

## **Hypokalemia and thrombocytopenia in alcohol withdrawal patients with and without delirium tremens - A comparative study**

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**Conflicts of Interest:** Nil

### **Abstract**

**Background:** Alcohol withdrawal (AW) occurs in alcohol-dependent individuals who abruptly reduce or discontinue their alcohol consumption. The most severe manifestation of alcohol withdrawal is delirium tremens (DT), which is characterised by a fluctuating disturbance of consciousness and a change in cognition that develops over a short period and tends to fluctuate throughout. Patients with delirium are a danger to themselves and others because of the unpredictability of their behaviour. Many risk factors for DT have been identified, including comorbid medical illness or infections, high blood urea nitrogen (BUN), Hypokalemia and Thrombocytopenia. Hence, the present study was undertaken to investigate the association of Delirium Tremens with hypokalaemia and Thrombocytopenia in our population.

**Aim and Objectives:** To compare the platelet counts, serum potassium levels of the alcohol withdrawal patients with and without delirium tremens.

**Methodology:** By using simple random sampling, 60 alcohol dependence syndrome patients currently in withdrawal (30 with and 30 without delirium tremens) admitted to the Psychiatry department at Basaveshwara Teaching and General Hospital, Kalaburagi, were enrolled in the study after meeting inclusion and exclusion criteria. Patients giving consent for the study were assessed for socio-demographic profile and alcohol history. The CIWA-AR scale was used for the assessment of alcohol withdrawal, and required investigation were carried out for the study. Data is analysed using IBM SPSS Software 20.0

**Results:** In our study, thrombocytopenia was observed in 18 (60%) of the delirium patients and 07 (23.33%) of the non-delirium patients, which was statistically significant ( $p < 0.0001$ ). Average platelet count is  $1.52 \pm 0.49$  L among patients with delirium and  $2.27 \pm 0.78$  L cells/mm<sup>3</sup> without delirium. The average platelet among both groups were statistically significant

( $p < 0.0001$ ). Hypokalemia was found in 13 (43.33%) of the delirium patients, compared to 5 (16.67%) of the non-delirium group, which was statistically significant ( $p < 0.0001$ ).

**Conclusion:** In our study, Thrombocytopenia and hypokalaemia were seen higher among alcohol withdrawal patients with delirium. A clinician should identify these risk factors in simple alcohol withdrawal which could predict the occurrence of delirium tremens.

**Keywords:** Delirium Tremens, Hypokalemia, Thrombocytopenia.

### Introduction

As per the WHO, an estimated annual three million deaths and 5.1% of Disability Adjusted Life Years (DALYs) of the world are attributed to Alcohol consumption.<sup>1</sup> Alcohol is one of the leading causes of death and disability in India. According to a national survey conducted by AIIMS in India, about 16 crore people consume alcohol, with 2.9 crore being alcohol dependent.<sup>2</sup>

The Alcohol withdrawal (AW) occurs in alcohol dependent individuals who abruptly reduce or discontinue their alcohol consumption.<sup>3</sup> It consists of early withdrawal symptoms like tremors, nausea, vomiting, paroxysmal sweats, anxiety, agitation etc.<sup>4</sup> The most severe manifestation of the alcohol withdrawal is Delirium Tremens (DT) which is characterized by a fluctuating disturbance of consciousness and a change in cognition that develops over a short period and tends to fluctuate throughout.<sup>4</sup>

Delirium Tremens is a medical emergency that can result in significant mortality (5-15%) and morbidity, owing to cardiac arrhythmias and respiratory failure.<sup>3</sup> Patients with delirium are danger to themselves and others because of unpredictability of their behaviour. DT has

been estimated to occur in 5-20% of the individuals who undergo treatment for alcohol withdrawal.<sup>3</sup> Many factors have been identified as increasing the risk for delirium tremens, including the number of days the patient has gone without alcohol, comorbid medical conditions or injury, high blood urea nitrogen (BUN) and the following parameters on the day of admission like increase respiratory rate, low albumin, increased systolic blood pressure, pulse rate  $> 100$  bpm, low platelet level, low potassium level, low zinc level and body temperature  $> 38^{\circ}\text{C}$ .<sup>5</sup> Identification of risk factors for development of DT is necessary for early treatment in patients with alcohol dependence syndrome so that delirium can be prevented.

Hypokalemia is one of the most common electrolyte disturbances seen in clinical practice. It is defined as a serum potassium ( $\text{K}^+$ ) level of less than 3.5 mEq/L. Potassium ( $\text{K}^+$ ) plays a key role in maintaining normal cell function.  $\text{K}^+$  is the main intracellular cation and almost all cells have the pump called 'Na<sup>+</sup>-K<sup>+</sup>-ATPase', which pumps sodium ( $\text{Na}^+$ ) out of the cell and  $\text{K}^+$  into the cell leading to a  $\text{K}^+$  gradient across the cell membrane, which is partially responsible for maintaining the potential difference across membrane. If potassium balance is disrupted (Hypokalemia or hyperkalaemia), this can also lead to disruption of heart electrical conduction, dysrhythmias and even sudden death.<sup>6</sup> Studies show that serum  $\text{K}^+$  levels decrease during alcohol withdrawal (Wadstein and Skude, 1978; Watson et al., 1984; Wetterling et al., 1994),<sup>7,8,9</sup> however others indicate that there is no linear relationship between potassium level and possible development of delirium tremens (Nanji and Blank, 1984).<sup>10</sup>

Thrombocytopenia (TP) is a reduction in platelet counts below 150,000 in a microliter of blood. Platelets are blood cells that help in blood clotting and wound healing. The risk of thrombocytopenia ranges from no danger at all to bleeding risks and thrombosis.<sup>11</sup> Alcohol consumption causes bone marrow toxicity resulting in reduced platelet production.<sup>12</sup> Kim et al. (2015),<sup>4</sup> Berggren et al. (2009),<sup>3</sup> Eyer et al. (2011),<sup>13</sup> and Monte et al. (2009),<sup>14</sup> demonstrated that platelet count in patients with DT was in Thrombocytopenia range ( $<150 \times 10^9/L$ ) whereas Huang et al. (2011),<sup>15</sup> showed nonsignificant lower platelet count in DT group compared to ND group. A recent systemic review and meta-analysis substantiated this observation.<sup>16</sup>

Hence, the present study is undertaken to investigate the association of Delirium Tremens with hypokalaemia & thrombocytopenia in our population. The findings can be used to predict the occurrence of delirium tremens in simple alcohol withdrawal patients, which could reduce morbidity and mortality.

### Objectives

- a) To compare the Platelet counts in the alcohol withdrawal patients with and without delirium tremens.
- b) To compare the Serum potassium levels in the alcohol withdrawal patients with and without delirium tremens.

### Material and Methodology

Study design: A cross sectional study

Place / Site / College – Hospital: Department of psychiatry at Basaveshwara Teaching and General Hospital, Kalaburagi.

Sample size: 60 alcohol dependence syndrome patients currently in withdrawal (30 with and 30 without delirium tremens)

Sampling method: Simple random sampling

By using simple random sampling, 60 alcohol dependence syndrome patients currently in withdrawal (30 with and 30 without delirium tremens) admitted to the Psychiatry department at Basaveshwara Teaching and General Hospital, Kalaburagi, were enrolled in the study after meeting inclusion and exclusion criteria. Patients giving consent for the study were assessed for socio-demographic profile and alcohol history. The CIWA-AR scale was used for the assessment of alcohol withdrawal, and required investigations were carried out for the study. Data is analyzed using IBM SPSS Software 20.0

### Inclusion criteria

- Patients above 18 years of age
- Patients who are diagnosed with Alcohol Dependence syndrome currently in Alcohol withdrawal state with delirium (F10.4) and Alcohol withdrawal state without delirium (F10.3) according to ICD-10

### Exclusion criteria

- Delirium due to other medical conditions like Infections, substance withdrawal except alcohol withdrawal, acute metabolic condition except hypokalaemia, trauma, CNS diseases, hypoxia, endocrinopathies, acute vascular conditions, toxins and heavy metal poisoning.
- Patients on medications which affect Platelet Count and Serum Potassium level like Furosemide, Penicillin, Quinine, Quinidine, Ranitidine, Sulfonamides, Statins, Insulin, Broncho dilators, Acetazolamide, Beta2 agonists, Diuretics.
- Medical conditions which affect Platelet Count and Serum Potassium level like Pancreatitis, Hepatic Cirrhosis, Septic Shock, DIC, Cancer, Diarrhea, Primary aldosteronism, Diabetic ketoacidosis.
- Any other substance use excluding Nicotine.

### Method of statistical analysis

The data collected will be analyzed statistically by using IBM SPSS software 20.0. For quantitative data, t-test and Anova tests are applied. For qualitative data analysis, Chi-square tests and Fisher exact tests are applied for statistical significance. p value <0.05 is considered as significant.

### Results

All the obtained parameters were noted on the Microsoft excel and analysed using SPSS 20.0 version.

A total of 60 alcohol dependence syndrome patients currently in with drawal (30 with and 30 without delirium tremens) were included in the study. Mean age of the patients with delirium and without delirium was 35.5±7.61 and 38.67±6.53. There was no statistically significant difference of mean age observed among AWS patients with and without delirium (P>0.01).

Table 1: Sociodemographic profile of those without and with delirium

Socio demographic Variables		Without Delirium [n (%)]	With Delirium [n (%)]
Age	20 to 30	05 (16.67)	01 (03.33)
	31 to 40	14 (46.67)	08 (26.67)
	41 to 50	09 (30.00)	09 (30.00)
	51 to 60	02 (6.67)	12 (40.00)
	Mean age	38.67±6.53	35.5±7.61
Gender	Male	30 (100)	30 (100)
	Female	-	-
Education status	Uneducated	05 (16.67)	08 (26.67)
	Primary School	10 (33.33)	14 (46.67)
	High School	09 (30.00)	02 (06.67)
	Graduate	06 (20.00)	06 (20.00)
	Professionals	-	-
Occupation	Unskilled	19 (63.33)	22 (73.33)
	Semi-Skilled	10 (33.33)	06 (20.00)
	Skilled	01 (03.33)	02 (06.67)
Domicile	Urban	18 (60.00)	20 (66.67)
	Rural	12 (40.00)	10 (33.33)
Socioeconomic status	Low	13 (43.33)	22 (73.33)
	Middle	16 (53.33)	05 (16.67)
	Upper	01 (03.33)	03 (10.00)
Religion	Hindu	26 (86.67)	27 (90.00)
	Muslim	03 (10.00)	03 (10.00)
	Christianity	-	-
	Other	01 (03.33)	-
Marital status	Single	08 (26.67)	09 (30.00)
	Married	21 (70.00)	21 (70.00)
	Widowed	01 (3.33)	-
	Separated	-	-
Type of Family	Nuclear	18 (60.00)	22 (73.33)
	Joint	12 (40.00)	08 (26.66)

Patients in the current study who did not have delirium were more prevalent between the ages of 31 to 40 years, accounting for approximately 46.67% (14/30). Among those with delirium, 40% are between the ages of 51 and 60, as compared to 30% (41-50), 26.67% (31-40), and 3.3% (20-30years). In our study, we found that delirium was higher among elderly patients. All the 60 (100%) patients recruited in our study were males.

In our study, 14(33.33%) from delirium group and 10(33.33%) from without delirium group had their education till primary school. 8(26.67%) and 5(16.67) patients from with and without delirium group are uneducated, 20% from each group are graduated

In our study, the majority of patients, 22 (73.33%) with delirium and 19 (63.33%) without delirium, were in an unskilled profession. Following that are 10 (33.33%) and 6 (20%) in semi-skilled professions. The rest had skilled professions

In the present study 18 (60%) and 12 (40%) patients were from urban and rural sector respectively in without delirium group. Whereas 20 (66.67%) and 10 (33.33%) patients in delirium group were urban and rural dwellers respectively.

In our study, 05 (16.67%) of the delirium group and 16 (53.33%) of the non-delirium group were from middle socio-economic status. The majority of patients with and without delirium are from lower socio-economic backgrounds, with 22 (73.33%) and 13 (43.33%), respectively.

In the current study, 3 (10%) patients in both groups are from the Muslim community. While 26 (86.67%) patients without delirium and 27 (90%) patients with delirium are from the Hindu community, the majority are from the Hindu community.

In the current study 08 (26.67%), 21 (70%) and 1 (3.33%) were single, married and widowed in without delirium group. Whereas 09 (30%) and 21 (70%) were belong to single and married in delirium group. Married people were higher in both groups with the distribution of 70% each.

In the present study 18 (60%) and 12 (40%) patients were from nuclear and joint family respectively in without delirium group. Whereas 22 (73.33%) and 08 (26.66%) patients in delirium group were from nuclear and joint family respectively.

In our study, 16 (53.33%), 11 (36.67%) and 3 (10%) patients in the group without delirium were continuous, frequent heavy drinkers and episodic drinkers respectively. whereas 17 (56.67%) and 13 (43.33%) patients were continuous and frequent heavy drinkers among those with delirium.

Table 2: Alcohol related variables of those without and with delirium

Alcohol related Variables		Without Delirium [n (%)]	With Delirium [n (%)]
Drinking pattern	Continuous Drinkers	16 (53.33)	17 (56.67)
	Frequent Heavy Drinkers	11 (36.67)	03 (43.33)
	Episodic Drinkers	03 (10.00)	-
Duration of alcohol consumption	<1 Years	02 (06.67)	-
	01-05 Years	04 (13.33)	07 (23.33)
	06-10 Year	13 (43.33)	09 (30.00)
	11-15 Year	06 (20.00)	10 (33.33)
	16-20 Year	04 (13.33)	03 (10.00)
Types of alcohol presently consuming	>20 years	01 (03.33)	01 (03.33)
	Toddy	-	-
	Arak	-	-
	Beer	09 (30.00)	07 (23.33)
	Wine	-	-
	IMFL-Whisky	17 (56.67)	20 (66.67)

	IMFL-Others (Brandy, rum)	04 (13.33)	03 (10.00)
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Whisky was the most commonly consumed type of alcohol in both groups, with 56.67% in without delirium and 66.67% with delirium. Followed by beer consumption, 30% and 23.33% among without and with delirium, respectively. The others used to drink brandy and rum.

In our study, 14 (46.67%) of the patients with delirium were found to have a previous history of delirium, compared to 4 (13.33%) of the patients without delirium. A significant number of the patients with delirium had a previous history of delirium (P < 0.05).

In our study, 10 (33.33%) of the patients with delirium were found to have a previous history of seizures, compared to 2 (6.67%) of the patients without delirium. A significant number of the patients with delirium had a previous history of seizures (P < 0.05).

In our study, 14 (46.67%) of the patients with delirium were found to have a previous history of hospital admission, compared to 7 (23.33%) of the patients without delirium. A significant number of the patients with delirium had a previous history of hospital admission (P < 0.05).

Table 3: Previous history of Delirium Tremens, Withdrawal Seizure and History of hospital admission for alcohol withdrawal of those without and with delirium.

Variable		Without Delirium [n (%)]	With Delirium [n (%)]	Significance (P)
Previous history of delirium tremens	Yes	04 (13.33)	14 (46.67)	*p <0.01
	No	26 (86.67)	16 (53.33)	
Previous history of withdrawal	Yes	02 (06.67)	10 (33.33)	*p <0.01
	No	28 (93.33)	20 (66.67)	

seizure				
History of previous admission	Yes	07 (23.33)	14 (46.67)	*p <0.01
	No	23 (76.67)	16 (53.33)	

In our study, among those without delirium, 3 (10%), 20 (66.67%), and 7 (23.33%) had a mild, moderate, and severe score, respectively. None of the patients in the delirium group were found to have a mild type of withdrawal, whereas only 1 (3.33%) patient belonged to the moderate category and 29 (96.66%) belonged to the severe category. This has a significant difference with a p value of <0.0001. The average score was 12.93±11.04 and 28.9±4.54 among those without and with delirium, respectively, with a significant p value of <0.0001.

Table 4: Distribution of CIWA-AR withdrawal type

CIWA-AR Withdrawal Type	Without Delirium [n (%)]	With Delirium [n (%)]	P value
Mild (<8)	03 (10.00)	-	<0.0001
Moderate (8-15)	20 (66.67)	01 (03.33)	
Severe (>15)	07 (23.33)	29 (96.66)	
Average score	12.93±11.04	28.9±4.54	<0.0001

Table 5: Distribution of platelet count and potassium levels between two groups

Reference Ranges		Without Delirium [n (%)]	With delirium [n (%)]	P value
Average platelet Count (Normal range 1.5-4.5 L cells/mm <sup>3</sup> )		2.27±0.78	1.52±0.49	<0.0001
Thrombocytopenia	Present	07 (23.33%)	18 (60%)	<0.0001
	Absent	23 (76.67%)	12 (40%)	
Average Potassium (Normal range 3.5-5.5 mmol/L)		3.76±0.62	3.66±0.67	0.55
Hypokalaemia	Present	05	13	<0.0001

		(16.67%)	(43.33%)
	Absent	25 (83.33%)	17 (56.67%)

In our study, thrombocytopenia was observed in 18 (60%) of the delirium patients and 07 (23.33%) of the non-delirium patients, which was statistically significant ( $p < 0.0001$ ). Average platelet count is  $1.52 \pm 0.49$  L among patients with delirium and  $2.27 \pm 0.78$  L cells/mm<sup>3</sup> without delirium. The average platelet among both groups were statistically significant ( $p < 0.0001$ ). Whereas, average potassium levels between without and with delirium patients were  $3.76 \pm 0.62$  and  $3.66 \pm 0.67$  mmol/L respectively, though there were quite reduced levels among delirium patients, there was no statistically significant. Hypokalemia was found in 13 (43.33%) of the delirium patients, compared to 5 (16.67%) of the non-delirium group, which was statistically significant ( $p < 0.0001$ ).

### Discussion

Mean age of the patients with delirium and without delirium was  $35.5 \pm 7.61$  and  $38.67 \pm 6.53$  years. There was no statistically significant difference of mean age observed among AWS patients with and without delirium ( $P > 0.01$ ). Sarkar et al.<sup>17</sup> found that patients with delirium had a mean age of  $42.85 \pm 10.92$  years, whereas those without delirium had a mean age of  $40.45 \pm 10.27$  years, which is similar to our study's findings. Among those with delirium, 40% are between the ages of 51 and 60, as compared to 30% (41-50), 26.67% (31-40), and 3.3% (20-30 years). In our study, we found that delirium was higher among elderly patients. Increased incidence of delirium is more common in older adults due to factors like higher rates of cognitive impairment, longer drinking history, and more susceptibility to alcohol withdrawal.<sup>18</sup>

All the 60 (100%) patients recruited in our study were males. Teer pat T et al reported male predominance in their study 97.6%.<sup>5</sup>Ristic DI et al reported the same findings (99.5%) with regard to gender as the current study.<sup>20</sup>This determined the significant association between male gender and alcohol dependence. There is male predominance in our study due to lack of cultural acceptability of women drinking in India.

Between patients with and without delirium, there was no significant correlation with educational status, marital status, occupation, or place of residence ( $P > 0.01$ ). Similarly, Sarkar et al also did not observe significant association with any of the socio demographic profile.<sup>17</sup>

In the present study, there was a significantly higher population that belonged to the Hindu religion. This could be due to the higher prevalence of Hindus in our study area, and Islam forbid or view alcoholic consumption as sinful or negative.<sup>25</sup>

In our study, a greater number of patients were continuous 17(56.67%) and frequent heavy drinkers 13(43.33%) in the delirium group compared to those without delirium (53.33% and 36.67%, respectively). Similar findings were also found in the study done by Sarkar et al., where 92.5%(n=37) were continuous drinkers in the delirium group and 72.5%(n=29) in the non-delirium group.<sup>17</sup> Episodic drinking patterns might have some effects on the restoration of the normalcy of cerebral depression, thus reducing delirium in contrast to chronic continuous drinking of alcohol, where cerebral depression persists.<sup>21</sup>

In our study, patients with previous history of delirium, seizures and hospitalizations were 46.67%, 33.33% and 46.67% respectively among those with delirium than in those patients without delirium (13.33%, 6.67% and 23.33% respectively), with statistically significant

association. According to Teerapat T et al, patients with a prior history of admission were strongly associated with current admission (54.2%).<sup>5</sup> Similar to our study, Sarkar et al reported that 47.5% (n=19) of patients had a history of delirium, and 45% (n=18) had a history of seizures in delirium patients. Sarkar et al even mention that past histories of delirium and continuous drinking habits are independent risk factors for delirium.<sup>17</sup> The concept of "kindling" is used here to explain how repeated detoxification can worsen the subsequent alcohol withdrawal state, resulting in delirium later on.<sup>21</sup>

Based on the CIWA AR classification, only 1 (3.34%) patient with delirium was classified as moderate, and 29 (96.66%) patients were classified as severe, compared to 20 (66.67%) and 7 (23.33%) patients without delirium who were classified as moderate and severe, respectively. This had a significant difference with a p value of <0.0001. Also, the average score was  $28.9 \pm 4.54$  and  $12.93 \pm 11.04$  (p <0.001) among those with and without delirium, respectively. Silczuk A et al reported that among delirium patients, 85% belonged to the severe category and 14% to the moderate category, similar to our current study.<sup>24</sup> Bakhla AK et al stated that CWI Ar is one of the potent classification scales in predicting the delirium in patients with withdrawal.<sup>22</sup>

In our study, thrombocytopenia was observed in 18 (60%) of the delirium patients and 07 (23.33%) of the non-delirium patients, which was statistically significant (p<0.0001). Teerapat T et al found that 60.4% (n = 32) of delirium patients had Thrombocytopenia, which is similar to our findings.<sup>5</sup> Average platelet count is  $1.52 \pm 0.49$  L among patients with delirium and  $2.27 \pm 0.78$  L cells/mm<sup>3</sup> without delirium. The average platelet among both groups were statistically significant (p<0.0001). Similarly, Berggren et al found that the

platelet level in the delirium tremens group was  $1.49 \pm 1.0$  L/mm<sup>3</sup>, and also mentioned that Thrombocytopenia has a higher sensitivity and specificity in predicting delirium tremens in withdrawal patients.<sup>3</sup> Thrombocytopenia and the development of DT are parallel phenomena, that is, they both reflect effects of long-term and heavy alcohol consumption.<sup>3</sup>

Excessive alcohol consumption is reportedly associated with thrombocytopenia, due to possible bone marrow toxicity resulting in reduced platelet production.<sup>21</sup>

In our study, average potassium levels between without and with delirium patients were  $3.76 \pm 0.62$  and  $3.66 \pm 0.67$  mmol/L respectively, though there were quite reduced levels among delirium patients, there was no statistically significant. Hypokalemia was found in 13 (43.33%) of the delirium patients, compared to 5 (16.67%) of the non-delirium group, which was statistically significant (p<0.0001). Similarly, Berggren et al found that the serum potassium level in the delirium tremens group was  $3.6 \pm 0.7$  L/mm<sup>3</sup>. Watson et al in 1984 had reported hypokalaemia in 46% (n=6) of the delirium patients compared to 14% (n=1) in non-delirium patients which is similar to our study.<sup>8</sup>

In delirium tremens, there will be an increased shift of potassium across the cell membrane. This could be due to an activation of Na<sup>+</sup>/K<sup>+</sup> ATPase in the cells mediated by catecholamines through beta 2 stimulation, which leads to high intracellular and low extracellular potassium, causing hypokalaemia.<sup>8</sup>

The major limitation of our study is that its findings cannot be broadly generalised as our study was done in a single tertiary multi-specialty hospital and had a small sample size. With the knowledge of the current results, we would like to undertake another randomised control trial to determine the sensitivity, specificity, and



accuracy of platelet count and serum potassium levels in predicting delirium tremens in alcohol withdrawal patients.

### Conclusion

The fatal complication of severe alcohol withdrawal syndrome is delirium tremens. Due to its high mortality and various associated complications, prevention of the condition is preferred over treatment of it. In the present study, past history of delirium tremens, past history of withdrawal seizure, and previous history of hospital admission emerged as significant clinical predictors of delirium tremens.

Thrombocytopenia and hypokalaemia increase the risk of delirium, and patients are more likely to develop delirium as their CIWA-AR severity score increases. Therefore, A clinician should identify these risk factors in simple alcohol withdrawal which could predict the occurrence of delirium tremens.

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