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Review Article

COMPARISON OF THE EFFECT OF QUETIAPINE WITH HALOPERIDOL IN TREATMENT OF DELIRIUM IN ICU PATIENTS

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Abstract

Introduction: Delirium is a relatively common disorder in ill patients. Haloperidol, a first-generation antipsychotic, is known to be the main treatment, but it has extrapyramidal side effects, whereas quetiapine is a second-generation antipsychotic and lacks these effects. In a recent study, we compared the effects of quetiapine with haloperidol in the treatment of delirium symptoms.

Materials and methods: This study was a clinical trial performed on patients with delirium. Patients were randomly divided into two groups, one group receiving haloperidol 2.5 mg daily and the other group receiving 25 mg daily quetiapine. Sedation status of patients was determined based on RASS scoring criteria and disease severity according to APACHE II criteria and finally data were analyzed by SPSS 20 software.

Results: The mean age of patients in quetiapine and haloperidol group was 59.83 with standard deviation of 16.51 and 64.90 with standard deviation of 21.34 years (p-value = 0.308). The ratio of male to female in the quetiapine and haloperidol group was 19 to 11 and 21 to 9, respectively (p-value = 0.392). Patients in quetiapine group had significantly better RASS and disease severity than patients in haloperidol group (p-value = 0.001).

Conclusion: According to the results, it is concluded that the use of quetiapine can not only be effective in improving sedation status and severity of disease in patients with delirium, but also better than haloperidol.

Keywords: Haloperidol, Quetiapine, Delirium.

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INTRODUCTION

Delirium is a common complication in patients with critical conditions characterized by the sudden onset of consciousness disorders (a clear decline in environmental awareness, inability to notice) and cognitive changes (memory impairment and other cognitive impairments). The disorder usually progresses in a short time and fluctuates over a day. In critical patients, many factors can contribute to the prognosis of this condition, including hypoxemia, infection and systemic inflammation (1). Delirium occurs frequently in critically ill patients and is associated with adverse outcomes such as increased ventilator time, increased hospitalization and ICU time, and increased cognitive impairments after discharge from ICU ward (2). The risk of delirium depends on the complex interactions between the prognostic factors. Because current therapeutic options for delirium are scarce, some studies suggest that efforts should be made to prevent this condition (3). The study on delirium showed that the prevalence of delirium per day in complete hospital samples was 19.6% with wide variation in packages between hospital wards (4). One study found that the prevalence of delirium in patients undergoing cardiac surgery was 23.5% in the ICU ward. It was also found that patients who had delirium after these operations were significantly older. One study found that the death rate in delirium patients increased by 11% every 48 hours with active delirium (5), indicating the importance of timely diagnosis and treatment. Pharmacological method and strategies as well as non-pharmacological strategies have accepted, but none have been globally successful. Various studies have investigated both pharmacological and non-pharmacological interventions in advanced delirium, but none of the studies have demonstrated the benefit of these methods (6). Haloperidol is a first-generation antipsychotic drug. The main mechanism of this drug is the antagonistic effect of cortical dopamine receptors and its degradation by acetylcholine. The use of haloperidol reduces the need for sedatives and analgesics in ventilator-assisted patients as well as potentially beneficial effects on the immune system. According to the guidelines, haloperidol is the drug of choice for the treatment of delirium in ICU patients (7). However, the major limitation for the use of this drug for patients is the presence of extrapyramidal symptoms, which is why other second-generation antipsychotic drugs can be used to treat these patients as an adjunct (8). There have been recent studies on the use of these drugs in the treatment of delirium, and some have found positive results (9). Quetiapine is a second-generation antipsychotic drug with very low affinity with dopamine receptors and very high affinity with serotonin receptors. It also has a high affinity for histamine and alpha-1 adrenergic, but has a low affinity for muscarinic M1 receptors. These properties of quetiapine make it effective in the treatment of delirium and also cause sedation without extrapyramidal side effects. It is absorbed quickly and has a short half-life of 3 to 6 hours, which makes it effective in the body. Common side effects of the drug include drowsiness, hypotension and dizziness. It also prolongs QTc in patients (10). Since no study has compared the two drugs so far, haloperidol is a first-generation antipsychotic drug and is known to be the main treatment, but it may have extrapyramidal side effects. Quetiapine is a second-generation antipsychotic drug it lacks these effects. In a recent study, we compared the effects of quetiapine with haloperidol in the treatment of delirium symptoms.

MATERIAL & METHODS

This prospective clinical trial study was performed on patients with delirium in the ICU ward of Valiasr Hospital in Arak. In this

study, the diagnosis of delirium was based on criteria described in Diagnostic and Statistical Manual 5 (DSM V). Inclusion criteria included all patients who were diagnosed with DSM V criteria for delirium who were over 18 years of age and exclusion criteria included all patients who were younger than 18 years of age or who requested to be excluded. Patients in the delirium condition were randomly divided into two groups using blocking method, in one group patients received 2.5 mg daily haloperidol, In the other group, patients received 25 mg quetiapine twice daily. Patients' sedation status was evaluated according to RASS scoring criteria at each shift and severity of disease was measured according to APACHE II criteria after 1, 3, 7 and 10 days and finally the results were compared between the two groups. Data were analyzed by SPSS software version 16 and chi-score and t-test were used for statistical analysis.

RESULTS

This recent study aimed at comparing the effect of quetiapine with haloperidol in the treatment of delirium in ICU patients in Valiasr Hospital, Arak, on 60 patients with delirium were divided into two groups of 30 each treated with haloperidol and quetiapine.

The results of the current study showed that the mean age of these patients was 62.36 years with a standard deviation of 19.09 years. Statistical studies aimed at comparing the mean age of the patients in the haloperidol and quetiapine intervention groups showed that these patients had no significant difference at the significant level of 0.05 with each other and these patients were similar in age. The mean age of patients in the quetiapine and haloperidol groups was 59.83 with a standard deviation of 16.51 years and 64.90 with a standard deviation of 21.34 years (p-value=0.308). The results of this study also evaluated the gender distribution of patients and it was found that the patients in the haloperidol and quetiapine groups did not have any significant difference in terms of gender distribution and out of 60 patients 40 patients equaled 66.7% of them were male and 20 patients equaled 33.3% were female. The ratio of male to female in the quetiapine and haloperidol group was 19 to 11 and 21 to 9, respectively (p-value = 0.392). Patients' vital signs including mean arterial hypertension, heart rate per minute, respiratory rate per minute, body temperature and oxygen saturation status at the beginning of the study also showed that the patients in the haloperidol and quetiapine groups were not significantly different (P> 0.05). The results of this study showed that patients' sedation status based on RASS scoring criteria and severity of disease based on APACHE II criteria at baseline were not significantly different between the haloperidol and quetiapine groups (P> 0.05). In this study, sedation status of patients in two groups based on RASS scoring criteria in 15 different shifts including first day's morning shift, first day's evening shift, first day's night shift, second day's morning shift, second day's evening shift, second day's night shift, third day's morning shift, third day's evening shift, third day's night shift, seventh day's morning shift, seventh day's evening shift, seventh day's night shift, tenth day's morning shift, tenth day's evening shift and tenth day's night shift was evaluated.

The statistical results of these evaluations showed that the group of patients receiving quetiapine had significantly better sedation status than the group of patients receiving haloperidol.

Table 1: Changes in sedation status of patients in different work shifts in two groups

P-value	Haloperidol Mean ± SD	Quetiapine Mean ± SD	Shift
0.096	0.82±2.50	0.96±2.83	first day's morning
0.048	0.69±2.26	0.95±2.70	first day's evening
0.005	0.86±1.93	0.73±2.53	first day's night
0.083	0.80±1.66	0.82±2.03	second day's morning
0.527	0.97±1.53	0.60±1.66	second day's evening
0.847	0.86±1.26	0.74±1.30	second day's night
0.811	1.28±0.73	0.80±0.80	third day's morning
0.321	0.94±0.73	50.0.86±	third day's evening
0.124	1.13±0.40	0.83±0	third day's night
0.061	0.97±0	-0.97±0.50	seventh day's morning
0.001	1.21±0.20	-0.89±0.76	seventh day's evening
0.038	-0.89±0.43	-0.80±0.90	seventh day's night
0.000	-1.00±0.17	-1.07±1.46	tenth day's morning
0.000	1.03±0.06	-1.43±1.73	tenth day's evening
0.000	0.97±0.20	-1.15±1.80	tenth day's night
	0.001*		**p-value***

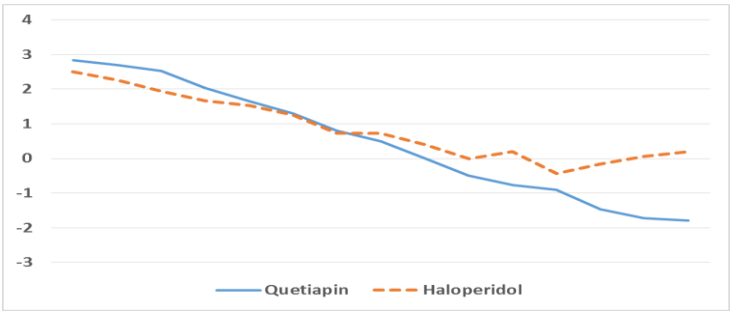

Diagram 1: Changes in sedation of patients in different work shifts in two groups

A comparative study of the severity of disease according to APACHE II criteria in the first, third, seventh and tenth days in patients receiving quetiapine and haloperidol it was observed that 10 days after starting the study, patients in the intervention group with quetiapine had a significantly lower severity of disease than patients receiving haloperidol. In fact, patients in the quetiapine group showed a greater improvement .

Table 2: Changes in disease severity according to APACHE II criteria in patients in two groups

P-value	Haloperidol Mean ± SD	Quetiapine Mean ± SD	Days
0.055	4.83±16.96	4.51±14.60	**First day**
0.042	5.50±13.86	5.69±10.86	**Third day**
0.007	7.15±14.20	5.21±9.70	**Seventh day**
0.002	5.81±12.03	4.28±7.83	**Tenth day**
	0.001*		**p-value***

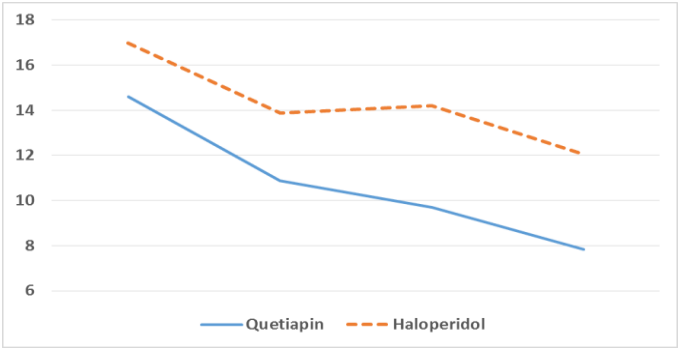

Diagram 2: Disease severity changes according to APACHE II criteria in patients in two groups

It should also be noted that the patients in the two groups of haloperidol and quetiapine patients were evaluated for the side effects of these drugs and no significant side effects were observed in these patients.

DISCUSSION

Delirium is a worrying issue in public hospitals. Depending on the patient population and the tools for measuring the prevalence of the disorder, it is reported to be between 10 to 42% (11). This clinical situation is associated with increased morbidity (14 to 25.9%), increased hospitalization, and increased mortality (12). Delirium behaviors (including agitation, hallucinations, delusions, and disturbances in the sleep and wake cycle) can cause major problems in managing and treating patients' condition and usually require medication (13). Several studies have suggested that delirium may caused by

various abnormalities in different neurotransmitters. Some of these neurotransmitters that cause this condition include dysregulation of dopamine and serotonin (14). Along with special treatments to treat the underlying disorder causing delirium, antipsychotic medications are commonly used to control the symptoms of delirium. Due to its short half-life, low anticholinergic effects and low sedation caused by haloperidol, this drug is used as the treatment of choice for delirium treatment (15).

However, the major limitation of this drug is its extrapyramidal side effects. In addition, few clinical trials have been conducted to compare the efficacy of different drugs to improve delirium symptoms. However, there are also atypical antipsychotic medications, some of which have minor extrapyramidal effects that can be used as surrogates (16). Quetiapine is an atypical antipsychotic drug that is highly effective in treating diseases such as schizophrenia, bipolar disorder, and major depressive disorder. Recent studies have shown that this drug has good efficacy to improving the symptoms and behavioral disorders of delirium and has been shown to be significantly safe (17). Although studies have supported the desirable effect of quetiapine to relieve delirium symptoms, many aspects of this treatment are still hidden and there is a need for more extensive studies. In the light of the aforementioned, in the present study, we decided to study the effect of haloperidol 2.5 mg daily with the effect of quetiapine 25 mg twice daily on the sedation status of patients. The basis of the RASS scoring criterion in different work shifts (including first day's morning shift, first day's evening shift, first day's night shift, second day's morning shift, second day's evening shift, second day's night shift, third day's morning shift, third day's evening shift, third day's night shift, seventh day's morning shift, seventh day's evening shift, seventh day's night shift, tenth day's morning shift, tenth day's evening shift and tenth day's night shift) and compare the severity of the disease according to APACHE II criteria at different treatment days (including day 1, day 3, day 7 and day 10) was evaluated. In this study we compared 60 patients with delirium in two groups of 30 each. These patients were randomly divided into two groups and underwent intervention. Based on the results of the current study, it was observed that patients in the two groups received haloperidol and quetiapine in terms of mean age, frequency of sex distribution, primary vital signs including mean arterial blood pressure, mean heart rate per minute, mean respiratory rate per minute, mean temperature and mean oxygen saturation were not statistically significant at the significant level of 0.05 and these patients were almost identical and these factors were not the confounding factors of the final results. The results of this study also showed that sedation status of patients according to RAAS criteria and severity of disease according to APACHE II criteria were similar in both groups at baseline. Based on these results, it was estimated that these patients had similar sedation status and disease severity at baseline. In the present study, it was observed that changes in sedation status of patients according to RAAS criteria during the study period were significantly lower in patients in quetiapine treated group than RAAS score of 2.83 reached -1.80 (average change is 4.63) and in patients treated with haloperidol, this score fell from a mean score of 2.50 to a score of 0.20 (mean change 2.3)

It was also observed in the evaluations of this study that the status of disease severity changes according to APACHE II criteria was significantly better in patients receiving quetiapine compared to those receiving haloperidol. The severity of disease according to APACHE II criteria in the Quetiapine group decreased from 14.60 to 7.83 (mean change 6.77) and in haloperidol group from 16.96 to 12.03 mean (mean change 4.93).

In a study by Devlin et al., Patients who received quetiapine were less likely to have delirium and had less agitation (18). It can be seen that the results of the study by Devlin and his colleagues are almost in line with the results of the recent study. In a study by Maneeton et al., They found that haloperidol and quetiapine had no significant difference in the delirium recovery process of patients with each other and their effect was equal (19). It is found that the results of the study by Maneeton and colleagues are not in agreement with the results of the present study, since the results of our study showed that quetiapine had more beneficial effects than haloperidol. In a study by Grover and colleagues, they found that there was no significant difference in response to treatment with delirium between haloperidol and quetiapine and that quetiapine, like haloperidol, could be effective in controlling the patient (8). A study by Lee et al., Also yielded similar results, stating that the potency of both haloperidol and quetiapine was similar (20). In a study by Hawkins and colleagues, it was found that quetiapine use decreased the duration of symptoms compared to placebo but was approximately equal to haloperidol (21). A similar finding was obtained by Ozbolt and colleagues, although our results showed that quetiapine not only had beneficial effects on delirium recovery but also had more favorable effects than haloperidol (22). In a study by Burry and colleagues in delirium patients admitted to non-ICU wards, they found that antipsychotic drugs had no significant effect on delirium severity, symptom relief, and mortality (23). It can be seen that the results of the study by Burry and his colleagues are in general contradictory to the results of our study. In a study by Mangan and colleagues aimed at evaluating the safety of quetiapine in delirium patients, they found that the drug generally had very few adverse effects (24). The results of our study also showed that none of the patients had any side effects. In a study by Yoon and colleagues it was found that the safety of haloperidol was similar in treatment with delirium compared to atypical antipsychotic drugs including risperidone, olanzapine and quetiapine (25). A recent study also found that the safety of haloperidol was similar to quetiapine.

CONCLUSION

Based on the results of the current study, it is concluded that the use of quetiapine antipsychotic drug can not only be effective in improving the sedation status of patients with delirium as measured by RAAS criteria in this study, but also It even works better than the drug of choice for the treatment of delirium, haloperidol. It was also found that the severity of the disease, as measured by the APACHE II criteria in this study, was better than that of haloperidol in patients taking quetiapine. The results also showed no significant adverse effects in delirium patients admitted to ICU.

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