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Original Article

Anaesthesia Section

Comparison of Haloperidol and Quetiapine for Treatment of Delirium in Critical Illness: A Prospective Randomised Double-blind Placebo-controlled Trial

RISHABAH GARG[1], VIPIN KUMAR SINGH[2], PRATISHRUTI[3], GP SINGH[4]

ABSTRACT

Introduction: Delirium is associated with an increased chance of death, prolonged hospitalisation, higher healthcare costs, and possibly long-term brain damage in survivors. Antipsychotics, both conventional and atypical, are the cornerstone of pharmacologic treatment for delirium in adults.

Aim: To find out whether typical and atypical antipsychotic medication would result in a shorter duration of delirium than placebo and would improve other outcomes.

Materials and Methods: This is a randomised, double-blind, placebo-controlled trial conducted on patients with delirium in Intensive Care Unit (ICU) of King George's Medical University, Lucknow, Uttar Pradesh, India from February 2021 to February 2022. Out of 45, 15 received enteral haloperidol (maximum dose 30 mg daily), 15 received quetiapine (maximum dose 300 mg daily) and 15 were controls receiving placebo through Ryle's tube. Delirium was detected with the use of Confusion Assessment Method for the ICU (CAM-ICU), and side-effects of the drugs were noted. Dose of a trial drug or placebo was placed halved or doubled at 12-hour intervals using these parameters. The primary end point was the number of days alive without delirium during the 14 day intervention period. Secondary end points included time to freedom from mechanical ventilation, time to ICU, hospital discharge and 30 day and 90 day survival.

Results: Out of 45 patients screened, 25 were males and 20 were females with no comparable differences. The mean number of days alive without delirium or coma was 9.45 in the haloperidol group, 8.64 in the quetiapine group, and 8.57 in the placebo group (p-value=0.63) for overall effect across trial groups. The use of haloperidol or quetiapine as compared with placebo, had no significant effect on the primary end point. There were no significant between-group differences in respect to the secondary end points .

Conclusion: The use of enteral haloperidol or quetiapine, as compared with placebo, did not significantly alter the duration of delirium in the critically-ill patients admitted in ICU.

Keywords: Antipsychotic, Confusion assessment method, Intensive care unit

INTRODUCTION

Delirium, defined as a brief and variable change in mental status associated with impaired cognition and consciousness, is a common occurrence in critically-ill individuals that can have dangerous long-term effects [1,2]. Delirium is associated with an increased chance of death, prolonged hospitalisation, higher healthcare costs, and possibly long-term brain damage in survivors. This type of brain dysfunction is prevalent in Intensive Care Unit (ICU) patients, and the scale of the problem is projected to rise in the coming years as our population ages and ICU demand increases.

Numerous assessment techniques have been created to aid for those who are not psychiatrists in diagnosing delirium. The most often utilised instrument is the Confusion Assessment Method (CAM) [3,4]. The CAM assesses four cognitive components- acute onset and changing course, inattention, disorganised thinking, and altered level of consciousness. To be diagnosed with delirium, a patient must exhibit elements 1 and 2 as well as one of the other three or four criteria. The CAM has been validated extensively in a variety of therapeutic situations.

The Society of Critical Care Medicine recently published clinical practice guidelines recommending broad screening for delirium in adults and therapy to shorten the duration of delirium and mitigate its long-term effects [5]. Antipsychotics, both conventional and atypical, are the cornerstone of pharmacologic treatment for delirium in adults [6,7]. Haloperidol, a typical antipsychotic medication, is frequently used in the ICU to treat hyperactive delirium, and surveys indicate that it is also used to treat hypoactive delirium [8].

Despite the fact, there is inconsistent evidence that haloperidol results in a shorter duration of delirium in the ICU when compared to placebo. Atypical antipsychotic medicines such as olanzapine, quetiapine, risperidone, and ziprasidone are also used for this purpose, with one placebo-controlled trial indicating efficacy [8,9].

There is no discrete information regarding the management of delirium in the ICU from small trials, meta-analyses, and practice guidelines [9].

This was a single-centered, randomised, double-blind, placebo-controlled trial to examine the effects of haloperidol or quetiapine on delirium during critical illness. The primary objective was the number of days alive without delirium during the 14 day intervention period. Secondary objectives included time to freedom from mechanical ventilation, time to ICU and hospital discharge and 30 day and 90 day survival.

MATERIALS AND METHODS

This randomised double-blind placebo-control study was conducted between February 2021 to February 2022 in Trauma Ventilatory Unit, Department of Anaesthesiology, King George's Medical University, Lucknow, Uttar Pradesh, India. Ethical clearance was taken from Institutional Review Board (ref: 104th ECM II B-Thesis/P6).

Inclusion criteria: After written informed consent, from either of the patients or guardian, patients with age more than 18 years, admitted in ICU with delirium who were accepting enteral were included in the study.

Exclusion criteria: Patients who at baseline had severe cognitive impairment, one who were at high risk for medication side-effects

because of pregnancy and breast feeding. Patients with history of torsades de pointes, neuroleptic malignant syndrome, or allergy to haloperidol or quetiapine were not considered. Also those who had ongoing treatment with antipsychotics, having rapidly resolving organ failure, moribund patients, and those who were blind or unable to speak or understand were excluded.

Sample size calculation: Kim et al., obtained the mean difference of 1.55 by comparing the duration of delirium (days) in placebo group (1.83±1.34) and quetiapine group (0.28±0.52) [10]. Considering 95% confidence interval and power of study 99% with 10% attrition bias, the minimum calculated sample size was 15 (in each group), by using Epi Info software (version 3.01). All patients were divided in three groups after simple random sampling:

– Group A: Haloperidol group
– Group B: Quetiapine Group
– Group C: Control group

Assigned patients received enteral haloperidol (maximum dose, 30mg daily), quetiapine (maximum dose, 300 mg daily), or placebo through Ryle's tube. With the use of the Confusion Assessment Method for the ICU, and of side-effects of the intervention ,dose of a trial drug or placebo was halved or doubled at 12 hour intervals.

Study Procedure

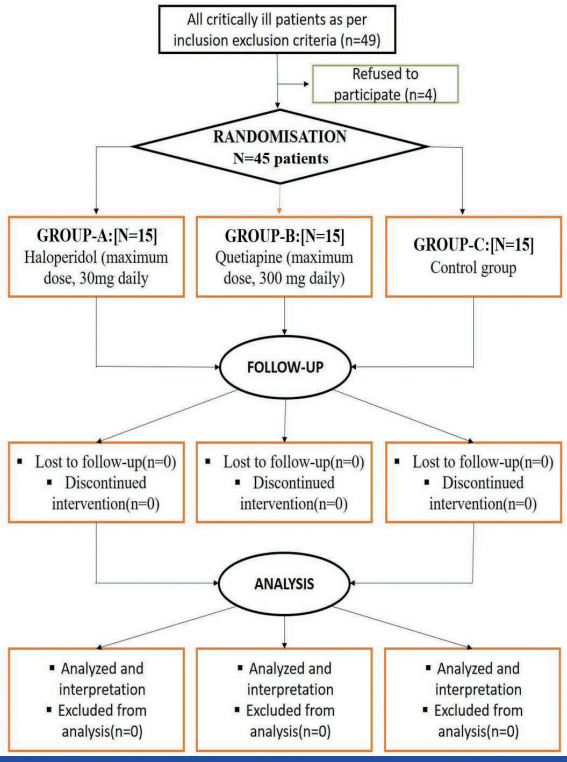
Delirium was detected with the use of the Confusion Assessment Method for the ICU (CAM-ICU) [3]. It is a validated tool that identifies delirium on the basis of an acute change or fluctuating course of mental status plus inattention and either altered level of consciousness or disorganised thinking.

STATISTICAL ANALYSIS

Data was entered in Microsoft excel and analysed using Statistical Package for Social Sciences software (SPSS) version 23.0 (Chicago, IL, USA). Student's t-test was used to analyse parametric data, while the Mann-Whitney U test was applied to non parametric data and Fisher's exact test to categorical data. Chi-square test was used to compare mortality. A p-value <0.05 was considered statistically significant.

RESULTS

Total of 49 patients were screened, of whom four patients or their representatives refused to participate [Table/Fig-1].



[Table/Fig-1]: CONSORT diagram.

All data were analysed using an intention-to-treat approach and compared the effects of oral haloperidol, quetiapine and placebo with respect to primary and secondary end points. There were no significant differences in baseline characteristics between the trial groups [Table/Fig-2].

Variables		Group A (n=15)	Group B (n=15)	Group C (n=15)	p-value
Age (year) (Mean±SD)		57.32±11.46	58.68±12.97	56.54±10.24	p=0.8780
Gender	Male	8 (53.3%)	9 (60%)	8 (53.3%)	p=0.913
	Female	7 (46.6%)	6 (40%)	7 (46.6%)	
APACHE II score at the time of admission (Mean±SD)		28.43±3.4	29.8±3.80	30.15±3.95	p=0.4167
SOFA score at randomisation (Mean±SD)		10.99±1.18	11.3±1.41	11.6±1.53	p=0.4871

[Table/Fig-2]: Baseline characteristics of the trial groups.

The mean of days alive without delirium for coma (14 days) in group A, group B and group C patients were comparable. The mean difference was statistically insignificant (p-value=0.6311). The mean of days to freedom from mechanical ventilation in group A, group B and group C patients were comparable. Difference was found to be insignificant among the groups (p-value=0.4230) [Table/Fig-3].

Days Mean±SD	Group A (n=15)	Group B (n=15)	Group C (n=15)	p-value
Alive without delirium (14 days)*	9.45±3.4	8.64±2.46	8.57±2.35	f=0.4654 p=0.6311
To freedom from mechanical ventilation	3.5±1.3	2.97±1.25	3.46±1.10	p=0.4230
ICU discharge	5.42±1.25	5.31±1.10	6.56±1.01	p=0.0065*
Hospital discharge	12.52±2.43	13.73±3.25	13.86±2.52	p=0.3498

[Table/Fig-3]: Days to freedom from delirium, mechanical ventilation, ICU discharge and hospital discharge in trial groups.
*Days to freedom from delirium, mechanical ventilation, ICU discharge and hospital discharge in trial groups

The mean of days to ICU discharge in group A and group B were shorter as compared to group C patients (p-value=0.0065), while mean of days to hospital discharge was statistically insignificant among groups (p-value=0.3498) [Table/Fig-3].

Majority of patients in all the three groups had a higher mortality at 90 day as compared to 30 days but this difference was found to be insignificant (p-value=0.966) [Table/Fig-4].

Death	Group A (n=15) n (%)	Group B (n=15) n (%)	Group C (n=15) n (%)	p-value
At 30 days	4 (26.67%)	5 (33.33%)	5 (33.33%)	χ^2=0.06823 p=0.9665
At 90 days	6 (40%)	6 (40%)	7 (46.67%)	

[Table/Fig-4]: Deaths at 30 days and 90 days among trial groups.
Chi-square (χ^2) were done to compare mortality

DISCUSSION

Patients in the ICU are more likely to experience delirium, which has an adverse effect on their prognosis and duration of stay, as well as a higher fatality rate. Intravenous antipsychotics have been used to treat delirium in hospitalised patients for more than 40 years now. Internationally, 66% of ICU intensivists reported using haloperidol to treat delirium, and 53% reported using atypical antipsychotic drugs to treat delirium [11]. ICU patients' delirium can be affected by antipsychotic drugs, but there are contradicting studies on this topic (ICU) [12]. The goal of this research was to see if enteral haloperidol and quetiapine work in critically-ill individuals with delirium.

In this randomised double-blind study, there was no evidence that either haloperidol or quetiapine led to a shorter duration of delirium. Patients who received treatment with haloperidol or quetiapine

and those who received placebo had similar outcomes, including survival and lengths of stay in the ICU and hospital.

Treating physicians were educated about the "ABCDE" treatment bundle (assess, prevent, and manage pain, both spontaneous awakening and breathing trials, choice of analgesia and sedation, assess, prevent, and manage delirium, and early mobility and exercise) and encouraged to perform the treatment bundle to decrease delirium among the patients in the ICU [11,12]. Throughout the trial, its use and adherence to each component of the bundle was ensured daily among the patients for whom informed consent was obtained.

In a 7 day double-blind, randomised controlled trial, Maneeton B aimed to compare the efficacy and tolerability of quetiapine and haloperidol in controlling delirious behavior. The results showed that low-dose quetiapine and haloperidol may be equally effective and safe in controlling delirium symptoms [13]. Few other studies also concluded that quetiapine lowers delirium symptoms faster than placebo, and is as effective as haloperidol and the atypical antipsychotic amisulpride [14-16]. In contrast, the present study showed no significant differences of quetiapine and haloperidol on delirium duration as compared to placebo. One probable reason for this contrast could be heterogenous uncertain bioavailability of enteral form of drugs. The results showed improved rate of ICU discharge in intervention group but time to freedom from mechanical ventilation, hospital discharge and mean survival rate were comparable among the trial groups.

Current study considered that increased dopamine signalling may play major role in pathogenesis of delirium in critically-ill patients. One possible reason behind no effect of haloperidol or quetiapine on delirium duration could be the heterogenous mechanism of brain dysfunction [17]. Strengths of this study include broad inclusion criteria, delivery of the trial drug or placebo in a double-blinded fashion and use of validated instruments administered by trained personnel.

Limitation(s)

This study included a heterogeneous group of patients who had delirium in the ICU. So, the findings allow for the possibility that some patients like non intubated patients with hyperactive delirium, those with alcohol withdrawal, or those with another delirium phenotype may benefit from antipsychotic treatment. Above all, enteral form of antipsychotic drugs was used that might lead to uncertain bioavailability among critically-ill patients.

CONCLUSION(S)

This double-blind, randomised, placebo-controlled trial found no significant differences in the number of days alive without delirium, mean survival rate, time to freedom from mechanical ventilation, and time to ICU and hospital discharge concluding that there is no evidence that the use of enteral haloperidol or quetiapine will affect the duration of delirium among patients in ICU.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Anaesthesiology, King George's Medical University, Lucknow, Uttar Pradesh, India.
2. Associate Professor, Department of Anaesthesiology, King George's Medical University, Lucknow, Uttar Pradesh, India.
3. Assistant Professor, Department of Anaesthesiology, SRMS IMS, Bareilly, Uttar Pradesh, India.
4. Professor, Department of Anaesthesiology, King George's Medical University, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Vipin Kumar Singh,
Rishita Celebrity Greens, A-1202, Sushant Golf City, Lucknow, Uttar Pradesh, India.
E-mail: vipintheazad@gmail.com

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