Comparative Study between Haloperidol and Quetiapine as Antipsycotic in Management of Delirium in Criticaly ill Patients

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Abstract: Delirium is an independent predictor of increased length of ICU stay, mortality, and treatment costs in critical care department. Its incidence may be underestimated or overestimated if delirium is assessed by using subjective clinical impression alone rather than an objective instrument. Different antipsychotics; either typical or atypical, are used for control of delirium in critically ill patients. In this comoarative study between haloperidol and quetiapine among adults critically ill patients using biological equivalent doses haloperidol and quetiapine are equally effective and safe in the treatment of delirium in the critically ill patients.

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1. Introduction

Delirium is a common, complex neuropsychiatric disorder with a high prevalence among critically ill patients, postsurgical patients, and cancer patients in advanced stages of illness. Typically, delirium shows an abrupt, rapid onset and a fluctuating course. The core features of delirium consist of disturbances in cognitive function such as attention, memory, thought, and language. However, its clinical presentation can be highly variable with a broad range of associated non-cognitive, behavioral symptoms that reflect the influence of distinct etiologies, medical comorbidities, or pharmacological treatments. (1)

In hospitalized Intensive Care patients, the prevalence of delirium ranges from 10 to 40%. Delirium is also associated with major adverse outcomes such as increased mortality, functional impairment, prolonged hospitalization, and increased cost of care. Regardless of the evident clinical significance, delirium tends to be under-diagnosed and under-treated. Therefore, early identification and effective treatment of delirium is important in the comprehensive care of critically ill patients. (2)

ICU patients are commonly intubated, sedated, and/or physically weak. These unique characteristics led to the development of five 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. (3)

The ICDSC and the CAM-ICU are the most well studied and widely implemented adult ICU delirium screening tools worldwide and are the two delirium screening tools recommended by recently updated clinical practice guidelines. (4)

The management of delirium includes ensuring safety with environmental or supportive interventions, identifying and treating the cause of delirium, and enhancing the patient's functioning. Regarding pharmacological intervention, antipsychotic medication has been considered as first-line pharmacotherapy of delirium. Haloperidol, a typical antipsychotic, has continued to be the most frequently used antipsychotic drug due to its effectiveness, relatively lesser sedative and hypotensive effects and fewer anticholinergic properties. However, haloperidol may induce adverse side effects such as extrapyramidal symptoms (EPSs) or prolongation of the QTc interval and fatal arrhythmia such as torsade de pointes among patients with delirium. (5)

Recently, atypical antipsychotics such as quetiapine have been increasingly used to treat delirious patients due to the lower incidences of EPSs associated with these drugs. (6)

In this study we seek to assess 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, compare the efficacy and safety of haloperidol versus atypical antipsychotic medications (risperidone and quetiapine) in managing delirium in critically ill patients, and to evaluate the effect of antipsychotic management of delirium on

ICU length of stay and need for mechanical ventilation.

Aim of Work

The primary objectives of this study are to:

- Compare the efficacy and safety of haloperidol versus atypical antipsychotic medications such as quetiapine in managing delirium in critically ill patients.
- Effect of antipsychotic management of delirium on the length of ICU stay and need for mechanical ventilation.

The secondary objectives of the study are to:

2. Patients and Methods:

60 critically ill patients are subjected to this study. Patients are selected sequentially on their admission to ICU. Excluded from them, those DCL ICU patients with one or more of the following criteria:

- Dementia.
- Co-morbidities

Study design:

The 60 patients involved in the study according to the inclusion and exclusion criteria described before are subjected to the followings along their stay in ICU:

- Full medical history taking.
- Clinical examination daily: with emphasis on full neurological assessment.
- Daily assessment of delirium along their stay in the ICU by two 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 physician in charge of the study using CAM-ICU worksheet
- Routine ICU monitoring: During ICU stay, the patients are kept on continuous rhythm, blood pressure and pulse oximetery monitoring.
- Laboratory analysis: This included complete blood analysis with complete blood picture, liver function tests, cardiac biomarkers, renal function tests.
- Management of delirium using different antipsychotic medications as follows:

Patients diagnosed with new onset delirium in ICU either by CAM-ICU scoring system or by subjective global assessment or by both are then subdivided into 2 equal groups;

Group 1: delirium is managed using haloperidol, a typical antipsychotic, to control delirium.

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 last bolus dose every 6 hours.

Haloperidol used in this study in IV form according to Möller et al. [7]clinical trial on efficacy and side effects of haloperidol in psychotic patients: oral versus intravenous administration in which they found the intravenous administration was slightly more effective during the first 3 hours, thereafter the route of administration did not make a difference in effectiveness. [7]

Group 2: delirium was managed using quetiapine, an atypical antipsychotic, to control delirium.

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.

Continuous assessment and follow up of patients diagnosed with delirium along their ICU stay.

3. Results

A- Incidence of delirium in the whole study population:

There are 20 patients diagnosed with delirium among the study population; either by CAM-ICU score, or by SGA, or by both, with a percentage of 33.3%.

B-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).

C-Comparative analysis between the two 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.
- Time needed for each antipsychotic to control delirium.
- Incidence of adverse effects in the three groups.
- Outcome of the included patients in each group.

A- Control of delirium by CAM-ICU score:

There is no statistically significant difference between the two used drugs regarding control of delirium by CAM-ICU score.

B- Dosage requirement for each antipsychotic drug used to control delirium:

There is no statistical significant difference between the two used drugs regarding dosage required to control delirium. (P = 0.248).

C- Time needed for each antipsychotic to control delirium:

There is no statistically significant difference between the two groups in the time needed to control delirium, (P = 0.781).

Table (1): Showing difference between SGA and CAM-ICU score in the diagnosis and exclusion of delirium.

	Delirium		Non		P value
	Count	%	Count	%	
SGA	20	33.3	40	66.7	0.287
CAM-ICU	18	30	42	70	

Table (2): Showing relation between the two used drugs regarding control of delirium by CAM-ICU score.

		Drug				
		Haloperidol		Quetiapine		P value
		Count	%	Count	%	
Control by CAM-ICU 1	**Yes**	3	30.0%	1	10.0%	0.847
	No	7	70.0%	9	90.0%	
Control by CAM-ICU 2	**Yes**	7	70.0%	6	60.0%	0.893
	No	3	30.0%	4	40.0%	
Control by CAM-ICU 3	**Yes**	10	100.0%	10	100.0%	-----
	No	0	.0%	0	.0%	

Table (3): Showing relation between two drugs regarding required dosage to control delirium.

		Drug				P value
		Haloperidol		Quetiapine		
		Count	%	Count	%	
Dose	**Usual dose**	8	80.0%	4	40.0%	0.248
	High dose	2	20.0%	6	60.0%	

Table (4): Relation between two groups regarding time needed to control delirium.

		Drug				P value
		Haloperidol		Quetiapine		
		Count	%	Count	%	
Time need to control delirium	**1st day**	3	30.0%	1	10.0%	0.781
	2nd day	4	40.0%	5	50.0%	
	3rd day	3	30.0%	4	40.0%	

D- Incidence of adverse effects in the three groups:

No prolongation of the QTc interval developed in the successive ECG performed and no extrapyramidal manifestations occurred in any of the two groups during the period of the study.

E- Outcome:

1. Need for ventilation:

Among the study population, only 1 patient (10%) in each group of the study needed mechanical ventilation during the study period; it occurred in the 3rd day in the group receiving haloperidol, and 1st day in the group receiving quetiapine, with no significant P value between the two groups.

2. ICU stay:

The mean duration of ICU stay in the 1st group receiving haloperidol is 15.2±9.96 days versus 12.3±7.06 days in the 2nd group receiving quetiapine (P = 0.744).

3. Mortality:

Among the study population, there is a 20% mortality rate among patients received haloperidol, and 10% mortality rate among patients received quetiapine, with no statistically significant difference between them, (p=0.847).

Regarding the incidence of delirium in the study These results are in accordance with Adamis et al. [8] performed a prospective study conducted on 71 patients in two Greek general ICUs, in which the applicability and validity of CAM-ICU was tested compared to the gold standard (DSM-IV). They found that the prevalence of delirium was 33.8% based on (DSM-IV) as a gold standard for diagnosing delirium. [8]

Considering the diagnostic tools for delirium used in our study Our results go parallel with Guenther et al. [9] in their observational cohort study which was performed in a surgical-cardio 31-bed intensive care unit of a university hospital. [9]

`Regarding efficacy of the two used antipsychotic drugs, This result is in accordance with Yoon et al. [10] who performed a 6-day, prospective, comparative clinical observational study of haloperidol versus atypical antipsychotic medications (risperidone, olanzapine, and quetiapine) in patients with delirium at a tertiary level hospital, the efficacy was evaluated using the Korean version of the Delirium Rating Scale-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 four groups, (P = 0.969). [10]

Considering mortality rate, Kales et al. [11] 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 thereafter (p=0.65). [11]

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 actually do not meet objective criteria for diagnosis of the condition.

Haloperidol and quetiapine are equally effective and safe in the treatment of delirium in the critically ill patients.

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