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Changes in Delirium Rating Scale Scores Among ICU Patients with Delirium Receiving Haloperidol Versus Quetiapine: A Seven-Day Prospective Study

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Abstract

Background: Acute delirium is common in intensive care units (ICUs) and requires prompt intervention. Although haloperidol has been the first-line treatment, atypical antipsychotics such as quetiapine are increasingly considered due to potentially fewer side effects.

Objectives: This study compared the efficacy and safety of quetiapine versus haloperidol for managing acute delirium in the ICU.

Methods: This prospective cohort study enrolled patients with acute delirium in the ICU of Ghaem Hospital who had no contraindications to either drug. Patients were assigned to haloperidol or quetiapine based on standard care. Demographic data were recorded. Delirium severity was assessed daily for seven days using the Delirium Rating Scale-Revised-98 (DRS-R-98), and side effects were monitored. Data were analyzed using SPSS version 20.

Results: A total of 76 patients were studied. The mean DRS-R-98 score on day 7 was significantly lower in the quetiapine group (26.58 ± 7.83) than in the haloperidol group (33.97 ± 6.36) ($p < 0.001$). The reduction in DRS score from baseline to day 7 was greater with quetiapine (−12.95 vs. −8.16, $p < 0.001$). Extrapyramidal side effects occurred exclusively in the haloperidol group. Hypersomnia was equally prevalent in both groups (36.8%). Delirium duration and other non-extrapyramidal side effects did not differ significantly between groups.

Conclusion: Quetiapine was associated with a greater reduction in delirium severity and a more favorable extrapyramidal safety profile compared to haloperidol in this cohort. However, due to the non-randomized design and baseline imbalances, these findings should be considered hypothesis-generating. Large-scale, randomized studies are needed to definitively establish quetiapine's efficacy in ICU delirium.

Keywords: Haloperidol, Quetiapine, Delirium, ICU

1. Introduction

Delirium is characterized by acute and fluctuating disturbances in attention and awareness, presenting a significant clinical challenge, especially in critical care settings. Its clinical manifestations are diverse and include memory deficits, altered levels of consciousness, hallucinations, lethargy, and psychomotor disturbances (1). The etiology of delirium is multifactorial, with risk factors including depression, dementia, substance abuse, and advanced age (2). Although delirium can occur at any age, older adults with pre-existing cognitive impairment, cerebrovascular disease, or a history of head trauma are particularly vulnerable (2, 3). A particularly distressing subtype is hyperactive delirium, in which patients exhibit agitation, aggression, and restlessness, posing substantial risks to both themselves and healthcare staff (4, 5).

The management of acutely agitated patients is a common and significant concern in emergency departments and ICUs. Statistics indicate that violent and agitated behaviors account for approximately 2.6% of emergency encounters, often impeding timely and appropriate medical care (6, 7). Thus, safe and effective management of agitation is a major priority for clinicians (8, 9). While verbal de-escalation is the recommended first-line intervention, pharmacological management becomes necessary when these techniques fail, offering a safer and more humane alternative to physical restraints (10, 11). Sedatives are crucial for rapidly reducing irritability, facilitating patient assessment, and preventing harm (8, 12, 13). In severe, untreated cases, agitation may progress to metabolic derangements, cardiac arrest, or death (14).

Historically, pharmacological options for agitation have relied heavily on benzodiazepines and first-generation antipsychotics, both of which carry significant side-effect burdens (8, 15, 16). Various regimens have been employed, including benzodiazepines (e.g., midazolam, lorazepam), first-generation antipsychotics (e.g., haloperidol, droperidol), second-generation antipsychotics (e.g., olanzapine, quetiapine), and their combinations (8, 17-20). Haloperidol has long been the cornerstone for managing delirium-related agitation (21). However, its use is associated with extrapyramidal symptoms (EPS), QTc prolongation, and cardiac arrhythmias. Benzodiazepines, while effective for sedation, increase the risk of respiratory depression, hypoxia, and may paradoxically worsen confusion (8, 15).

Quetiapine is commonly used in ICUs for delirium management (22). Its pharmacokinetic profile is favorable for acute settings: it is rapidly absorbed, reaching peak plasma concentrations within one hour, with an initial half-life of approximately seven hours. It is metabolized primarily by hepatic CYP3A4, so its efficacy and optimal dosing depend significantly on liver function (23). Its pharmacodynamic action is dose-dependent. At lower doses, quetiapine acts primarily as a sedative by blocking histamine H1 and muscarinic receptors, aiding sleep and reducing anxiety with minimal risk of worsening delirium (24). It also partially agonizes 5-HT1A receptors, further enhancing its calming effect. At higher doses, its stronger impact on dopamine D2 and serotonin 5-HT2A receptors positions it alongside other atypical antipsychotics, making it effective for more severe agitation and delirium (25).

The adverse effect profile of first-generation agents has driven evaluation of second-generation antipsychotics for delirium. Among them, quetiapine has garnered attention due to its low propensity for EPS and pronounced sedative effect (26). Several studies suggest that quetiapine is effective in resolving delirium, showing superiority over placebo (27, 28) and comparable efficacy to haloperidol (26) and amisulpride (29). Data indicate that quetiapine is associated with faster delirium resolution and better agitation control in the ICU compared to placebo (27). However, severe agitation and hyperactivity may take longer to manage than other symptoms such as mood disturbances and inattention (30).

Despite these promising findings, evidence supporting quetiapine remains limited. The total number of patients treated with quetiapine for delirium across all published studies is fewer than 200, and no single trial has enrolled more than 25 patients in the quetiapine group (21, 26, 27, 30). This lack of robust data is reflected in conflicting international guidelines. For instance, American guidelines caution against using haloperidol for delirium prevention, whereas the European Society of Anaesthesiology endorses its use (31, 32). This discrepancy underscores the absence of a clear, evidence-based clinical algorithm for managing patients with delirium in the ICU (33).

Therefore, further clinical evidence is needed to directly compare the efficacy and safety of haloperidol and quetiapine for delirium in critically ill patients. This study was conducted to explore changes in delirium rating scale scores among ICU patients with delirium receiving haloperidol or quetiapine over a seven-day follow-up, and to compare delirium duration and side-effect profiles between the two treatment groups.

2. Methods

2.1. Study Design and Participants

This prospective cohort study was conducted in 2025 in the ICUs of Ghaem Hospital, Mashhad. The study population consisted of adult patients (≥18 years) hospitalized with a diagnosis of acute delirium and agitation requiring pharmacological intervention as determined by the treating physician.

Inclusion criteria: definitive diagnosis of acute delirium, age ≥18 years, and presence of agitation requiring pharmacological intervention.

Exclusion criteria: pregnancy or lactation, history of major psychiatric disorders, concurrent use of specific interfering medications (e.g., fentanyl or benzodiazepines), poorly controlled diabetes, history of dangerous cardiac arrhythmias (e.g., Torsades de Pointes), history of neuroleptic malignant syndrome, or known hypersensitivity to haloperidol or quetiapine.

Eligible patients were assigned to either the haloperidol or quetiapine group based on the treating physician's clinical decision (non-randomized) and followed for seven days. Although randomized controlled trials (RCTs) are the gold standard for interventional studies, a prospective cohort design was used for ethical and clinical reasons: both drugs are part of standard treatment protocols for acute delirium in the ICU, and the treating physician selected the drug based on individual patient characteristics (e.g., side-effect profile, comorbidities, drug interactions). Random allocation would have precluded individualized treatment, making it ethically challenging. This "usual care" approach reflects real-world clinical practice and enhances ecological validity.

2.2. Sampling Method and Sample Size

Consecutive sampling was used. Sample size was calculated based on Yoon et al. (34) using PASS software version 15 (two independent groups, unequal variances). Assuming mean changes in DRS-R-98 score of 9.7 (SD 1.3) for haloperidol and 11.0 (SD 2.4) for quetiapine, with $\alpha = 0.05$ and power = 80%, the required sample size was 36 patients per group. Accounting for a 5% dropout rate, 38 patients per group (76 total) were enrolled.

2.3. Procedure

After ethical approval and informed consent, eligible consecutively admitted ICU patients were assigned to the haloperidol or quetiapine group per physician decision. A researcher-designed questionnaire recorded demographic information (age, sex), reason for admission, drug type and dosage, and adverse effects (hypoxia, hemodynamic changes, nausea/vomiting, need for intubation, extrapyramidal symptoms). Delirium severity was assessed daily for seven days using the DRS-R-98.

2.4. Data Collection Tools

Two primary tools were used: (1) a researcher-designed questionnaire for demographics, clinical parameters, and adverse effects; (2) the DRS-R-98, a standardized 16-item scale. The first 13 items constitute the severity score (range 0–39), measuring key symptoms from cognitive deficits to psychotic features. Three additional items aid differential diagnosis. The severity score (first 13 items) served as the primary efficacy indicator.

2.5. Data Analysis

Data were analyzed using SPSS version 20. Descriptive statistics (mean, SD, frequency) were calculated. Independent t-test was used for between-group comparisons of quantitative variables, and chi-square test for qualitative variables. Repeated measures ANOVA was used to compare DRS-R-98 score trends over time between groups. A significance level of $p < 0.05$ was considered statistically significant.

3. Result

A total of 76 ICU patients with delirium were included (38 haloperidol, 38 quetiapine). Haloperidol dose range: 5–30 mg/day; quetiapine dose range: 25–50 mg/day.

3.1. Baseline Demographic and Clinical Characteristics

Age and day-7 DRS scores were normally distributed (Kolmogorov–Smirnov). Day-1 DRS and delirium duration were non-normally distributed in at least one group. As shown in Table 1, the two groups were comparable in sex distribution, mean age, and prevalence of comorbidities (diabetes mellitus, hypertension, ischemic heart disease) ($p > 0.05$ for all). No seizure or psychotic disorders were observed.

Table 1. Baseline characteristics of patients receiving haloperidol or quetiapine

Variable	Category	Haloperidol n (%)	Quetiapine n (%)	p-value
Gender	Female	18 (47.4)	21 (55.3)	0.647
	Male	20 (52.6)	17 (44.7)	
Age (years)	Mean ± SD	78.45 ± 6.16	76.42 ± 6.42	0.165
Comorbidities	Diabetes mellitus	10 (26.3)	17 (44.7)	0.150
	Hypertension	8 (21.1)	16 (42.1)	0.083
	Ischemic heart disease	6 (15.8)	11 (28.9)	0.271
	Seizure	0 (0)	0 (0)	—
	Psychiatric disorder	0 (0)	0 (0)	—

3.2. Changes in Delirium Rating Scale (DRS-R-98) Scores

As shown in Figure 1 and Table 2, mean DRS score decreased from 42.13 ± 6.75 (day 1) to 33.97 ± 6.36 (day 7) in the haloperidol group, and from 39.53 ± 6.77 to 26.58 ± 7.83 in the quetiapine group. Despite baseline imbalance, after ANCOVA adjustment for baseline DRS, the group difference remained significant ($p < 0.001$, adjusted mean difference = 5.35, Table 3). However, given the non-randomized design, residual confounding cannot be excluded.

The observed mean difference (4.79 points) was larger than the 1.3-point difference assumed from Yoon et al. for sample size calculation. Post hoc power for the observed difference was approximately 94% (independent t-test, $\alpha = 0.05$).

Table 2. Comparison of DRS-R-98 scores between haloperidol and quetiapine groups

Variable	Time	Haloperidol (Mean ± SD)	Quetiapine (Mean ± SD)	95 % Confidence Interval	p-value
DRS score	Day 1	42.13 ± 6.75	39.53 ± 6.77	(-0.48, 5.69)	0.097
	Day 7	33.97 ± 6.36	26.58 ± 7.83	(4.13, 10.65)	<0.001
Difference		-8.16 ± 3.29	-12.95 ± 6.25	(2.49, 7.08)	<0.001

At baseline, there was no statistically significant difference between the two groups (p=0.097, d=0.38). However, on day 7, a significant difference was observed between the groups, with a large effect size (p<0.001, d=1.04). Moreover, the change from day 7 to day 1 differed significantly between the groups, indicating a greater reduction in group 2 (p<0.001, d=0.96)

Table 3. ANCOVA Results for DRS Scores on Day 7 Adjusted for Baseline DRS

Variables	Parameter	95 % Confidence Interval	p-value	Effect size
DRS Score Day 1	0.78	(0.62, 0.95)	<0.001	0.55
Group, Haloperidol	5.35	(3.11, 7.59)	<0.001	0.24

ANCOVA showed that baseline scores (Day 1) were a significant predictor of Day 7 scores indicating a moderate-to-large association between initial and final scores. After adjusting for baseline, there was a statistically significant difference between the groups on Day 7. Group Quetiapine performed better than Group Haloperidol, because Group 1 had higher adjusted Day 7 scores. Although this between-group difference was statistically significant, the effect size was small, suggesting that the magnitude of the difference was limited from a practical/clinical perspective.

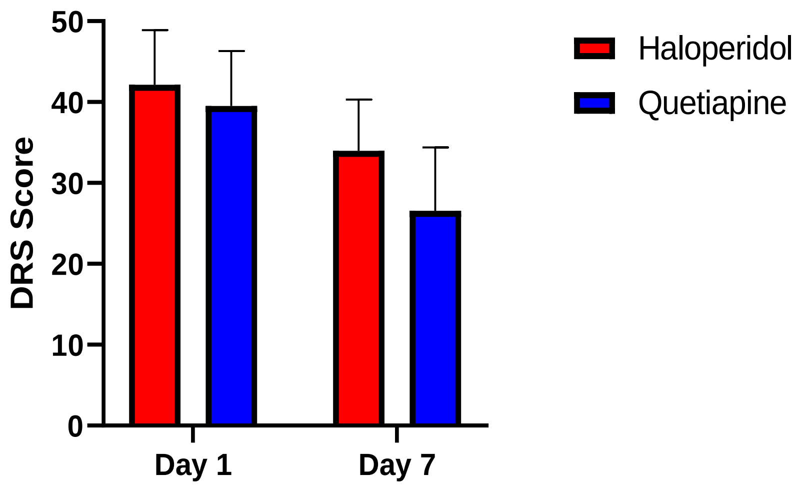

Figure 1: Mean DRS scores on day 1 and day 7 in haloperidol and quetiapine groups.

3.3. Duration of Delirium

Mean delirium duration was 4.34 ± 1.10 days in the haloperidol group and 4.11 ± 1.50 days in the quetiapine group (p = 0.216, Figure 2).

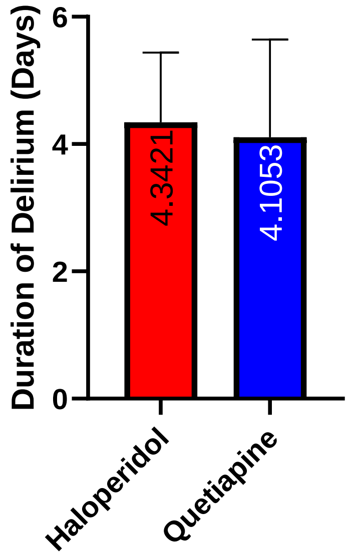

Figure 2: Mean duration of delirium (days) in the haloperidol and quetiapine groups.

3.4. Adverse Drug Reactions

Hypotension and hypersomnia were the most common side effects, with no significant between-group differences. Akathisia occurred in 39.5% of haloperidol-treated patients and none in the quetiapine group ($p < 0.001$, Fisher's exact test). Other adverse events (dystonia, rigidity, tremor, bradycardia) were infrequent and comparable between groups ($p > 0.05$, Table 4).

Table 4. Comparison of adverse drug reactions between haloperidol and quetiapine groups

Adverse Effect	Haloperidol n (%)	Quetiapine n (%)	p-value
Hypotension	1 (2.6)	4 (10.5)	0.358
Hypersomnia	14 (36.8)	14 (36.8)	>0.99
Dystonia	4 (10.5)	0 (0)	0.115
Rigidity	2 (5.3)	0 (0)	0.493
Bradycardia	1 (2.6)	5 (13.2)	0.200
Tremor	3 (7.9)	0 (0)	0.240
Akathisia	15 (39.5)	0 (0)	<0.001

4. Discussion

The primary finding of this cohort study was that both quetiapine and haloperidol were associated with reductions in delirium severity; however, quetiapine showed a greater reduction in DRS scores by day 7. This adds to the growing body of evidence supporting quetiapine's potential role in delirium management (28, 35). The quetiapine doses used in our study were consistent with mean doses reported previously (final dose range 42.2–93.7 mg/day) (28, 36, 37).

Our findings differ from several prior reports. Maneeton et al. reported equivalent efficacy between haloperidol and quetiapine

(38), and Grover et al. as well as Zakhary et al. found no significant difference between the two agents (39, 40). These discrepancies may reflect differences in patient populations, delirium etiology, assessment instruments, or dosing regimens.

In our study, overall delirium duration was similar between groups (4.34 ± 1.1 vs. 4.11 ± 1.5 days; p = 0.216), consistent with Maneeton et al. (38). Thus, although quetiapine was associated with a greater reduction in DRS scores, it did not shorten the total duration of delirium. Because this was a non-randomized study, these findings should be interpreted cautiously and considered hypothesis-generating rather than definitive.

Adverse events were a critical component of our analysis. No extrapyramidal symptoms (akathisia, tremor, rigidity, dystonia) were observed in the quetiapine group, consistent with quetiapine's receptor binding profile (strong 5-HT2A antagonism, weak D2 antagonism) (41). Although hypotension and bradycardia were slightly more frequent in the quetiapine group, these differences were not statistically significant (Table 4), but they remain clinically relevant and warrant monitoring.

The incidence of hypersomnia was similar between groups, in line with Maneeton et al. (38). This is notable given quetiapine's known sedative properties; the comparable rate in the haloperidol group may reflect haloperidol's sedative effects or hypersomnia as part of the delirious state itself.

Overall, quetiapine was well tolerated in our study, consistent with prior reports (36, 42). However, the mortality benefit of antipsychotics in delirium remains uncertain and continues to be a major concern in updated clinical guidelines (43).

Limitation: This study has limitations as follow:1. Non-randomized design that may introducing potential selection bias and confounding by indication.2. Lack of blinding (outcome assessors were not blinded to treatment), which may have introduced detection bias.3. Baseline imbalance (despite statistical adjustment), that may cause to residual confounding cannot be ruled out.4. Low quetiapine doses (dose escalation was limited by adverse effects (hypotension)) in this elderly population, limiting generalizability.5. Single center design that caused to the findings may not be generalizable to other ICUs with different patient populations or protocols.

5. *Conclusion*

In this prospective cohort study of ICU patients with delirium, quetiapine was associated with a greater reduction in DRS-R-98 scores over seven days and a more favorable extrapyramidal safety profile compared to haloperidol. Delirium duration and most other adverse effects did not differ significantly between groups.

However, due to the non-randomized design, baseline imbalances, lack of blinding, and other methodological limitations, these findings do not support a claim of superiority. They should be considered hypothesis-generating. A large, double-blind, randomized controlled trial with standardized dosing and blinded outcome assessment is required to determine whether quetiapine offers any advantage over haloperidol for the management of acute delirium in the ICU.

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Conflicts of interests: The authors declared no conflict of interest.

Ethical Considerations: This study was conducted after obtaining an ethical code (IR.MUMS.IRH.REC.1402.096) from the Institutional Ethics Committee of Mashhad University of Medical Sciences. All research procedures were in accordance with the Helsinki Declaration.

Author contributions: Sh.S study design, A.A Kh Data acquisition, M.K data analysis, A.A Kh and M.K drafting, Sh.S critical reviewing, E.Sh data analysis, drafting.

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