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Original Research Article

Efficacy Of Olanzapine V/S Haloperidol In Treating Delirium In Intensive Care Settings – A Comparative Study From Southern Rajasthan.

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Abstract

Background: Delirium is a common yet often under diagnosed entity in medical and surgical intensive care (ICU) settings. Being a preventable and potentially reversible condition, the early recognition and optimal treatment of delirium is of vital importance in preventing its potential mortality. The FDA has approved haloperidol as well as olanzapine for treating ICU psychosis (delirium). This study aims to compare the efficacy of both drugs in treating ICU psychosis, while exploring their comparative safety profiles.

Methodology: A total sample population of 100 ICU patients diagnosed with delirium was recruited in the study and randomly divided in two treatment groups – haloperidol and olanzapine, after excluding delirium due to alcohol withdrawal (delirium tremens). Maximum dose of haloperidol administered was 2.5 mg/day (oral or parenteral) and of olanzapine was 5 mg/day. After taking consent from patient's family member, the Delirium Screening Checklist, Delirium Rating Scale and Richmond Agitation Sedation Scale were applied in suspected delirium cases to record delirium severity score at zero hour. After drug administration, the scoring was repeated at 72 hours. Patient demographics and relevant clinical variables, along with any adverse drug effects were also recorded for further analysis.

Results: Severity of delirium significantly reduced in both treatment groups, regardless of underlying cause or comorbidity. Adverse drug effect of extrapyramidal signs was more seen with the use of haloperidol as compared to olanzapine. The underlying illness and dose of medication did not have a significant correlation with the extent of treatment response in both groups.

Conclusion: Adding to existing literature, this study reiterates that efficacy of both antipsychotics (typical – haloperidol and atypical – olanzapine) does not significantly differ in the treatment of delirium in ICU settings. The use of olanzapine seems to be overall safer as compared to haloperidol.

Keywords: ICU psychosis, delirium, antipsychotics, haloperidol, olanzapine.

Introduction:

Delirium is an acute disturbance in attention and awareness, often fluctuating over the course of the day, and is especially prevalent in critically ill patients.[(1)]ICU delirium affects nearly 30–80% of patients, depending on the population studied and diagnostic criteria applied. [(2)] Assessing patients at risk for recent (within hours or days) changes or fluctuations that may indicate delirium include: Cognitive function -worsened concentration, slow responses, confusion, Perception - visual or auditory hallucinations, Physical functions - reduced mobility, reduced movement, restlessness, agitation, changes in appetite, sleep disturbance and Social behavior - difficulty engaging with or following requests, withdrawal, or alterations in communication, mood and/or attitude. [(3)] The management of delirium involves identifying and treating underlying causes, environmental modifications, and pharmacological interventions. Although, Haloperidol has long been the mainstay of pharmacologic treatment, recent evidence has suggested that atypical antipsychotics such as Olanzapine may offer similar benefits with potentially fewer extrapyramidal side effects.[(4,5)]

Material and Methods:

Study Design and Setting: This randomized controlled, comparative and observational study was conducted in the tertiary care ICU setting of Pacific Medical College and Hospital, Bedla, Udaipur, Rajasthan, India between 2023-2024.

Study population - The study group comprised of 100 consecutive adult patients (18years and above) with Delirium (ICU Psychosis) due to any underlying cause (except delirium due to Alcohol withdrawal), admitted at Intensive Care Unit (ICU) and had a minimum of one week of stay were recruited for the study who were admitted in the Intensive Care Unit of the Institution and fulfilled the criteria of the study.

Ethical Clearance: The study was initiated after approval from the Institutional Ethics Committee of the Institute dated 15/02/2023 – ref no – PMU/PMCH/IEC/2023/235.

Instruments of the study: A semi structured proforma including socio-demographic profile of patients and clinical parameters were recorded along with Richmond Agitation and Sedation Scale (RASS)[6] and Intensive Care Delirium Screening Checklist (ICDSC)[7], and Delirium Rating Scale (DRS)[8] were administered in each patient.
The socio-demographic profile proforma inquired about name, age, sex of the patient, diagnosis of the patient, length of stay in the ICU, adverse drug reactions, and mortality or recovery status.

Richmond Agitation Sedation Scale – A 10-level, structured assessment of sedation and agitation designed to be useful within the context of sedative medication titration. The RASS is a 10-point scale that ranges from +4 to −5. A score of 0 signifies a calm and alert patient. Positive RASS scores denote levels of aggressive behavior, and negative RASS scores denote less responsiveness, and differentiate between response to verbal (−1 to −3) and physical stimuli (−4 and −5).Developed as part of a collaborative effort with practitioners representing critical care physicians, nurses, and pharmacists, the scales' psychometric properties were examined across multiple samples of consecutive, intensive care unit (ICU) patients presenting with a variety of physical ailments. [6]

Delirium Screening Checklist – The Intensive Care Delirium Screening Checklist (ICDSC) is an 8-item checklist of delirium symptoms evaluated over an 8–24 hour period. Patients are given one point for each symptom that manifests during the specified time frame (zero points if symptom did not manifest). The eight symptoms are: level of consciousness, inattention, disorientation, hallucinations, delusions, psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbances, and symptom fluctuation. A score ≥4 indicates a positive ICDSC and the presence of delirium. Key symptoms of delirium can be part of a focused evaluation from the bedside clinician. Presence of any symptoms noted during an initial focused evaluation can immediately be scored on the ICDSC. The patient can subsequently be observed and scored for additional symptoms that manifest or fluctuate during the remainder of the specified time period. [7]

Delirium Rating Scale - The DRS is a numerical rating scale for delirium. It is a 10-item scale, with items scored from 0 to 3 or 0 to 4 in the following domains: (1) temporal onset, (2) perceptual disturbance, (3) hallucinations, (4) delusions, (5) psychomotor behavior, (6) cognitive status, (7) physical disorder, (8) sleep–wake cycle disturbance, (9) lability of mood, and (10) variability of symptoms. A score of 12 or greater is diagnostic of delirium. [8]

Baseline Assessment (Day 0): On the first day, patients who were enrolled for this study were made to undergo structured assessments which included:
- Richmond Agitation and Sedation Scale (RASS)[6]: Monitored the levels of agitation or sedation.
- Delirium Screening Checklist [7]: Assisted in initial screening of Intensive care patients having Delirium or not.
- Delirium Rating Scale [8]: Assessed the severity of symptoms of Delirium in the patients.

Drug Intervention Protocol: The drug intervention was based on the severity levels observed during the assessments:
- Medication dosing was adjusted according to the daily RASS assessments.
- Interventions aimed to minimize the adverse effects, along with close monitoring for complications that could have arose.
- Treatment success was defined as an improvement in the overall RASS score within 72 hours of initiation of intervention.

Data Collection and Monitoring: Data collection continued for one week (07 days) post the initial assessment and it included:
- Recording of the vital parameters and delirium scores three times in a day.
- Any changes that took place were duly noted.
- Monitoring of the risk factors associated with delirium was carefully documented.
- Adjustments in the medication dosing based on daily observations and RASS assessments were also documented.

Consent Process Details: The consent process included:
- Detailed explanation of the intervention protocols and potential adverse drug reactions.

- Documentation of the caregiver relationship with the patient and responsibilities in providing consent.
- Information on the potential risks and adverse effects of the drug intervention.

Outcome Measurement: Two types of outcome were taken into consideration which were as follows –

- The primary outcome was to note the improvement of the RASS score within 72 hours of initiating the intervention.
- Secondary outcomes included tracking delirium severity progression and identifying the relevant risk factors.

Statistical analysis: Statistical analysis was done with the help of the software SPSS version 22. Chi-square and t-tests were used to compare outcomes between the two groups, with $p < 0.05$ considered statistically significant.

Results: Our study evaluated 100 ICU patients (aged ≥18 years) presenting with delirium, randomized to receive either Olanzapine (n=50) or Haloperidol (n=50). Patients were monitored over 72 hours using the Richmond Agitation-Sedation Scale (RASS), with additional observations on mortality, adverse drug reactions (ADRs), and ICU stay duration which has been described in detail as follows:-

Table 1: Efficacy (RASS Score Improvement)

Group	Mean RASS Improvement	SD (assumed)*	t-value	p-value	Interpretation
Olanzapine	+1.26	0.4	1.32	0.19	Not statistically significant ($p > 0.05$)
Haloperidol	+1.16	0.4			Comparable efficacy

Table 2: Adverse Drug Reactions (ADRs)

ADR Type	Olanzapine (n = 50)	Haloperidol (n = 50)	χ^2-value	p-value	Interpretation
Mild Sedation	5 (10%)	3 (6%)	0.53	0.47	Not statistically significant
Extrapyramidal Symptoms	4 (8%)	6 (12%)	0.44	0.51	Not statistically significant
Hypotension	1 (2%)	2 (4%)	0.34	0.56	Not statistically significant
Total ADR Cases	10 (20%)	14 (28%)	0.89	0.34	Not statistically significant

Table 3: Mortality and ICU Stay

Outcome	Olanzapine (n = 50)	Haloperidol (n = 50)	Test Used	Test Statistic	p-value	Interpretation
Mortality	1 (2%)	2 (4%)	Chi-square	0.34	0.56	No significant difference
ICU Stay (mean)	5.9 days	6.6 days	t-test	1.97	0.052	Borderline non-significant trend

Interpretation: Mortality was lower and ICU stay shorter in Olanzapine group, but not statistically significant (ICU stay: $p = 0.052$, close to threshold).

Table 4: Risk Factors for Delirium (Overall in Study Population)

Risk Factor	Frequency (n = 100)	Percentage
Sepsis	32	32%
Postoperative Complications	24	24%
Metabolic Imbalances	18	18%
Head Injury & Drug-induced	26	26%

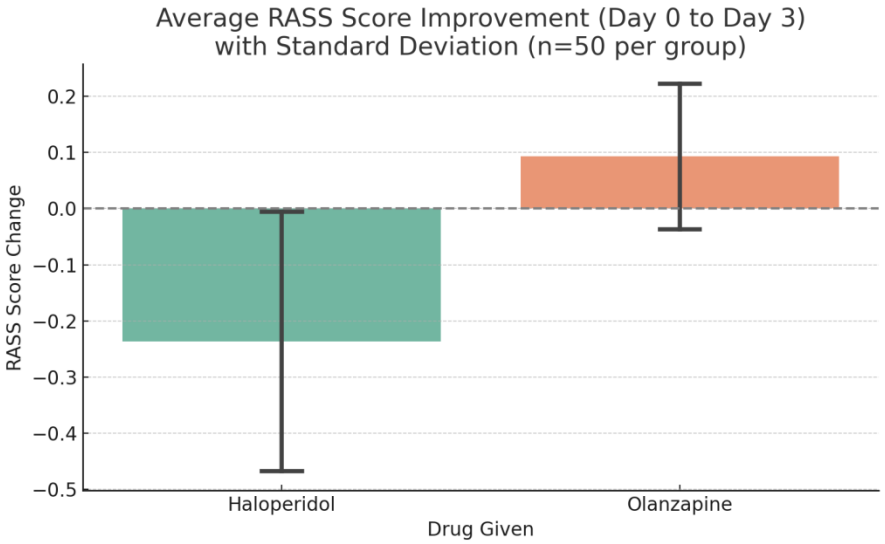
Interpretation: Sepsis and postoperative complications were the most common risk factors associated with delirium.

- **T-tests** were used for continuous variables (RASS score, ICU stay).
- **Chi-square tests** were used for categorical variables (ADRs, mortality).

 p < 0.05 considered statistically significant — none of the differences reached significance except for ICU stay, which was borderline.

Delirium study with graphical representation -

1. Average RASS Improvement (Day 0 to Day 3)

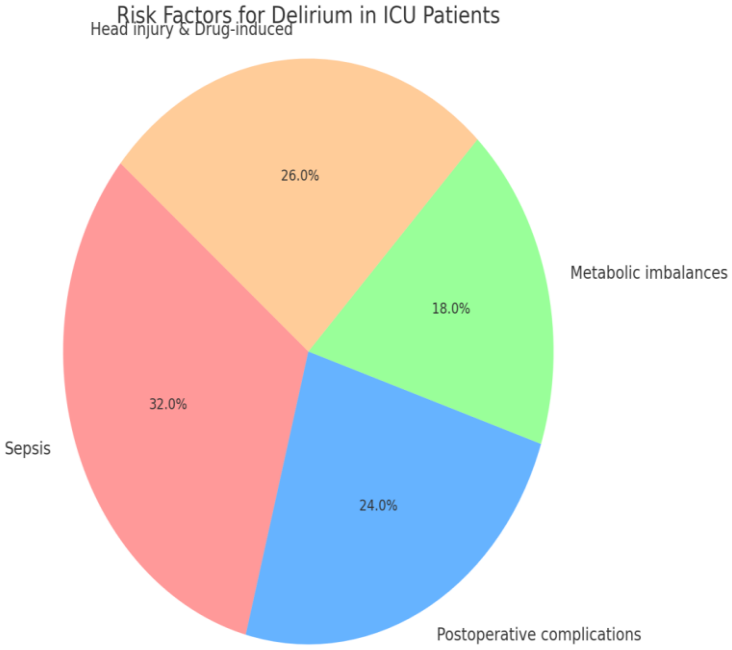


This bar chart shows the average change in RASS scores from Day 0 to Day 3, comparing the effectiveness of Olanzapine and Haloperidol in improving patient alertness levels.

RASS score comparison chart:

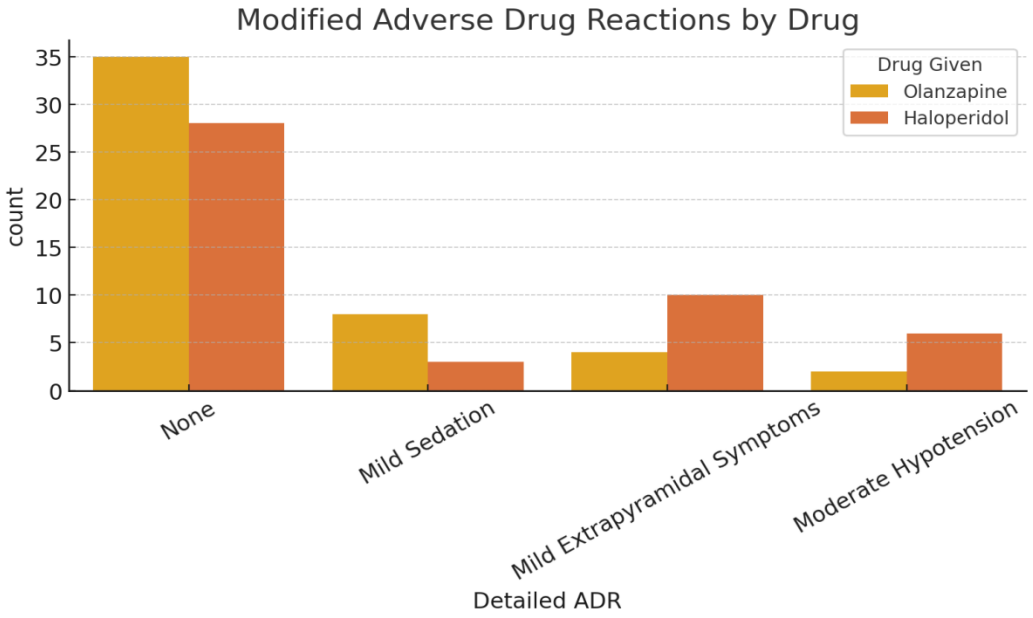
- Shows the **mean change in RASS scores from Day 0 to Day 3** for both drug groups.
- **Error bars** represent the **standard deviation**..
- Each group has **50 patients** (total = 100 delirium patients in ICU).
- **Olanzapine** group shows a **positive mean change**, indicating improved alertness.
- **Haloperidol** group has a **negative mean change**, suggesting either less improvement or increased adverse effects such as Extra pyramidal side effects, hypotension.

2. Reasons for Delirium in ICU patients –



This pie chart illustrates the distribution of underlying causes for delirium in the patient population.

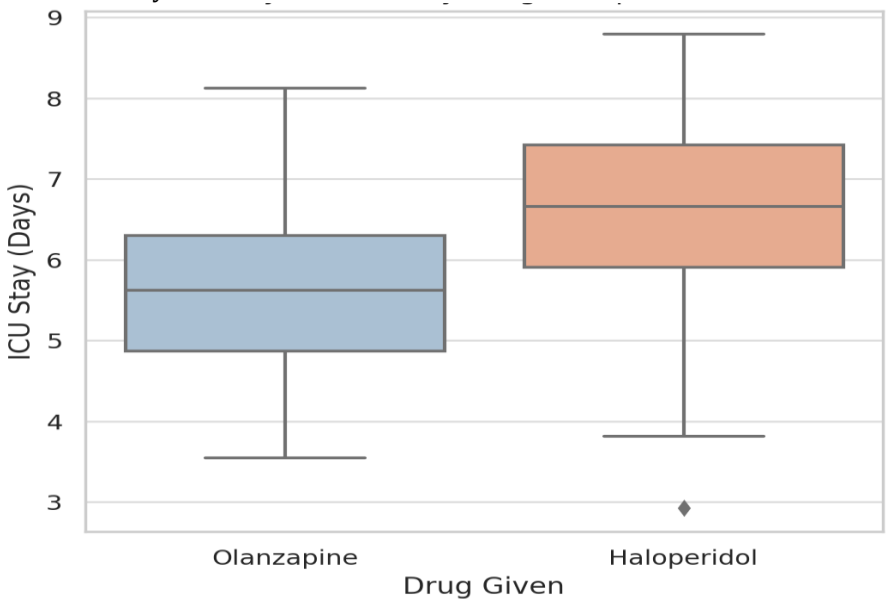
3. Adverse Drug Reactions by Drugs – Olanzapine and Haloperidol -



This bar chart displays the types and frequencies of adverse drug reactions observed in patients receiving either Olanzapine or Haloperidol.

4. **ICU stay durations** for both the groups -

- **Olanzapine**: Mean ~5.9 days.
- **Haloperidol**: Mean ~6.6 days.



This box plot compares the length of ICU stay between the two drug groups, indicating median values and variability among patients.

Discussion:

Consistent with earlier studies [3]Girard et al., 2008; and [4] Devlin et al., 2010; our findings suggest that use of low-dose antipsychotics can significantly alleviate the symptoms of delirium (also known as ICU Psychosis). Haloperidol continues to be effective and also have an average of lesser span of stay in the Intensive care settings but it may bear a greater burden of motor adverse effects. However, Olanzapine offers a favorable alternative with a

wider safety margin, though sedation must be carefully monitored and documented. Given the multifariousness of delirium pathophysiology and patient characteristics, the need for individualized tailored and patient centric treatment remains to be of paramount significance.

Given below are catalogues of studies that had similar outcomes and matched our findings of the study. An open-label randomized controlled trial conducted at Chandigarh, India in 2017 by Jain R, et al.,[9], involving 100 patients compared the efficacy of low-dose haloperidol (1–4 mg/day) and olanzapine (2.5–10 mg/day) for delirium treatment. Both the groups showed significant improvement in delirium severity with no statistically significant difference between them. In a multicenter Phase III RCT study undertaken between (2011-2016) by van der Vorst MJ et al., [10] involving 98 patients with advanced cancer and delirium, the trial found no significant difference in delirium response rates between Olanzapine (45%) and Haloperidol (57%).Also, Olanzapine was associated with fewer severe adverse events (10.2% vs. 20.4%) which was in tone with our study as well. Furthermore, a comparative study in 2010 by Grover S, et al., [11] was undertaken to assess the efficacy and safety of Olanzapine, Risperidone, and Haloperidol in 64 patients with delirium which found that all the three antipsychotic drugs were equally effective, with Olanzapine displaying fewest side effects amongst the three. Yet another Indian double blind trial conducted by Garg. R, et al.,[12] in 2022, reportedly compared Olanzapine, Haloperidol, and Quetiapine in ICU patients with delirium found that all the three antipsychotic drugs were equally effective in reducing agitation over 10 days, with Olanzapine and Quetiapine carrying lesser chances of extrapyramidal side effects.

While we enlisted several studies which were akin to results of our study findings, we also found a handful of studies that bore contradictory findings which we have discussed below.

A randomized controlled trial in 2020-21 by Malik AK et al.,[13] that took place in India, which assessed the effectiveness of a delirium prevention bundle in mechanically ventilated ICU patients reported a 20% reduction in delirium incidence (36% vs. 56%), which wasn't statistically significant (p = 0.156). Secondary outcomes such as length of stay and mortality were also similar between the study groups. Jacob A, et al in 2023 [14] conducted a randomized, placebo-controlled trial to investigate the prophylactic use of low-dose risperidone to prevent ICU delirium. They found no significant differences in the incidence of delirium, adverse events, or complications between the risperidone and placebo groups, which highlighted the complexity of delirium's etiology and the challenges in its prevention.

Conclusion:

From the results of the current study we can conclude that both Olanzapine and Haloperidol are effective in managing ICU delirium, with Olanzapine showing a slightly better safety profile, fewer adverse reactions. While Haloperidol remains a gold standard, Olanzapine being a second generation, atypical antipsychotic may serve as a safer alternative, especially in patients who are at risk of developing extrapyramidal symptoms or hemodynamic instability.

Given the shared efficacy but differing adverse effect profiles, individualized patient assessment should guide the choice of antipsychotic use in delirium management. Moreover, sepsis and postoperative complications remain the most prevalent risk factors, thereby, highlighting the need for proactive delirium screening in such vulnerable populations.

Strengths: A consistent, quantifiable measurement of delirium severity and treatment response was noted through the help of this study. Comprehensive Data was captured that included ADRs, ICU stay, and mortality for holistic evaluation.

Limitations: There were short follow –up duration (72 Hours) which may have missed the late-onset effects or relapses of delirium. The study limited generalizability due to localized demographics and clinical practices. Furthermore, it restricted the statistical power for detecting small but relevant differences. In addition to this, possibility of observer bias due to the awareness of treatment groups could have resulted in the changes that were found.

Future Directions: This study underpins the need for larger, multi-centric trials to further delineate the role of newer atypical antipsychotics in this population for holistic approach with reference to managing ICU psychosis (delirium).

Implications for research: There is currently paucity of prospective observational studies that investigate the use of antipsychotic drug for Delirium patients especially prevalent in the elderly group. Very few studies from our geographical area have been reported so far and thus we perceived the need to undertake this study. Observational studies are required since it can create usage patterns (e.g. indications for administration purposes, dosages and mode of application) and the effect on patients and the course of delirium. In addition, the extent to which early non-pharmacological treatment referrals are made for consideration to start

antipsychotic medication in such population needs to be researched. The fiscal impact of diminishing antipsychotic usage in delirium management is yet to be explored.

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Conflict of interest: No conflict of interest declared.

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