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Delirium in the Critically Ill Patients: Is It Easily Diagnosed? What is the Incidence and What is the Management?

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ABSTRACT

Introduction: *Delirium is common in critically sick patients and related prolonged length of medical intensive care unit (ICU) and long-run psychological impairment.* ***Aim of the study:*** *The aim of the study is to assess the incidence of delirium in critically ill patients. Evaluate the effectiveness of diagnosing delirium by subjective global assessment compared to CAM-ICU score in critically ill patients. Evaluate the effect of haloperidol versus atypical antipsychotic drugs in the treatment.* ***Methods:*** *Total 200 critically ill patients selected sequentially on their admission to ICU and subjected for full medical history taking, clinical examination daily with emphasis on full neurological assessment, daily assessment of delirium along their stay in the ICU by 2 methods: subjective global assessment which is the subjective individual clinical impression performed by the attending resident in the ICU. CAM-ICU score which is performed by the physician in charge of the study using CAM-ICU worksheet.* ***Results:*** *Delirium is a frequent complication in the intensive care unit. The CAM-ICU scoring system appears to be rapid, valid, and reliable for diagnosing delirium in the ICU setting and may be a useful instrument for both clinical and research purposes. Use of objective criteria may identify patients mistakenly thought to have delirium who do not meet objective criteria for the diagnosis of the condition. The degree of agitation is an essential indicator of the dosage of the used antipsychotic drug, need for additional antipsychotics.* ***Conclusion:*** *Delirium is a common problem in critically ill patients and is not easy to manage.*

Keywords: Delirium, Scoring systems of agitation, Haloperidol, Atypical antipsychotics

INTRODUCTION

Delirium is a serious disturbance in mental abilities that results in confused thinking and reduced awareness of the environment. The start of delirium is usually rapid-within hours or a few days. Delirium is common in critically sick patients and related prolonged length of keep within the medical care unit (ICU) and long-run psychological impairment. The pathophysiology of delirium has been explained by neuroinflammation, AN aberrant stress response, and neurochemical imbalances. Delirium develops principally in vulnerable patients (e.g., cognitively impaired) within the throes of critical illness. Treatment of delirium will be improved with frequent monitoring, as early detection and the resulting treatment of the underlying condition will improve outcome.

Aim of the Study

The primary objectives of this study are to:

- Assess the incidence of delirium in critically ill patients
- Evaluate the effectiveness of diagnosing delirium by subjective global assessment compared to CAM-ICU score in critically ill patients
- Evaluate the degree of agitation in patients diagnosed with delirium using agitated behavior scale [ABS]

The secondary objectives of the study are to:

- Compare the efficacy and safety of haloperidol versus atypical antipsychotic medications (risperidone and quetiapine) in managing delirium in critically ill patients

Effect of antipsychotic management of delirium in ICU length of stay and need for mechanical ventilation.

MATERIALS AND METHODS

Total of 200 critically ill patients was subjected to this study. Patients were selected sequentially on their admission to ICU and those patients with one or more of the following criteria: pregnant patients, patients under the age of 18 years and patients with an altered level of consciousness due to organic or metabolic brain lesions were excluded from the study.

Study Design

According to the inclusion and exclusion criteria described before, the 200 patients involved in the study were subjected to the followings along with their stay in ICU:

1. Full medical history taking
2. Clinical examination daily with an emphasis on full neurological assessment
3. Daily assessment of delirium along with their stay in the ICU by 2 methods:
    a. **Subjective global assessment:** Which is the subjective individual clinical impression performed by the attending resident in the ICU
    b. **CAM-ICU score:** Which is performed by the physician in charge of the study using CAM-ICU worksheet described in supplementary materials
4. Routine ICU monitoring: During ICU stay, the patients were kept on continuous rhythm, blood pressure, and pulse oximetry monitoring
5. Laboratory analysis: This included complete blood analysis with complete blood picture, liver function tests, cardiac biomarkers, renal function tests
6. Management of delirium using different antipsychotic medications: Patients diagnosed with new-onset delirium in ICU either by CAM-ICU scoring system or by subjective global assessment or by both was then subdivided into 3 equal groups:
    a. **Group 1:** Delirium is managed using haloperidol, a typical antipsychotic, to control delirium. The dose of Haloperidol used in this study was 2-10 mg IV of haloperidol lactate which needed to be repeated every 15-30 minutes with doubling the initial dose in severe agitation. When calm achieved, we administered 25% of the last bolus dose every 6 hours
    b. **Group 2:** Delirium is managed using Risperidone, an atypical antipsychotic, to control delirium. The dose of Risperidone used in the study was 1-2 mg daily PO to be increased with 1-2 mg/day at intervals ≥ 24 hours in severe cases of agitation
    c. **Group 3:** Delirium was managed using quetiapine, another atypical antipsychotic, to control delirium. The dose of quetiapine used in this study was 50 mg/day PO divided q12hr to be increased daily in increments of 25-50 mg q8-12hr in severe cases of agitation

Patients who don't respond to the high dose of the used antipsychotic were subjected to adding other antipsychotics or adding sedative agents if delirium still not controlled.

7. Continuous assessment and follow up of patients diagnosed with delirium along with their ICU stay: All pateints diagnosed with delirium are subjected daily to:
    a. Continuous assessment and evaluation to detect control of delirium with the subjective global assessment
    b. Cam-ICU scoring system to detect control of delirium with CAM-ICU score
    c. Detailed neurological examination for early detection of the occurrence of extrapyramidal manifestations
    d. Daily Electrocardiogram (ECG): ECG was performed for early detection of prolonged QTc interval as a complication of the used antipsychotic drug
    e. Agitated behavior scale to categorize the severity of agitation classified to mild, moderate and severe, this scale is carried out as described in the supplementary materials

8. Evaluation of the efficacy and safety of the used antipsychotic drugs: All patients are followed up daily along their ICU stay for:
    a. Control of manifestations of delirium assessed by CAM-ICU score and SGA
    b. The dose of the used antipsychotic drug needed to control delirium
    c. The duration between the time of onset and time of control of delirium
    d. Need for other antipsychotic drugs to control delirium
    e. Need for sedation to control of delirium
    f. Need for mechanical ventilation
    g. The occurrence of extrapyramidal manifestations
    h. The occurrence of prolonged corrected QT (QTc) interval
    i. The outcome regarding the length of ICU stay and mortality

Statistical Analysis

All data obtained were statistically analyzed. Data were coded and entered using the Statistical package SPSS (Statistical Package for the Social Science) version 22. Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were made using the non-parametric Kruskal-Wallis test [1].

For comparing categorical data, Chi-square (χ^2) analysis was performed. Exact test was used instead when the expected frequency was less than 5. The p-values of less than 0.05 were considered statistically significant [2].

RESULTS

Our results will be presented as follows:

- Descriptive data of all (200) patients enrolled in the study
- The incidence of delirium in the study population
- Diagnostic tools of delirium used in the study; evaluation of Subjective global assessment (SGA) versus CAM-ICU scoring system
- Evaluation of the responsiveness to treatment with different antipsychotics; Evaluation of Subjective global assessment (SGA) versus CAM-ICU scoring system
- Assessment of degree of agitation by Agitated behavior scale (ABS) in the study population diagnosed with delirium
- Comparative analysis between the three antipsychotic drugs used to control delirium in our study population, using the CAM-ICU score as a gold standard

Descriptive Data of all Patients Enrolled in our Study

Demographic data:

- Age: Mean age of study patients was 62.20 ± 13.34 years, with a median age of 65 years
- Gender: There were 112 males with a percentage of 56% and 88 females with a percentage of 44% enrolled in our study

Comorbidities:

- Diabetes mellitus: There were 116 diabetic patients with a percentage of 58% in screened patients enrolled in this study

- Hypertension: There were 142 hypertensive patients with a percentage of 71% in screened patients enrolled in this study
- Chronic renal disease: There are 88 patients with a percentage of 44% of screened patients enrolled in this study had a history of chronic renal disease
- Chronic Obstructive Pulmonary Disease (COPD): There are 44 patients diagnosed to have COPD with a percentage of 22% of screened patients enrolled in this study

Cause of ICU admission: Out of the 200 patients enrolled in the study, 82 patients were admitted with cardiac emergencies (including the diagnosis of myocardial infarction, heart failure, cardiogenic shock, life-threatening arrhythmias, and heart block), 58 patients with sepsis (including diagnosis of severe sepsis and septic shock), 20 patients with pulmonary disorders (including diagnosis of respiratory failure, COPD exacerbation, and ARDS), 14 patients with renal emergencies (including diagnosis of acute renal failure, and electrolytes disorders), 14 patients with DKA, and 12 patients with obstetric emergencies (including diagnosis of preeclampsia, eclampsia, and postpartum hemorrhage).

Incidence of Delirium in the Study Population

Incidence of delirium in the whole study population: There were 72 patients diagnosed with delirium among the study population; either by CAM-ICU score, or by SGA, or by both, with a percentage of 36%. About 12 patients of them didn't continue the study (8 patients died, and 4 patients were discharged against medical advice). Therefore, a total of 60 patients completed the study.

Incidence of delirium in the different age groups: The highest incidence of delirium is in both age groups from 60-70 years and those above 70 years with a percentage of 45.45% and 50% respectively as shown in Table 1.

Table 1 Showing incidence of delirium in different age groups

Age (Years)	Delirium	Non-delirium	Total	Incidence of Delirium
15-30	2	6	8	25.00%
30-40	6	12	18	33.33%
40-50	2	*20*	22	9.09%
50-60	10	32	42	23.81%
60-70	30	36	66	45.45%
>70	22	22	44	50.00%

Incidence of delirium in males and females: There were 42 females diagnosed with delirium with a percentage of 47.73%, and 30 males diagnosed with delirium with a percentage of 26.79% among the study population.

Incidence of delirium with different comorbidities:

- Diabetes mellitus: Diabetes mellitus has an incidence rate of 58% in the study population, where 36 patients developed delirium with a percentage of 31.01%
- Hypertension: Hypertension has an incidence rate of 71% in the study population, where 52 patients developed delirium with a percentage of 36.62%
- Chronic renal diseases: Chronic renal diseases have an incidence rate of 44% in the study group, where 28 patients developed delirium with a percentage of 31.81%
- COPD: COPD have an incidence rate of 10% in our study population, where 3 patients developed delirium with a percentage of 30%

Incidence of delirium with different admitting diagnoses to the ICU: Among this study population, sepsis has an incidence rate of 29%, where 16 patients developed delirium with a percentage of 27.59%. Cardiac emergencies have an incidence rate of 41%, where 30 patients developed delirium with a percentage of 36.59%.

Diagnosis of pulmonary disorders has an incidence rate of 10%, where 12 patients developed delirium with a percentage of 60%. Renal diseases have an incidence rate of 7%, 4 patients developed delirium with a percentage of 28.57%. Diagnosis with DKA has an incidence rate of 7%, 6 patients developed delirium with a percentage of

42.85%. While obstetric emergencies have an incidence rate of 6%, 6 patients developed delirium with an incidence rate of 33.33% as shown in Table 2.

Table 2 Showing incidence of delirium in different clinical diagnoses on ICU admission of the study population

Diagnosis	Delirium (N=72)	Non-delirium (N=64)	Total	Incidence of Delirium (%)
Sepsis	16	42	58	27.59%
CARDIAC	30	52	82	36.59%
Pulmonary disease	12	8	20	60.00%
Renal disorders	4	10	14	28.57%
DKA	6	8	14	42.85%
Obstetric emergencies	4	8	12	33.33%

Time of onset of delirium: Mean day of onset of delirium in the study population is 11.29 ± 8.40 days.

Diagnostic Tools of Delirium used in the Study; Evaluation of Subjective Global Assessment (SGA) versus CAM-ICU Scoring System

Diagnosis of delirium with SGA: Among the study population, 35% of patients are diagnosed to have delirium with SGA, while 65% were excluded from the diagnosis with delirium.

Diagnosis of delirium with CAM-ICU score: Among the study population, 28% of patients were diagnosed to have delirium with CAM-ICU score, while 72% were excluded from the diagnosis of delirium.

Evaluation of SGA versus CAM-ICU score in diagnosing delirium: There is no statistical difference between SGA and CAM-ICU score as a tool used for the diagnosis or exclusion of delirium (p=0.287). Additionally, when taking CAM-ICU score as a reference for diagnosing delirium in the critically ill patients, the sensitivity of SGA was 85.7%, while its specificity was 84.7% as shown in Table 3.

Table 3 Showing sensitivity and specificity of SGA in diagnosing delirium

Diagnosed by SGA	Diagnosed by CAM-ICU			
	Yes		No	
	Count	%	Count	%
Yes	48	85.70%	22	15.30%
No	8	14.30%	122	84.70%

Cohen's k-value was used to determine if there was an agreement between CAM-ICU score and SGA in diagnosing delirium, it was shown that there was a strong agreement between them (k=0.793, p<0.001).

Assessment of the Responsiveness to Treatment with different Antipsychotics; Evaluation of Subjective Global Assessment (SGA) versus CAM-ICU Scoring System

In this study, all (60) patients diagnosed with delirium were controlled by the 3rd day of antipsychotic drugs administration. So the responsiveness to treatment was evaluated during the initial 3 days of antipsychotic drugs administration.

Evaluation of control of delirium by different antipsychotics using SGA during the first 3 days of treatment:

- Day 1: By the 1st day of therapy, delirium was controlled in only 4 (20%) patients in the 1st group that received haloperidol, while the other 4 groups treated by risperidone and quetiapine failed to control manifestations of delirium
- Day 2: By the 2nd day of treatment, delirium was controlled in 14 (70%) patients of the 1st group that received haloperidol, 10 (50%) patients in the 2nd group that received risperidone, and 8 (40%) patients in the 3rd group that received quetiapine
- Day 3: By the 3rd day of treatment, delirium was controlled in all patients treated in the 3 divided groups of the study

Evaluation of control of delirium by different antipsychotics using CAM-ICU during the 1st three days of treatment:

- Day 1: By the 1st day of therapy, delirium was controlled in 6 (30%) patients of the 1st group that received haloperidol, 4 (20%) patients in the 2nd group that received risperidone, and 2 (10%) patient in the 3rd group that received quetiapine
- Day 2: By the 2nd day of treatment, delirium was controlled in 14 (70%) patients of the 1st group that received haloperidol, 10 (50%) patients in the 2nd group that received risperidone, and 12 (60%) patients in the 3rd group that received quetiapine
- Day 3: By the 3rd day of treatment, delirium was controlled in all patients treated in the 3 divided groups of the study

SGA versus CAM-ICU score: By taking the CAM-ICU score as a reference tool for evaluating control of delirium, SGA is evaluated in the initial 3 days of the treatment as follows:

- Day 1: By the 1st day, delirium was controlled in 12 patients regarding CAM-ICU score and 4 patients regarding SGA with no statistically significant relationship between the 2 evaluation tools (p=0.366). The sensitivity of SGA is 16.7% while its specificity is 95.8%
- Day 2: By the 2nd day, delirium was controlled in 36 patients regarding CAM-ICU score and 32 patients regarding SGA with a statistically significant positive relationship between the 2 evaluation tools (p<0.001). The sensitivity of SGA is 83.3% while its specificity is 91.7%
- Day 3: By the 3rd day, delirium was controlled in all patients regarding SGA and CAM-ICU score

Assessment of Degree of Agitation by Agitated Behavior Scale (ABS) in Patients with Delirium

The results in this part will be described under the following headlines

- The incidence of different degrees of agitation in the study population using ABS
- Evaluation of the effect of the antipsychotic drugs used in this study for controlling the severity of agitation
- The relation between the degree of agitation and dose of the used antipsychotic drug needed to control delirium
- The relation between the degree of agitation and the need for additional antipsychotic drugs to control delirium
- The relation between the degree of agitation and the need for additional antipsychotic drugs to control delirium

Incidence of different degrees of agitation in our study population using ABS: Regarding ABS, ten patients were diagnosed to have mild agitation with a percentage of 16.7%, 36 patients were diagnosed to have moderate agitation with a percentage of 60%, and 14 patients were diagnosed to have severe agitation with a percentage of 23.3%.

Evaluation of the effect of the antipsychotic drugs used in the study for controlling the severity of agitation: Haloperidol was used to control 2 patients with mild agitation, 14 patients with moderate agitation and 4 patients with severe agitation. Risperidone was used to control 4 patients with mild agitation, 14 patients with moderate agitation and 2 patients with severe agitation. Quetiapine was used to control 4 patients with mild agitation, 8 patients with moderate agitation, and 8 patients with severe agitation. There is no statistically significant difference between the 6 groups regarding the severity of agitation (p=0.583).

The relation between the degree of agitation and dose of the used antipsychotic drug needed to control delirium: Haloperidol was used to control delirium in this study population with a usual dose of 2-10 mg IV of haloperidol lactate which needed to be repeated q15-30 min with doubling initial dose in severe agitation. Risperidone was used to control delirium in the study population with the usual dose of 1-2 mg daily PO to be increased with 1-2 mg/day at intervals ≥ 24 hours in severe cases of agitation. Quetiapine was used to control delirium in the study population with a usual dose of 50 mg/day PO divided q12hr to be increased daily in increments of 25-50 mg q8-12hr in severe cases of agitation.

All patients diagnosed with mild agitation (100%) were controlled with the usual dose of the used antipsychotic drug. Total 26 patients with moderate agitation (72.2%) were controlled with the usual dose while 10 patients (27.8%) were

controlled with a higher dosage of antipsychotics. However, all patients diagnosed with severe agitation (100%) were controlled with the higher dosage of the used drug.

There is a statistically significant relationship between the degree of agitation and dose of the used antipsychotic drug needed to control delirium; the dose of the used antipsychotic medication is increasing with the increase in the severity of agitation ($p<0.001$).

The relation between the degree of agitation and the need for additional antipsychotic drugs to control delirium: Among the study population, all patients diagnosed with mild agitation didn't need additional antipsychotic to control delirium, while 50% of patients with moderate agitation needed additional antipsychotic, 71.4% of patients with severe agitation needed other antipsychotics. There was a statistically significant relationship between the degree of agitation and the need for additional antipsychotic drugs ($p=0.049$).

The relation between the degree of agitation and the need for sedation to control delirium: All patients diagnosed with mild agitation didn't need sedation. Meanwhile, only 2 patients with moderate agitation (5.6%) required sedation, 12 out of 14 patients with severe anxiety (85.7%) needed sedation. There was a statistically significant relationship between the degree of agitation and the need for sedation to control delirium ($p<0.001$).

Comparative analysis between the three antipsychotic drugs used to control delirium, using CAM-ICU score as a gold standard: In this part of the study, results will be presented under the following headlines:

- Control of delirium by different antipsychotics
- Dosage requirement for each antipsychotic drug used to control delirium.
- The time needed for each antipsychotic to control delirium
- Need for additional antipsychotics to control delirium in the 3 groups
- Need for sedation to control delirium among the 3 groups
- The incidence of adverse effects in the 3 groups
- The outcome of the included patients in each group

Control of delirium by CAM-ICU score:

- Haloperidol: The 1st group of patients received haloperidol to control delirium, 6 (30%) patients were controlled in the 1st day, 14 (70%) patients were controlled in the 2nd day, and all patients (100%) were controlled in the 3rd day
- Risperidone: The 2nd group of patients received risperidone to control delirium, 4 (20%) patients were controlled in the 1st day, 10 (50%) patients were controlled in the 2nd day, and all patients (100%) were controlled in the 3rd day
- Quetiapine: The 3rd group of patients received quetiapine to control delirium, 2 (10%) patient was controlled in the 1st day, 12 (60%) patients were controlled in the 2nd, and all patients (100%) were controlled in the 3rd day
- The relation between 3 groups regarding control of delirium in the 3 days of the study: There is no statistically significant difference between the 3 used drugs regarding control of delirium by CAM-ICU score

Dosage requirement for each antipsychotic drug used to control delirium:

- Haloperidol: The 1st group of patients received haloperidol to control delirium, 16 (80%) patients were controlled using a usual dose, while 4 (20%) patients were controlled using higher doses
- Risperidone: The 2nd group of patients received risperidone to control delirium, 12 (60%) patients were controlled using a usual dose, while 8 (40%) patients were controlled using higher doses
- Quetiapine: The 3rd group of patients received quetiapine to control delirium; 8 (40%) patients were controlled using a usual dose, while 12 (60%) patients were controlled using higher doses.

- Relation of dosage requirement between 3 groups: There was no statistically significant difference between the 6 used drugs regarding dosage required to control delirium (p=0.248)

Time needed for each antipsychotic to control delirium:

- Haloperidol: The 1st group of patients received haloperidol to control delirium, 6 (30%) patients were controlled in the 1st day, 8 (40%) patients were controlled in the 2nd day, and 6 (30%) patients were controlled in the 3rd day
- Risperidone: The 2nd group of patients received risperidone to control delirium, 4 (20%) patients were controlled in the 1st day, 6 (30%) patients were controlled in the 2nd day, and 10 (50%) patients were controlled in the 3rd day
- Quetiapine: The 3rd group of patients received quetiapine to control delirium, 2 (10%) patient was controlled in the 1st day, 10 (50%) patients were controlled in the 2nd day, and 8 (40%) patients were controlled in the 3rd day
- The relation between 3 groups regarding the time needed to control delirium: There is no statistically significant difference between the 3 groups in the time required to control delirium (p=0.781)

Need for additional antipsychotics to control delirium in the 3 groups:

- Haloperidol: The 1st group of patients received haloperidol to control delirium, and no patient needed other antipsychotic to control delirium
- Risperidone: The 2nd group of patients received risperidone to control delirium, 16 (80%) patients needed additional antipsychotic in the 1st day, 10 (50%) patients required additional antipsychotic in the 2nd day, and 6 (30%) patients needed additional antipsychotic in the 3rd day
- Quetiapine: The 3rd group of patients received quetiapine to control delirium, 12 (60%) patients required additional antipsychotic in the 1st day, 8 (40%) patients needed additional antipsychotic in the 2nd day, and 4 (20%) patients needed additional antipsychotic in the 3rd day
- The relation between the 3 groups regarding the need for other antipsychotics to control delirium: By comparing the 3 groups, 2nd and 3rd groups show statistically significant need for additional antipsychotics to control delirium in the 1st and 2nd day of treatment (p=0.001 and 0.038 respectively); however there was no statistically significant difference between the 3 groups in the 3rd day of the study (p=0.321)

Need for adding a sedative agent to control delirium in the 3 groups:

- Haloperidol: The 1st group of patients receiving haloperidol to control delirium, 4 (20%) patients needed adding sedation to control delirium only in the 1st day of the study
- Risperidone: The 2nd group of patients receiving risperidone to control delirium, 2 (10%) patient needed adding sedation in the 1st day, and 2 (10%) patient also in the 2nd day required adding sedation to control delirium
- Quetiapine: The 3rd group of patients receiving quetiapine to control delirium, 8 (40%) patients needed adding sedation in the 1st day, while only 2 (10%) patient in the 2nd day required adding sedation to control delirium
- The relation between 3 groups of the study regarding the need for adding sedation to control delirium: There is no statistically significant difference between the three groups of the study in need for adding sedation to control delirium, (p=0.43 and 1 in the 1st and 2nd days respectively)

Incidence of adverse effects in the 3 groups:

- Prolonged QTc interval: No prolongation of the QTc interval developed in the successive ECG performed to any of the 3 groups during the period of the study
- Extrapyramidal manifestations: No extrapyramidal manifestations occurred in any of the 3 groups during the period of the study

Outcome:

- Need for ventilation: Among the study population, only 2 (10%) patient in each group of the study needed

mechanical ventilation during the study period; it occurred in the 3rd day in the group receiving haloperidol, 2nd day in the group receiving risperidone, and 1st day in the group receiving quetiapine, with no significant p-value between the 3 groups

- ICU stay: The mean duration of ICU stay in the 1st group receiving haloperidol is 15.2 ± 9.96 days versus 14.0 ± 7.63 days in the 2nd group receiving risperidone and 12.3 ± 7.06 days in the 3rd group receiving quetiapine (p=0.744)
- Mortality: Among the study population, there is a 20% mortality rate among patients received haloperidol, 30% mortality rate among patients received risperidone, and 10% mortality rate among patients received quetiapine, with no statistically significant difference between them, (p=0.847)

DISCUSSION

Delirium in critically ill patients is a common occurrence that has previously received little attention. Recent guidelines by the Intensive Care Society (ICS) and the Society of Critical Care Medicine (SCCM) recommend daily monitoring of sedation scores and delirium in all Intensive care unit (ICU) patients. Recent studies have increased knowledge and interest in the treatment and prevention of delirium [3]. ICU patients are commonly intubated, sedated, and physically weak. These unique characteristics led to the development of 5 adult delirium screening tools that are validated against the American Psychiatric Association's DSM criteria for the diagnosis of delirium: the ICDSC, the CAM-ICU, the Nursing Delirium Screening Scale, the Delirium Detection Score, and the Cognitive Test for Delirium [4,5].

The ICDSC and the CAM-ICU are the most well studied and widely implemented ICU delirium screening tools worldwide and are the 2 delirium screening tools recommended by recently updated clinical practice guidelines [6].

Antipsychotics are a group of drugs that are used to treat a handful of psychiatric disorders characterized by disturbed thought and behavior. Although they are not curative, they relieve some of the debilitating symptoms of this group of diseases. There are 2 categories of antipsychotics, typical or first-generation antipsychotic drugs as haloperidol and atypical or second-generation antipsychotic drugs as risperidone and quetiapine [7].

In this study, we tried to assess the incidence of delirium in critically ill patients, evaluate the effectiveness of diagnosing delirium by subjective global assessment compared to CAM-ICU score, and to evaluate the degree of agitation in patients diagnosed with delirium using Agitated behavior scale (ABS).

Additionally, we tried to compare the efficacy and safety of haloperidol versus atypical antipsychotic medications (risperidone and quetiapine) in managing delirium in critically ill patients using CAM-ICU score as a tool for evaluation of the control of delirium.

This study is a prospective, comparative clinical observational study, where 200 critically ill patients admitted to the ICU were evaluated for the diagnosis of delirium using the CAM-ICU scoring system and Subjective global assessment (SGA).

The demographic data of all our included patients show that mean age of study patients was 62.20 ± 13.34 years with a median age of 65 years, both males and females are represented in a ratio of 56% and 44% respectively. There were no statistically significant differences in results regarding demographic data, co-morbidities, or different admitting diagnoses to ICU.

Regarding the incidence of delirium in the study, 36% of all our study population developed delirium during their ICU stay with a higher incidence of delirium in the age groups from 60 to 70 years and those above 70 years with a percentage of 45.45% and 50% in each age group respectively. These results are in accordance with Thomason, et al., [8].

In their prospective cohort investigation of 261 consecutively admitted medical ICU patients during hospitalization at a tertiary-care, university-based hospital. They found that 125 (48%) patients experienced at least 1 episode of delirium. Patients who underwent delirium were older (mean ± SD: 56 ± 18 versus 49 ± 17 years). Ouimet, et al., performed a prospective study in a 16-bed medical-surgical Intensive care unit (ICU), and included 820 consecutive patients admitted to ICU for more than 24 hours, they used the Intensive care delirium screening checklist for diagnosing delirium in their study, they found that delirium occurred in 31.8% of 764 patients, but they found no relationship between the incidence of delirium and age [9].

The difference between our study and these studies regarding the percentage of incidence of delirium and its relation with age is that we used the CAM-ICU scoring system with SGA in the diagnosis of delirium, but other studies used different assessment tools of delirium with different sensitivities and specificities, On the other hand, the sample size and age characteristics of the studied populations may also have a role.

Considering the diagnostic tools for delirium used in our study, SGA diagnosed 35 patients to have delirium with a percentage of 35% and excluded the diagnosis of delirium in 65 patients with a percentage of 65%. On the other hand, the CAM-ICU score diagnosed 28 patients with delirium with a percentage of 28% and excluded 72 patients from the diagnosis of delirium with a percentage of 72%. There was no statistical difference between SGA and CAM-ICU score as a tool used for the diagnosis or exclusion of delirium, ($p=0.287$). Additionally, Cohen's k-value was used to determine if there was an agreement between CAM-ICU score and SGA in diagnosing delirium, we found that there was a strong agreement between them, ($k=0.793$ and $p<0.001$). Our results go parallel with Guenther, et al., in their observational cohort study on 160 patients whose delirium status was rated daily by bedside nurses by subjective individual clinical impressions and by medical students by scores on the objective Confusion Assessment Method for the Intensive Care Unit [CAM-ICU] [10]. They found that 38.8% (n=62) had delirium according to objective criteria at some time during their stay in the intensive care unit. A total of 436 paired observations were analyzed. Delirium was diagnosed in 26.1% of observations (n=114) with the objective method. This percentage included 6.4% (n=28) in whom delirium was not recognized via subjective criteria. According to subjective criteria, delirium was present in 29.4% of paired observations (n=128), including 9.6% (n=42) with no objective indications of delirium. Although the use of objective criteria helped to detect delirium in more patients and also identified patients mistakenly thought to have delirium, there was no statistically significant difference between both tools of evaluation. Agreement between subjective clinical impression and the results of the CAM-ICU was high (>90%) for delirious, agitated patients and no delirious, calm and alert patients [11].

Regarding the degree of agitation of patients included in this study, patients diagnosed with delirium were classified to have mild, moderate or severe agitation with percentages of 16.7%, 60.0%, and 23.3% respectively. A prospective cohort study was performed by Woods, et al., in 18-bed MICU in a 964-bed tertiary care center. The study included 143 ventilated patients aged 18 years or older. Severe agitation, the primary outcome variable, was defined as two or more Motor Activity Assessment Scale (MAAS) scores above 4 in a 24-h period. They found 23 (16.1%) of the all enrolled patients exhibited severe agitation [12].

The difference between the current study and that of Woods, et al., regarding the percentage of incidence of different degrees of agitation is that we used ABS to identify and classify the degree of agitation, while other study used other tools with different sensitivities and specificities. The small sample size and the short duration of our study may also have a role.

Discussing the relationship between the degree of agitation and dose of the used antipsychotic drug, all patients diagnosed with mild agitation (100%) were controlled with the usual dose of the used antipsychotic medication, 72.2% of patients with moderate agitation were controlled with the usual dose. All patients with severe agitation (100%) were controlled with the higher dosage of the used antipsychotic.

This result is supported by Riker, et al., who performed a study on a consecutive sample of 8 patients requiring mechanical ventilation who had severe agitation which was refractory to intermittent bolus treatment with benzodiazepines, narcotics, and haloperidol in 34-bed multidisciplinary intensive care. They used continuous infusions of haloperidol to agitation, they found that continuous infusion of haloperidol effectively controls severe agitation in the studied group of critically ill patients, the daily number of bolus administrations of sedatives decreased from 23 to 7 ($p=0.01$) after 1 day of continuous infusion of haloperidol, and also they found that of the 5 patients discharged alive (37.5% mortality rate), 4 were successfully weaned from assisted ventilation during continuous infusion of haloperidol. About 2 of these 4 patients were difficult to wean because of agitation and over sedation [13].

Considering the relation between the degree of agitation and need for additional antipsychotics and sedation, there is a strong positive relation between severity of agitation and need for additional antipsychotics and adding sedation to control agitation, ($p=0.049$ and $p<0.001$ respectively).

This result is supported by Woods, et al., who found that benzodiazepines, narcotics, and neuromuscular blocking agents were administered more frequently and at higher doses in the severely agitated patients [12]. Mayo-Smith,

et al., also supports our result who performed structured review and meta-analysis on articles with original data on the management of alcohol withdrawal delirium, they found that meta-analysis of 9 prospective controlled trials demonstrated that sedative-hypnotic agents are more effective than neuroleptic agents alone in reducing the duration of delirium and mortality [13].

Regarding the efficacy of the three used antipsychotic drugs, there is no statistically significant difference between the three used antipsychotic drugs (haloperidol, risperidone, and quetiapine) considering their efficacy to control delirium. This result is in accordance with Yoon, et al., who performed a 6-day, prospective, comparative clinical observational study of haloperidol versus atypical antipsychotic medications (risperidone, olanzapine, and quetiapine) in patients with delirium, the efficacy was evaluated using the Korean version of the Delirium RatingScale-Revised-98 (DRS-K) and the Korean version of the Mini-Mental Status Examination (K-MMSE). They found that there were no significant differences in the improvement of DRS-K or K-MMSE scores among the 4 groups, (p=0.969) [14].

Maneeton, et al., conducted another prospective, double-blind, randomized controlled trial on 52 medically ill patients with delirium from June 2009 to April 2011 to compare the efficacy and safety of haloperidol vs. quetiapine in the treatment of delirium, they used the Delirium rating scale-revised-98 (DRS-R-98) for daily assessment. They found that mean (standard deviation) doses of quetiapine and haloperidol were 67.6 (9.7%) and 0.8 (0.3%) mg/day, respectively. Over the trial period, means (standard deviation) of the DRS-R-98 severity scores were not significantly different between the quetiapine and haloperidol groups (-22.9 (6.9%) versus -21.7 (6.7%); p=0.59) [15].

As regards the need for additional antipsychotics, there is a statistically significant difference between 3 groups regarding the need for additional antipsychotic to control delirium; atypical antipsychotics (risperidone and quetiapine) showed a significant need for additional antipsychotics to control delirium on the 1st and 2nd day of treatment, (p=0.001 and 0.038 respectively); however there was no statistically significant difference between the 3 groups in the 3rd day of the study (p=0.321).

These results are supported by Devlin, et al., who performed prospective, randomized, double-blind study on 36 adult intensive care unit patients with delirium in 3 academic medical centers. They found that quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation, and a higher rate of transfer to home or rehabilitation [16].

As regards the mortality rate, there is a 20% mortality rate among patients received haloperidol, 30% mortality rate among patients received risperidone, and 10% mortality rate among patients received quetiapine to control their delirium. However, there was no statistically significant difference between the 3 groups in the mortality rate among the included critically ill patients (p=0.847).

Kales, et al., performed a retrospective cohort study using national data from the U.S. Department of Veterans Affairs (fiscal years 1999-2008), involving 33,604 patients aged 65 years and older who began outpatient treatment with an antipsychotic (risperidone, olanzapine, quetiapine, or haloperidol). The individual drug groups were compared for 180-day mortality rates. The authors analyzed the data using multivariate models and propensity adjustments. They found that haloperidol was associated with the highest mortality rates followed by risperidone, olanzapine, and quetiapine. They also found that the mortality risk with haloperidol was highest in the first 30 days (p<0.001) but decreased significantly and sharply after that (p=0.65) [17]. The difference between our study and this study regarding mortality rates among different antipsychotics may be referred to the small sample size and short duration of our study compared to this study.

CONCLUSION

Delirium is a frequent complication in the intensive care unit. The CAM-ICU scoring system appears to be rapid, valid, and reliable for diagnosing delirium in the ICU setting and may be a useful instrument for both clinical and research purposes. Use of objective criteria may identify patients mistakenly thought to have delirium who do not meet objective criteria for the diagnosis of the condition. The degree of agitation is an essential indicator of the dosage of the used antipsychotic drug, need for additional antipsychotics, and need for adding sedation. Haloperidol, risperidone, and quetiapine are equally effective and safe in the treatment of delirium in critically ill patients.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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