Original Research Article

The Comparison of the effect of Olanzapine and Haloperidol and quetiapine on the resolution of individual delirium symptoms in ICU patients: a double-blind, clinical trial study

Abstract

Introduction: Considering that haloperidol is a first-generation antipsychotic drug and is known as the main treatment for delirium, but it causes extrapyramidal side effects and olanzapine and quetiapine are second-generation antipsychotic drug without extrapyramidal side effects. In this study, we compared the effects of olanzapine and quetiapine with haloperidol on the resolution of individual delirium symptoms.

Materials and Methods: In a double-blind clinical trial study, 90 patients admitted to the ICU in three groups received haloperidol at a dose of 2.5 mg/day while in the second group patients received olanzapine at a dose of 10.5-2.5 mg/day. In the third group, they received quetiapine at a dose of 12.5 to 75 mg on a daily basis. Then, patients' sedation levels were measured according to RASS criteria and their disease severity was evaluated according to APACHE II criteria.

Results: During 15 work shifts in the first, second, third, seventh, and tenth days, sedation scores in all three groups decreased significantly (p-v <0.05), and all three drugs were effective in subsiding patients' agitation in 10 days. In the evening and night of the first day, the sedation score in the quetiapine group was higher than the other two groups, however, after the treatment period and in the work shifts of the seventh and tenth days, the patients in the quetiapine group had the lowest sedation score on the RASS scale. Also, after starting drug treatment in the three groups, the mean severity of the disease was significantly different in the three groups (p-v <0.05), so that on the third and seventh day, the olanzapine group had the lowest and the haloperidol group had the highest disease severity. But on the tenth day, the severity of the disease was lowest in the patients in the quetiapine group.

Conclusion: As a result of this study, it was found that quetiapine, olanzapine, and haloperidol had the greatest effect in improving the sedation level of patients with delirium according to RASS criteria, respectively, and the use of atypical antipsychotic drugs had more favorable effects than typical ones in controlling patients' delirium.

Keywords: Quetiapine, Olanzapine, Haloperidol, Delirium

Introduction

Delirium is a relatively common mental disorder that is characterized by a sudden onset of disturbance of consciousness (a marked decrease in environmental awareness and impairment of attention) and a change in cognition (such as memory deficit, disorientation, and language disturbance). The disorder usually makes progress over a short period of time and fluctuates diurnally. In critical patients, many factors can play a role in the prognosis of this condition, including hypoxemia, infection, and systemic inflammation. (1) Delirium frequently occurs in patients with critical conditions and may be followed by negative consequences such as increased ventilating, Hospitalization, and ICU admission time and also associated with an escalate in cognitive impairment after being discharged from the ICU. (2) The risk of delirium depends on complex interactions between predictors and prognostic factors. Because current treatment options for delirium are scarce, some studies suggest that efforts should be made to prevent the onset of the condition. A study on delirium showed that the prevalence of delirium in hospital samples was 19.6% per day. (4) another study found that the prevalence of delirium in patients undergoing heart surgery in the ICU was 23.5% and the patients who developed delirium after these surgeries were significantly older ones (5). In one study, it was observed that the death rate in delirium patients, suffering an active delirium state, increases by 11% every 48 hours (6), which indicates the importance of on-time diagnosis and treatment of this disorder. In preventing methods, both pharmacological and non-pharmacological methods and strategies were successful, but not globally. Various studies have considered both pharmacological and non-pharmacological interventions in advanced delirium states, but none of them have clearly verified the benefits of these methods. (7) Haloperidol is a first-generation antipsychotic drug. The main mechanism of this drug is its antagonistic effect on cortical dopamine receptors and the subsequent increase in acetylcholine. haloperidol reduces the need for sedatives and analgesics especially in patients connected to a ventilator and also has potentially beneficial effects on the immune system. According to the guidelines, haloperidol is the drug of choice and recommended for the treatment of delirium in ICU patients. (8) However, the biggest limitation in the use of this drug is the presence of extrapyramidal symptoms which second-generation antipsychotic drugs can be used as a side choice for them. The role of these drugs in the treatment of delirium has been studied and some positive findings have been reported. (10)

Olanzapine is a second-generation antipsychotic drug with a very low affinity for dopamine receptors but a very high affinity for serotonin receptors. It also has a high affinity for histamine and alpha 1 adrenergic receptors but has a very low one for the M1 muscarinic receptor.

These characteristics, make it effective in treating delirium and also provide sedation without any extrapyramidal side effects. olanzapine is rapidly being absorbed and has a short half-life of 3 to 6 hours,

which makes a fast effect on the body. drowsiness, hypotension, and dizziness are some of its common side effects. It also prolongs QTc in patients on ECG. (11) Quetiapine is a second-generation antipsychotic drug, from benzothiazepines, which is effective in treating schizophrenia, major depression, and the depressive phase of bipolar disorder and mania. This drug, also treats the positive and negative symptoms of psychotic disorders by antagonizing various neurotransmitters in the brain, including receptors for dopamine (D1 and D2), histamine (H1), adrenergic (alpha 1 and alpha 2), and a variety of serotonin 1 and 2 receptors (5HT1A and 5HT2). It has no effect on benzodiazepines and cholinergic muscarinic receptors (12,13). Quetiapine, however, has a very low affinity for dopamine receptors and a very high affinity for serotonin receptors. It also has a high affinity for histamine and alpha 1 adrenergic receptors but has a very low one for the M1 muscarinic receptor. These aspects of quetiapine make it potent in treating delirium and also can help to sedate patients without any extrapyramidal side effects. It is being rapidly absorbed in the body and has a short half-life of 3 to 6 hours, which makes it effective in the body. Common side effects of this drug include drowsiness, hypotension, and dizziness. It also prolongs QT in patients on ECG. This atypical and common antipsychotic drug is used as a monotherapy to treat mania in bipolar disorder. In studies about the effect of quetiapine in the treatment of bipolar disorder, the drug is started at a dose of 100 mg/day and reaches a dose of 600 to 800 mg/day on days 5 to 6. The average effective dose to respond to the treatment is 600 mg/day (12). The Richmond Agitation Sedation Scale (RASS) is an instrument designed to assess the level of alertness and agitated behavior in ICU patients. this is a 10 point scale ranging from -5 to +4. Levels -1 to -5 denote 5 levels of sedation, starting with “awakens to voice” and ending with “unarousable”. Levels +1 to +4 describe increasing levels of agitation. The lowest level of agitation starts with apprehension and anxiety, and peaks at combative and violent. RASS level 0 is “alert and calm”. This standard has been used many times in researches. Most of these scales for measuring delirium are based on DMS criteria. Like DRS-R-98, MDSA, and CAM. The DRS-R-98 is a valid measure of delirium severity over a broad range of symptoms that includes 16 criteria Which would be checked within 24 hours. This scale is useful for repeated measurements during research when delirium is diagnosed and also can detect delirium from dementia, depression, and schizophrenia with a sensitivity of nearly 91%. [14] Haloperidol as a first-generation antipsychotic drug is known as the main treatment for delirium but it causes extrapyramidal side effects while olanzapine and quetiapine as second-generation antipsychotic drugs cause no extrapyramidal side effects. With regard to this, we decided to evaluate the effects of olanzapine, quetiapine, and haloperidol in the treatment of individual delirium symptoms in this study.

If it is proved, based on this study, that olanzapine and quetiapine have similar effects to haloperidol, considering their less extrapyramidal side effects, these drugs could be used as a good alternative to haloperidol in the treatment of this disorder.

materials and methods

this is a double-blind clinical trial study that was performed on patients in a delirious state. and the diagnosis of delirium was based on the criteria set out in the Diagnostic and Statistical Manual of DSM V. the criteria are as follow:

1. Disorders of attention and awareness

2. Delirium typically increases from a few hours to a day over a short period of time (initial awareness changes throughout the day)

3. There are other cognitive impairments such as memory, language, and comprehension impairment

4. The presence of a neurological disorder increases the level of delirium.

5. There must also be some evidence to determine the causes of delirium (for example, physiological causes, toxins, etc.) (15)

After obtaining informed consent, 90 patients admitted to the intensive care unit of selected hospitals were randomly selected by envelope method and divided into three groups. they were in a delirium condition and were being treated during the completion of the research sample. The study was a double-blind clinical trial. As much as possible, the drugs were prepared in one color and one size and prescribed according to the protocols. In the first group, haloperidol (Sobhan Daru Company - Iran) with a dose of 5.2 mg per day and in the second group, olanzapine (Sobhan Daru Company - Iran) with a dose of 10-10.5 mg per day (16) and in the third, quetiapine (Bakhtar Shimi company - Iran) with a 12.5 to 75 mg per day dosage were administrated and were given to patients through the NG tube.

In the envelope method, we selected a number of envelopes as the first group and the same number for the second and third groups. The envelopes were randomly selected and then merged with one card, it was extracted and its allocation was recorded and this process Continued until the sample size was completed. In the end, patients were divided into 3 groups based on the letters on the envelopes. Patients' sedation status was checked in each working shift according to RASS scoring criteria (Richmond Agitation And Sedation Score). (17)

Disease severity was assessed according to APACHE II (Acute Physiology and Chronic Health Evaluation II) criteria.

findings

This study aimed to evaluate the effects of three drugs, olanzapine, haloperidol, and quetiapine on delirium symptoms of 90 ICU patients with a mean age of 59.57 years and 61.1% of the patients were male.

recording the initial vital signs of the patients (including mean systolic blood pressure, heart rate, respiration, body temperature, and oxygen saturation status) at the beginning of the study we found no significant differences. Therefore, it can be concluded that the initial vital signs of patients as an underlying confounding factor in the three groups were almost the same and may have inconsiderable effects on the results of this study.

evaluating the level of consciousness of patients considering the Glasgow Coma Scale, we found that the average GCS of the patients in the range of 3 to 15 was 11.58 and the level of consciousness of patients in the three groups was statistically significant. The level of consciousness of patients of all three groups, at the beginning of the study, was almost the same and the possible effects of this variable on the final results could be almost negligible. the sedation status of study patients was evaluated based on RASS criteria and was almost the same in all three groups.

Assessing the severity of the disease showed the same results in all three groups. Therefore, it can be concluded that all patients in the three groups were almost identical in terms of sedation status and disease severity.

The results demonstrate that in terms of sedation, all patients in three study groups were initially in the state of agitation and checking during the 15 (8 hours) work shifts on the first, second, third, seventh, and tenth day the sedation score decreased significantly in all groups and all three administrated drugs were effective in improving patients' agitation in 10 days. during the evening and night of the first study day, the sedation score in the quetiapine group was higher than the other two groups, however, after the treatment period and in the work shifts of the seventh and tenth days, the patients in the quetiapine group had the lowest sedation score ~~on~~ according to the RASS scale. Also, on the last day of treatment (day 10), the sedation rate of patients in the olanzapine group was less than the haloperidol group (Figure 1). Therefore, it can be concluded that after 10 days, quetiapine and olanzapine, and haloperidol, respectively had the greatest effect on the resolution of the patients' sedation. as in the results, changes in the level of the disease severity were also investigated and it had a decreasing trend in all three groups studied in the first, third, seventh, and tenth days. Also, after starting drugs as a treatment in study cases, the mean disease severity in the three groups was significantly different, so that on the third and seventh day, the olanzapine group had the lowest and the haloperidol group had the highest disease severity. However, on the tenth day, the severity of the disease was lowest in patients in the quetiapine group (Figure 2). Therefore, it can be concluded that treatment of delirium with all three drugs haloperidol, olanzapine, and quetiapine was effective in reducing the severity of the disease over a period of ten days. Olanzapine also had a faster effect on the treatment of the severity of the disease, but quetiapine had the greatest effect on the severity of the disease. However, various factors could have been intervening with the mechanism of action of the above drugs which can therefore affect the severity of the disease over ten days and the improvement of the severity of the disease can not be attributed exclusively to the treatment of delirium with the administration of above drugs.

Discussion

In the study of Grover et al., There was no significant difference in the response rate of the two groups treated with quetiapine and haloperidol. In this study, the researchers concluded that quetiapine, like haloperidol, could have an effective role in controlling the patient's symptoms. (18)

Lee YJ and Benchalak Maneeton obtained similar results to the above in two separate studies and concluded that the effects of haloperidol and quetiapine on the treatment of delirium were the same (19, 20)in Our study on the other hand, not only quetiapine aren't as effective as haloperidol in treating delirium but even within 10 days investigation, quetiapine has been shown more effective.

Kiberd et al. also demonstrated the equal effect of olanzapine and haloperidol in treating delirium. [16] (21, 22) As is clear the results of the above studies, could be a good conformation of ours; In our study, olanzapine was as effective as haloperidol in treating delirium, but unlike our previous studies, olanzapine was even more effective than haloperidol on patient's sedation and the disease severity.

Conclusion

As a result of this study, quetiapine, olanzapine, and haloperidol had the greatest effect on improving the sedation in patients with delirium according to RASS criteria, and the use of atypical antipsychotic drugs had more favorable effects on patients' delirium than the typical ones.

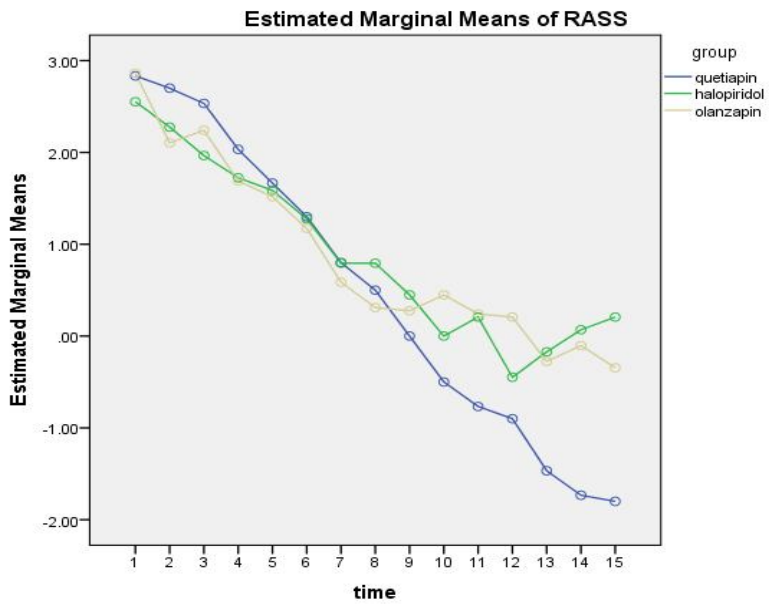

Figure number 1

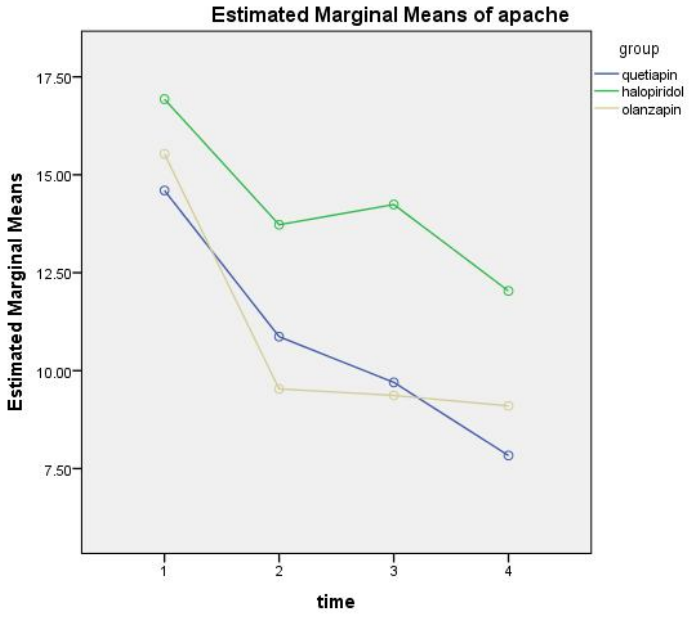

Figure number 2

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Comparison of the effect of Olanzapine and Haloperidol and quetiapine on the Treatment of delirium in Intensive care unit (ICU) patients

has been approved in Iranian Registry of Clinical Trials at 2020-10-13.

Your registration reference is IRCT20200927048852N1.

Best Regards

Iranian Registry of Clinical Trials (IRCT)

Evaluated by: ARAK UNIVERSITY OF MEDICAL SCIENCES

Approval Date:2020-10-13

Approval statement: The project was found to be in accordance with the ethical principles and the national norms and standards for conducting Medical Research in Iran.

Data Availability

All relevant data are within the manuscript and its Supporting Information files.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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