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Original Article

The correlation between delirium subtypes and treatment efficacy and biochemical parameters: A preliminary study

Mehmet Gurkan Gurok[1], Asli Kazgan[1], Mehmet Onur Kaya[2], Murad Atmaca[1]

[1]Firat University Faculty of Medicine, Department of Psychiatry, Elazig, Turkey
[2]Firat University Faculty of Medicine, Department of Biostatistics and Madical Informatics, Elazig, Turkey

Abstract

Aim: Delirium is one of the most important emergency cases in geriatric patient population with high morbidity and mortality rates. In clinical practice, three delirium types are defined as hyperactive, hypoactive and mixed according to the psychomotor activity and the level of wakefulness. In the present study, the purpose was to examine the treatment response of the subtypes of delirium and its relation with possible biochemical parameters.

Material and Methods: Thirty patients, who were diagnosed with delirium and who were hospitalized for treatment were included in the present study. Following the classification of the patients according to the subtypes of delirium, they were evaluated before the treatment and on the 7th day of the treatment. In both interviews, the Delirium Rating Scale (DRS), Richmond Agitation and Sedation Scale (RASS), and Memorial Delirium Rating Scale (MDRS) were applied to the patients. In addition, the biochemical parameters that were required for the patients in relevant clinics were recorded.

Results: Delirium patients consisted of a total of 30 patients. The patients of all three subtypes of delirium responded to the treatment scores at significant levels in terms of scale scores. However, when the Hyperactive, Hypoactive and Mixed subtypes were evaluated in terms of the difference of change on the 1st and 7th days of the treatment separately, it was determined that the difference of change values were significantly higher in the hyperactive type in terms of RASS, DRS and MDRS (p=0.004; p=0.002; p=0.001, respectively).

Conclusions: As a result, the findings of the present study showed that patients who are diagnosed with delirium might show different treatment responses according to motor subtypes. Further studies are required to be conducted with bigger sampling groups.

Keywords: Delirium; treatment efficacy; biochemical parameters.

INTRODUCTION

Delirium is a rapid onset neuropsychiatric syndrome induced by temporary deterioration of cerebral homeostasis and accompanied by changes in consciousness, perception, thought, and sleep-wake cycle. It usually develops acutely due to a medical condition, exhibits fluctuations during the day, and is often a temporary condition (1). Symptoms usually last between 3 and 5 days. The symptoms disappear slowly and this phase could last between 6 and 8 weeks. It was reported that it could be observed in 10% -20% of all hospitalized adult patients, 30-40% of hospitalized elderly patients and 80% of intensive care patients (2). Delirium; It is known that delirium is associated with increased mortality rate, prolonged hospitalization, impaired cognitive functions and worsening in dementia symptoms (3,4).

Cerebral neurotransmission that may vary due to etiologic factors may lead to different delirium symptoms (5). In clinical environment, three types of delirium were defined based on psychomotor activity and alertness level: hyperactive, hypoactive and mixed types (6,7). It was reported that the diagnosis rate of delirium motor subtypes may be associated with treatment results, pathophysiology and delirium period (8). Hyperactive type hallucinations, delusions, agitation, disorientation and orientation disorders are prominent. Patients are more irritable and exhibit high responses to external stimuli (1,9). It was reported that the prognosis of hyperactive subtype could be better than other subtypes (10). Mixed type bears the characteristics of both types. It is usually observed as hypoactive during the day and hyperactive at night (11). Mixed type has similar prognosis and treatment response with the hyperactive subtype (10). In hypoactive type, confusion and sedation are prevalent and patients exhibit a fatigued outlook. Both the amount

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Corresponding Author: Mehmet Gurkan Gurok, Firat University Faculty of Medicine, Department of Psychiatry, Elazig Turkey
E-mail: mggurok@hotmail.com

and the speed of speech and movements are reduced. The association of the patients with their environment is decreased (2,9). Hypoactive subtype is associated with poor prognosis and mortality independent of age, comorbid diseases and severity of dementia (12,13). Since poor prognosis of hypoactive delirium could be neglected due to the properties of its symptoms, it was associated with misdiagnosis and confusion with diseases such as dementia and depression (9,13). Certain studies suggested that prognosis, diagnosis rate, pathophysiology and treatment outcomes may be different based on delirium motor subtypes (9,13,14). This suggested that identification of motor subtypes was important for treatment options and approach to the patient.

The literature emphasized that there were difficulties in the diagnosis, evaluation and treatment of delirium (14, 15). Studies on delirium motor subtypes were usually conducted to investigate the effects of predisposing factors (10,16). However, studies on delirium motor subtypes in the literature are limited considering the importance of their clinical impact (12,16). Thus, there is a need for research on motor subtype characteristics and the factors that could be associated with motor subtypes. Understanding the characteristics of subtypes could be important in etiopathogenetic understanding, prognosis and treatment decision (9).

The present study aimed to investigate the effectiveness of treatment in delirium inpatients based on motor subtypes, change in clinical picture, and possible differences between biochemical parameters.

MATERIAL and METHODS

The study included thirty patients, who were diagnosed with delirium based on the DSM-V diagnostic criteria and for whom a psychiatric consultation was requested between 01.03.2018 and 28.02.2019 in internal medicine and surgery clinics. The required consent of the local ethics committee was obtained prior to the study. Although 36 patients were included in the first records in the study, 6 patients were excluded due to various reasons.

The treatment was initiated with Haloperidol drip at the dose based on the patient symptoms and the patients were reevaluated on the 7th day in terms of activity and the medication requirements. The study forms were completed by the consulting psychiatrist. The treatment was started with haloperidol of 0.5 mg (five drops) as first choice according to patients, clinical presentation. By the clinical presentation change the doses were changed by consultant psychiatrist. Dose changes are presented in table 2. In patients no extrapyramidal side effects and drug interactions were determined we included solely patients who were receiving haloperidol, the most reliable agent for drug interaction and most used one in treatment delirium in our clinic. Scale scoring and control examinations by a senior consultant psychiatrist(A.K) at baseline and at the and of first week. Patients were detected as hyperactive, hypoactive and mixed type based on clinical interviews, DSM-5 diagnostic criteria, family interviews and evaluation scales applied by the interviewer. Furthermore, biochemical parameters that were required by the clinics where the patients were treated, in other words, Aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, glucose, hemoglobin (Hg), c reactive protein (CRP), white blood cell (WBC), sodium (Na), potassium (K), chlorine (Cl), calcium (Ca) and arterial blood gas analyses; PO_2, PCO_2, pH levels were recorded on the 1st and 7th days of treatment.

The Scales Utilized in the Study

Sociodemographic and Clinical Data Form: A sociodemographic and clinical data form developed by the authors based on clinical experience, the information available in the reviewed resources and the study objectives was utilized. This was a semi-structured form that included sociodemographic information such as age, gender, marital status, education level, occupation, place of residence, economic status, family structure, and clinical data such as disease duration.

Delirium Rating Scale (DRS): This is a 10-item scale developed to determine the severity of delirium. The evaluation is conducted by the interviewer. The scale is a 4-point Likert type scale. The highest possible score is 30. DRS is a diagnostic tool that measures both cognitive and psychotic symptoms in delirium. This scale analyzes delirium based on psychomotor activity, orientation, attention, memory, perception, process of thought, thought content, disturbance in the sleep-wake cycle, daytime variability-fluctuation, and fluctuation in mood. Aydemir et al. (17) conducted the validity and reliability studies in Turkish language. It was observed that the scale was suitable to identify delirium and its subtypes.

Richmond Agitation and Sedation Scale (RASS): RASS is a frequently used scale despite the lack of previous validity and reliability studies and measures the response level of the patient to stimuli and evaluated between -5 (unresponsive) and +4 (aggressive). RASS includes six levels and the ideal sedation level was defined as 2. In the scale, 0 indicates the ideal level patient who is alert, calm and aware of the environment, while the values up to +4 reflect increasing agitation and values up to -5 reflect increasing level of sedation (18).

Memorial Delirium Assessment Scale (MDAS): This is a scale with 10 items that aims to assess the changes in the state of wakefulness and consciousness level, cognitive dysfunctions such as memory, attention, orientation and thought disorders and changes in psychomotor activity. Each item is scored between 0 and 3 and possible total score varies between 0 and 30. Its content integrates behavioral observations and objective cognitive assessment. Validity studies were conducted by Breitbart et al. (19).

Statistical Analysis

The statistical analysis was conducted with IBM SPSS 22 statistics software. Shapiro-Wilk test was used to

determine whether the data exhibited normal distribution. The descriptive statistics are indicated with median (minimum: maximum) for continuous variables without normal distribution and categorical variables are indicated with frequency and percentages [(n)%]. Kruskal Wallis test was used for comparison between or more independent groups for the data without normal distribution. Wilcoxon Signed Rank test was used for intra-group comparisons in the analysis of time-dependent variables. The level of significance was determined as P = 0.05. The statistically significant values are indicated in bold in the tables.

RESULTS

When the patients were classified based on delirium motor subtypes, it was determined that 18 patients were hyperactive (60%), 6 patients were mixed (20%) and 6 patients were hypoactive (20%). The mean age of the patients was 72.9 ± 11.2. Patient sociodemographic characteristics are presented in Table 1. Twelve patients (40%) were female and 18 (60%) were male. Fourteen patients (46.7%) were inpatients in surgical clinics and 16 (53.3%) patients were treated in intensive care and internal clinics.

When the scale score differences and treatment doses on the 1st and 7th days were compared between the delirium motor subtypes, it was determined that the differences between Richmond difference score (DS) in 3 motor subtypes were statistically significant (p = 0.021). The difference was significant between hyperactive and hypoactive groups, while the differences between hyperactive and mixed groups and hypoactive and mixed groups were not significant (p= 0.378; p = 0.240) (Table 2).

Comparison of the scale scores on the 1st and 7th days of treatment based on motor subtypes demonstrated that the median RASS score was 2 on the 1st day of the treatment in the hyperactive group, and the median RASS score decreased to 1 on the 7th day of the treatment, and there was a significant difference between the mean RASS scores on the 1st and 7th days (p = 0.004). Furthermore, in the hyperactive group, it was determined that the decrease in the median DRS and MDAS scores between the first and seventh days of treatment was statistically significant (p = 0.002; p = 0.001, respectively) (Table 3). In the mixed motor sub-type, the decrease in mean RASS scores was not statistically significant between the 1st day of the treatment and the 7th day of treatment (p = 0.713). On the other hand, the decrease in median DRS and MDAS scores between the 1st day of treatment and the 7th day of treatment was statistically significant (p = 0.046; p = 0.028, respectively) (Table 3). In the hypoactive group, similar to the mixed group, the decrease in median RASS score was not statistically significant (p = 0.098). The decrease in the median DRS and MDAS scores was statistically significant between the 1st day of treatment and the 7th day of treatment (p = 0.027; p = 0.027, respectively) (Table 3).

It was observed that the patients in all three motor subgroups responded significantly to haloperidol treatment. The need for haloperidol dose alteration was not statistically significant in all 3 subtypes (p = 0.054) (Table 2). Furthermore, there was no correlation between the haloperidol dose and Richmond DS, DRS DS, and MDAS DS in motor subgroups.

There was no significant statistical correlation between biochemical parameters and delirium motor subtypes and treatment response. When biochemical parameters were compared by motor subtypes non statistical significance was found. Data belonging to 1st and 7th days are followings; ALT (p=0.652; p=0.410), AST (p=0.906; p=0.911), glucose (p= 0.563; p=0.392), Urea (p= 0.279; p=0.921), creatinine, (p=0.119; p=0.067), Hg (p=0.915; p=0.300), WBC (p=0. 539; p=0.757), K (p= 0.214; p=0.316), Na (p=0.01; p=0.351), Cl (p=0.797; p=0.129), Ca (p=0.315; p=0.895), pH (p=0.776; p=0.427), PCo_2 (p=0.127; p=0.159), PO_2 (p=0.510, p=0.635), CRP (p=0.874; p=0.670) respectively.

Table 1. Characteristics parameters of patients

	n (%)
Age	**72.9±11.2**
Motor subtypes	
Hyperactive	18 (60%)
Hypoactive	6 (20%)
Mixed	6 (20%)
Sex	
Female	12 (%40)
Male	18 (%60)
Education	
Uneducated	7 (23.3%)
Primary school	13 (43.3%)
Secondary school	5 (16.7%)
High school	4 (13.3%)
University	1 (3.3%)
Department of Patients Clinic	**N**
Urology	8 (26.7%)
Medical Intensive Care	3 (10%)
General Surgery	4 (13.3%)
Chest Disease	3 (10%)
Nephrology	3 (10%)
Hematology	2 (6.7%)
Cardiology	2 (6.7%)
Cardiovascular Surgery	2 (6.7%)
Infectious Disease	2 (6.7%)

Table 2. Scales and treatment dose in motor subtypes comparison of difference scores

	Hyperactive (minimum: maximum)	Hypoactive (minimum: maximum)	Mixed (minimum: maximum)	p	p
RASS DS	-1 (-3:1)	1.5 (-1:2)	-0.5 (-2:5)	0.021*	Hyperactive-Hypoactive: 0.004*
					Hyperactive -Mixed: 0.378
					Hypoactive -Mixed: 0.240
DRS DS	-4.5 (-27:5)	-6.5 (-16:-2)	-7.5 (-15:1)	0.688	-
MDAS DS	-4.5 (-22:4)	-7.5 (-19:-1)	-7 (-18:-2)	0.767	-
Haloperidol Dose DS	1.2 (0.6:1.5)	1 (0.6:1)	1.4 (1:2)	0.054	-

RASS DS: Richmond Agitation and Sedation Scale Difference Score, DRS DS: Delirium Rating Scale Difference Score, MDAS DS: Memorial Delirium Assessment Scale Difference Score

Table 3. Comparison of scale scores between day 1 and day 7 of motor subtype treatment

Hyperactive	1. day hydrangea (minimum:maximum)	7. day hydrangea (minimum:maximum	p
RASS	2 (0:4)	1 (0:2)	0.004*
DRS	18 (8:28)	13.5 (1:24)	0.002*
MDAS	21.5 (8:28)	15.5 (2:25)	0.001*
Mixed			
RASS	1 (-4:2)	0.5 (-1:1)	0.713
DRS	16.5 (12:20)	9 (2:18)	0.046*
MDAS	19.5 (12:26)	11 (3:23)	0.028*
Hypoactive			
RASS	-2 (-3:1)	-5 (-1:0)	0.098
DRS	15 (4:19)	5.5 (2:12)	0.027*
MDAS	19.5 (5:25)	7.5 (2:16)	0.027*

*p<0,05 *Wilcoxon. RASS: Richmond Agitation and Sedation Scale, DRS: Delirium Rating Scale, MDAS: Memorial Delirium Assessment Scale

DISCUSSION

Description of delirium motor subtypes could be useful in predicting the treatment response and prognosis. It may also help us to understand the possible etiopathogenesis of the disease. Due to the above-mentioned potential benefits of subtypes, studies on this topic have increased in recent years (4,9,10,12). In the present study, the correlations between motor subtypes with treatment response and biochemical parameters were investigated in inpatients diagnosed with delirium during psychiatric consultation. The study findings demonstrated that the response of the patients in all three motor subtypes was significant to haloperidol treatment. No statistically significant difference was determined between the subtypes based on dose requirements. When the difference between the motor subtype scale scores was examined, the changes in RDS were significant in all motor subtypes (p = 0.021), however there was no statistically significant difference between the DRS and MDAS scale scores.

Furthermore, the difference between hyperactive and hypoactive groups was significant (p = 0.04), while there were no significant differences between the other groups. Since the RASS scale focuses on the symptoms of agitation and sedation, it could be concluded that these symptoms responded better to treatment when compared to cognitive symptoms. It could also be concluded that hyperactive type, which is characterized by increased agitation and movements, provided a better response to treatment when compared to the hypoactive subtype. However, it should be kept in mind that hypoactive subtype was less identifiable and seldom diagnosed due to silent symptoms. This may be considered as one of the reasons for patient limitation in the present study. The poor prognosis of hypoactive subtypes could be explained by late diagnosis, more resistance to treatment (10,20), and comorbid physical and cognitive disorders (9,12,21). Furthermore, the less problematic prognosis of the hypoactive subtype prevented adequate and effective treatment when compared to the other subtypes (9). Thus, the fact that early diagnosis could improve prognosis and mortality rates in hypoactive subtypes should be noted (20,21). However, there are studies which reported that there was no difference between the subtypes based on delirium prognosis (22). There are also studies reporting that it is not effective in preventing antipsychotics treatment for delirium. (22,23).

In one of the limited number of studies on the effect of antipsychotic therapy on delirium subtypes, Boettger et al. (24) reported that the patients had a favorable response to treatment in all three subtypes treated with aripiprazole and haloperidol. In another study that investigated the efficiency of the treatment, Breitbart et al. (25) emphasized

that hypoactive subtype, along with advanced age and dementia history negatively affected the treatment response in olanzapine treatment. Based on the present study findings, we concluded that the improvement in the symptoms in hyperactive subtype was higher, although all three motor subtypes responded significantly to treatment. Since all three delirium subtypes were associated with the dementia process (12), it is important to provide the necessary guidance after discharge. In the present study, 60% of the patients were hyperactive, 20% were hypoactive and 20% were mixed subtype. There are previous studies which determined that hyperactive subtype was more prevalent (9) or hypoactive subtype was more prevalent (12) among delirium patients.

Fundamental management of delirium includes identification and management of any potentially reversible causes. For patients who do not respond adequately to these management, pharmacologic agents may be required. Haloperidol is often the first-line treatment option, and other antipsychotics such as chlorpromazine, quetiapine, olanzapine and risperidone represent potential alternatives (26,27). For patients with resistant delirium, the treatment include escalating the dose of the same neuroleptic, rotation to another neuroleptic or combination therapy. In delirium treatment, increasing number of studies are supporting the other atypical antipsychotics but haloperidol remains the gold standard (28). In addition, non-pharmacologic interventions such as environmental control and orientation aids, and administering is important (26).

Biochemical parameters such as disorders in serum sodium, potassium, glucose levels, low hemoglobin, hypocalcemia, azotemia, impaired liver functions, hyperamylasemia, hyperbilirubinemia, metabolic acidosis are important delirium risk factors in patients with surgery history (29,30). Although there are several studies that investigated biochemical risk factors in delirium, we could access only the study by Balan et al. (31). Balan et al. (31) found that the 6-SMT levels, which is a methane metabolite, were high in hypoactive type and low in the hyperactive type. In the present study, however, no significant statistical correlation was found between biochemical parameters, delirium motor subtypes and treatment response. This might be related to the limited sample in the present study the biochemical parameters were limited with the routine parameters required in relevant services. The differences between prognosis and treatment response in motor subtypes suggested further studies on biochemical markers.

The present study has certain limitations. First, the sample size may be insufficient to produce clear results, thus further studies with a higher number of patients could be recommended. Second, the collected data could have been affected by unpredicted factors due to the multifactorial neurobiology of delirium. Third, the biochemical patient data were limited to the routine examinations conducted at relevant clinics, thus limiting the data collection in these areas. Finally in existence of validity and reliability studies of RASS and MDAS is another limitation.

CONCLUSION

Although delirium is prevalent in clinical practice, probability of misdiagnosis, leading to the non-treatment of the patients, is a common risk. In conclusion, the present study findings suggested that delirium motor subtypes were important in predicting treatment response and prognosis. It is important for the clinicians to become aware of delirium motor subtypes, especially the hypoactive subtype, early and initiate the treatment. In addition, further studies on this topic may contribute to predict the treatment response and etiopathogenesis in delirium.

Mehmet Gurkan Gurok ORCID: 0000-0001-8998-0743
Aslı Kazgan ORCID: 0000-0002-0312-0476
Mehmet Onur Kaya ORCID: 0000-0001-8052-0484
Murad Atmaca ORCID: 0000-0003-2772-4124

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