7**	**<0.0001**	**1.6(1.3-2)**
	YES	**339**	**28.8**	**159**	**39.3**		
Metabolic acidosis	**NO**	**990**	**84.2**	**286**	**70.4**	**<0.0001**	**2.2(1.7-2.9)**
	YES	**186**	**15.8**	**120**	**29.6**		
Respiratory acidosis	NO	1092	92.9	377	92.9	1	1(0.6-1.5)
	YES	84	7.1	29	7.1		

Table 3- Precipitating factors of delirium in the present study

PRECIPITATING FACTORS		%
Toxins	Drug or Alcohol overdosage	1.5
	Alcohol withdrawal	2.7
Metabolic conditions	Hyponatremia	19.5
	Hyperglycaemia	6.2
	Hypoglycaemia	2.5
	Hypercarbia	5.7
	Uraemia	25.1
	Hepatic encephalopathy (hyperammonemia)	22.7

Infections	Systemic infective causes	16.5
	Meningitis/ Encephalitis	8.9
Central Nervous System causes	Hypoperfusion states	14.5
	Hypertensive encephalopathy	5.9
	Cerebrovascular accident (CVA)	7.6
	Intracranial space occupying lesion (ICSOL)	5.4
	Seizures	10.3
	Psychiatric illness	4.9

Discussion:

Delirium is classified into hyperactive, hypoactive and mixed type. Hyperactive subtype is present if there is definite evidence in the previous 24 hours of at least two out of the following factors - increased quantity of motor activity, loss of control activity, restlessness, wandering. Hypoactive subtype is present if there is definite evidence in the previous 24 hours of at least two of the following factors - decreased amount of activity, decreased speed of actions, reduced awareness of surroundings, decreased amount of speech, decreased speed of speech, listlessness, reduced alertness, withdrawal. Mixed subtype is present if there is evidence of both hyperactive and hypoactive subtypes in the previous 24 hours[5]. Percentage of patients with hypoactive delirium was high in this study (52%). Hypoactive delirium often carries relatively poor prognosis, occurs more commonly in elderly patients and is frequently overlooked or misdiagnosed as having depression or a form of dementia.

In the present study, delirium was more prevalent in the elderly population. Most of the elderly patients will have multiple risk factors making them more vulnerable to delirium. Delirium is often the only sign of an underlying serious medical illness in an elderly patient and particular attention should be given to identify and correct the underlying illness.

History of alcohol consumption of more than 2 units per day, prior to admission of the patient, was the major risk factor contributing to delirium in this study (OR = 6.54). This was similar to other studies done by Bart[1] et al & Ouimet[6] et al where consumption of more than 3 units of alcohol (OR 3.23) & 2 units of alcohol (OR 2.03) respectively, was a significant risk factor for delirium. Patients with a previous psychiatric illness were at increased risk for delirium in this study (OR – 3.73). However, other studies explaining its importance in contributing to delirium were not available. Previous cognition impairment was a significant risk factor contributing to delirium (OR = 2.73). The study by Bart[1] et al found that previously diagnosed dementia was an important risk factor (OR = 2.41). Positive correlation with dementia was reported by McNicoll et al[7] (RR 1.4) and Pisani et al[8] (OR 6.3). Usage of sedatives (OR = 2.48) at the time of admission was a significant risk factor for developing delirium. Bart[1] et al found that use of psychoactive medication may disturb the neurotransmission in the brain provoking a delirious state and use of benzodiazepines is a risk factor for delirium (OR – 3.34). Pandharipande[3] et al found that Lorazepam was an independent risk factor for daily transition to delirium (OR – 1.2). Pisani[8] et al found that use of benzodiazepines was a significant risk factor for developing delirium with odds ratio of 3.4. Uncorrected visual disturbances were a significant risk factor for developing delirium in this study (OR-2.22). Inouye[9] et al found that vision impairment (adjusted relative risk – 3.5) was an independent baseline risk factor for delirium. Bowel and bladder disturbances were a significant risk factor contributing to delirium in this study (OR – 1.67). Morley[10] opined that constipation is a frequent, often overlooked precipitating factor for delirium. Tony[11] et al was of the opinion that a careful history and physical, including a rectal examination with consideration of disimpaction, may be helpful in assessing and managing delirious patients. Waardenburg[12] concluded that significant urinary retention can precipitate or exacerbate delirium, a disorder referred to as cystocerebral syndrome. Liem and Carter[13] suggested that increased sympathetic tone and catecholamine surge triggered by the tension on the bladder wall may contribute to delirium. Metabolic acidosis and hyperbilirubinemia were significant metabolic parameters contributing to delirium in this study.Similar findings were reported by Aldemir[14] et al.

Among delirious patients, most common precipitating factors for delirium in this study were uraemia (25.1%), hepatic encephalopathy (22.7%) and hyponatremia (19.5%). Alterations of serum electrolytes, renal function predispose to delirium[15]. Hyponatremia causes delirium and the mechanism is not well understood[16, 17]. Blood urea nitrogen/creatinine ratio greater than 18 is an independent risk factor for delirium in general medical patients[9].Hepatic failure leads to hyperammonemia, which leads to excessive NMDA (N-methyl-D-aspartate) receptor activation, resulting in dysfunction of glutamate-nitric oxide-cGMP pathway and causing impaired cognitive function in hepatic encephalopathy[18].Excess activation of NMDA receptors results in neuronal degeneration and death[19]. In hepatic failure, there may be a shift in regional cerebral blood flow and cerebral metabolic rates from cortex to subcortex resulting in delirium[20].

Patients who develop delirium during their stay in hospital have higher 6-month mortality rates, longer hospital stay, increased economic burden and a higher incidence of cognitive impairment at hospital discharge[21]. Limitation of this study was long term follow up of patients who developed delirium was not done.

Conclusion:

Delirium is common in intensive care unit patients and hypoactive delirium is more common. Major risk factor contributing to delirium was alcohol consumption before

admission. Most common precipitating factors contributing to delirium were deranged metabolic parameters.

Delirium in ICU patients especially hypoactive delirium is easily missed. Hence, all ICUs should implement both RASS and CAM-ICU for early detection of delirium. Future research needs to be directed at development of scoring systems for detection of delirium, which are easy to use and are accurate.

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Competing Interests

None declared

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