Original Article

Efficacy and Safety of Antipsychotic Medications in the Treatment of Delirium

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Objective: To examine the therapeutic effects and adverse events in patients with delirium after treatment by antipsychotics, which are haloperidol, risperidone, and quetiapine.

Materials and Methods: Fifty-six delirious inpatients treated by haloperidol, risperidone, and quetiapine participated in this study. The type and dosage of medication depended on the judgment of psychiatrists who took care of each patient. Investigators observed the clinical progression without being involved in any treatment methods. Severity of delirium was evaluated using the Memorial Delirium Assessment Scale [MDAS]. The extrapyramidal side effect [EPS] was assessed via the Modified Simpson-Angus Scale [MSAS]. All measures were applied at the baseline (prior to the treatment) and repeated daily throughout the 7-day study. The mixed model regression analysis was used.

Results: Eleven (19.6%), 14 (25%), and 31 (55.4%) participants received haloperidol, risperidone, and quetiapine, respectively. At baseline, MDAS score (mean) of haloperidol, risperidone, and quetiapine groups were 14.5, 19.3, and 18.0, which were not statistical different. At study end, the MDAS score improved the most in risperidone group (-8.3), followed by haloperidol (-7.3), and quetiapine group (-5.9). The mixed model analysis indicated no significant differences in the improving scores between treatment groups. About 30% of patients had experienced adverse events. Most common side effects were sedation (14.3%) and EPS (10.7%). There were no statistical significant differences in side effect profiles between groups.

Conclusion: Haloperidol, risperidone, and quetiapine are similarly effective in the management of delirium. No different side-effect profile was found.

Keywords: Efficacy, Safety, Delirium, Antipsychotics, Haloperidol, Risperidone, Quetiapine, Extrapyramidal side effect [EPS]

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Delirium is a common neuropsychiatric symptom that occurs in hospital. Its incidence varies by the age of the patient and illness severity[1]. In the general hospital setting, the average prevalence of delirium is 10% to 20%[2] and may reach 40% in the hospitalized elderly[3]. Delirium is characterized by disturbances of consciousness, attention, cognition, and perception with an abrupt onset and fluctuating course. It usually has underlying physiological etiology[3]. An occurrence of delirium is associated with worsening outcomes due to increasing morbidity, mortality, length of hospital stay, and poor functional outcome[4].

Management of delirium consists of specific treatment and symptomatic treatment. The specific treatment is early detection and removal of all probable causes. Symptomatic treatment includes providing a safe and supportive environment. In addition, psychopharmacological treatment is one of essential symptomatic treatment modalities for decreasing behavioral and emotional disturbances in moderate to severe cases[5].

The guidelines for the management of delirium published by the American Psychiatric Association [APA] recommend the use of typical antipsychotics, haloperidol. Because of haloperidol's short half-life, little sedation, and low anticholinergic side effects, it is the drug of choice for delirium although its use is limited by its extrapyramidal side effects [EPS][6]. Atypical antipsychotics, although used as off-label, are the first choice for treatment of delirium in clinical practice due to a lower rate of side effects. Several studies have suggested the safety and efficacy of risperidone[7] and quetiapine[8] in the treatment of delirium. Currently, there is no standard practice guideline for delirium used in Thailand.

The aim of the present study was to examine the therapeutic effects and adverse events, particularly EPS, in patients with delirium after treatment by

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antipsychotic medication, haloperidol, risperidone and quetiapine in a hospital setting.

Materials and Methods

This 7-day prospective observation study was carried out in the physically ill patients admitted to Phramongkutklao Hospital, Thailand, between April and August 2015. The research proposal was approved by the Ethics Committee of the study site. Prior to participation, informed consent was obtained from a first-degree relative of each subject after the study details had been fully explained.

Participants

Fifty-six participants were inpatients with delirium, which were consulted to the psychiatric department, Phramongkutklao Hospital and were treated by antipsychotics haloperidol, risperidone, and quetiapine oral route. The diagnosis of delirium was made according to DSM-IV criteria by psychiatrists. The author excluded the participants taking any antipsychotic medication prior to the study, critical medical condition that the patients could not be assessed for symptoms of delirium, and substance-induced delirium (i.e., alcohol withdrawal delirium).

Medication

Only delirious patients who received haloperidol, risperidone, and quetiapine were included. The psychiatrists who took care of each patient decided the type and dose of medication. The researcher did not interfere with any treatment methods.

Outcome measures

Demographic data and medical variables such as age, sex, history of previous confusion, psychiatric comorbidity, type, and dose of antipsychotic medication were recorded at the baseline assessment. The efficacy of antipsychotics in delirium was evaluated by using the Memorial Delirium Assessment Scale [MDAS], a 10-item, four-point clinician-rated scale (range 0 to 30). MDAS score greater than 10 identifies the presence of delirium and MDAS score less than 10 is defined as the resolution of delirium[9]. The EPS was assessed by using the Modified Simpson-Angus Scale [MSAS] (9 items). The MSAS is a 5-point scale of nine items of abnormal movement (shoulder shaking, elbow rigidity, arm dropping, wrist rigidity, leg pendulousness, tremor, head dropping, glabellar tap, and salivation), with a maximum score of 81 points[10]. The item of gait stability was excluded because the patients might not cooperate properly during the assessment. Other side effects were determined by observation and medical records of psychiatrists. All measures were applied at baseline (prior to the treatment) and repeated daily throughout the 7-day study. The mean scores of T1 (day 1: baseline), T2 (day 2 to 3), and T3 (day 4 to 7) were recorded. The measurements were stopped before seven days if the patients could not tolerate the antipsychotic or another antipsychotic medication initiated. After seven days, the study ended, and patients continued the medication as necessary.

Statistical analysis

Data were analyzed using Stata 14.0. Categorical measures were summarized using frequencies and percentages. Continuous measures were described by means and standard deviations. The treatment effect was assessed by using one-way ANOVA for between group differences, and multilevel mixed effects linear regression for multivariable analysis. All tests were performed at a significance level of 0.05.

Results

Patient characteristics

Between April and August 2015, 85 delirious patients were consulted for psychiatric assessment and treatment. Of those, 29 did not meet the inclusion criteria or meet the exclusion criteria. Fifty-six patients, including 27 males (48.2%) and 29 females (51.8%), participated in the present study. The patients' ages varied from 37 to 96 years (mean 73.6 years, SD 13.3 years). Most patients had multiple diagnoses and etiologies. Twenty-seven patients (47.4%) had one or more previous history of confusion and 13 patients (23.2%) had comorbid diagnosis of dementia.

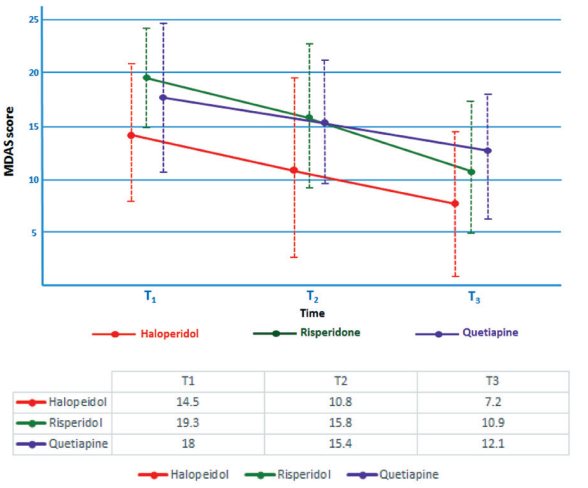
Eleven (19.6%), 14 (25%), and 31 (55.4%) participants received haloperidol, risperidone, and quetiapine, respectively. The age and gender distribution of the patients did not differ among groups of medications. Previous history of confusion was found mainly in quetiapine group (p = 0.038). The prevalence of preexistent dementia also found in quetiapine group more than the others, but without statistical significance. Table 1 summarizes the patients' demographic and clinical characteristics of the study.

Efficacy

Treatment characteristics. The median dosages (percentiles 25%, 75%) of haloperidol, risperidone, and quetiapine were 0.5 (0.5, 0.8) mg/day, 0.5 (0.25, 1)

mg/day, and 25 (20.3, 30.27) mg/day, respectively (Table 1).

Treatment responses. The severity of delirium at baseline (T1) did not differ among the three medication groups (p = 0.127). MDAS scores decreased in all groups from baseline through T2 to T3. In the haloperidol-managed patients, the mean MDAS score decreased from 14.5 (T1) to 10.8 (T2) and 7.2 (T3). In risperidone-managed patients, the mean MDAS score decreased from 19.3 at baseline to 15.8 at T2, and 10.9 at T3. Quetiapine-managed patients had a baseline MDAS score of 18.0, declining to 15.4 and 12.1 at T2 and T3, respectively. There were no significant differences in the decreasing scores among the treatment groups (one-way ANOVA: between-group difference, p = 0.242). In addition, the delirium resolution rates at T3 were 63.6% (haloperidol), 50% (risperidone), and 48.4% (quetiapine). These resolution rates were not significantly different among the medications either (p = 0.94). Table 2 summarizes the treatment response of haloperidol, risperidone, and quetiapine and Figure 1 shows the declining of MDAS score in three medication groups.



	T1	T2	T3
Haloperidol	14.5	10.8	7.2
Risperidol	19.3	15.8	10.9
Quetiapine	18	15.4	12.1

Figure 1. Mean difference of MDAS scores from baseline over time after treatment with haloperidol, risperidone, and quetiapine.

Adverse events

About 30% of the patients experienced adverse events. Most common events, which seemed to be the side effects of antipsychotic medications, were sedation (14.3%), EPS (10.7%), and arrhythmia (3.6%), subsequently. Anticholinergic side effects and abnormalities of laboratory parameter were not reported. Table 2 summarizes the adverse events occurred in the present study.

EPS were assessed by using the MSAS. Only six had MSAS scores increased from baseline and were determined to be EPS. EPS was most frequently observed in the risperidone treatment group (2/14, 14.3%) followed by quetiapine (3/31, 9.7%), and haloperidol (1/11, 9.1%). However, no differences between three treatment groups were determined to be statistically significant.

Based on the adjusted multilevel mixed effects linear regression model, some factors that might be associated with delirium outcome, including age, gender, history of previous confusion, and dementia[11] were analyzed. The improvement of MDAS scores among the three medications in the present study was equal despite controlling those confounding factors. Multilevel mixed-effects linear regression model is presented in Table 3.

Discussion

The present study is the first investigation that use a mixed model approach to analyze the MDAS and antipsychotics over the study period.

The results of the present study are consistent with previous studies regarding the efficacy of

Table 1. Baseline and medical characteristics of patients

	Haloperidol (n = 11)	Risperidone (n = 14)	Quetiapine (n = 31)	Total (n = 56)	p-value
Gender, n (%)					0.228
Male	8 (72.7)	6 (42.9)	13 (41.9)	27 (48.2)	
Female	3 (27.3)	8 (57.1)	18 (58.1)	29 (51.8)	
Age (year), mean (SD)	70.5 (17.3)	69.4 (15.7)	76.4 (10.1)	-	0.197
Preexisting dementia, n (%)	2 (18.2)	1 (7.14)	10 (32.3)	13 (23.2)	0.198
Previous confusion, n (%)	4 (36.4)	3 (21.4)	19 (61.3)	26 (46.4)	0.038
Baseline MDAS, mean (SD)	14.5 (6.2)	19.3 (4.4)	18.0 (6.3)	-	0.127
Mean dosage, mean (SD)	0.9 (0.9)	0.6 (0.5)	26.7 (12.2)	-	-
Dosage (mg/day), median (P25, P75)	0.5 (0.5, 0.8)	0.5 (0.25, 1)	25 (20.8, 30.27)	-	-

MDAS = Memorial Delirium Assessment Scale

Table 2. Management characteristics of haloperidol, risperidone, and quetiapine

	Haloperidol (n = 11)	Risperidone (n = 14)	Quetiapine (n = 31)	*p*-value
MDAS scores, mean (SD)				
Baseline; T1	14.5 (6.2)	19.3 (4.4)	18.0 (6.3)	
T2	10.8 (8.7)	15.8 (6.2)	15.4 (6.0)	
T3	7.2 (6.4)	10.9 (5.8)	12.1 (5.2)	
Intra-group different (T3-T1)	-7.3 (5.3)	-8.3 (4.6)	-5.9 (4.4)	0.242*
Delirium resolution at T3, n (%)	6 (63.6)	7 (50.0)	15 (48.4)	0.940
Side effect, n (%)				
Any side effects	3 (27.3)	7 (50.0)	7 (22.6)	0.175
Sedation	1 (9.1)	4 (28.6)	3 (9.7)	0.211
EPS	1 (9.1)	2 (14.3)	3 (9.7)	0.851
Orthostatic hypotension	0 (0.0)	0 (0.0)	1 (3.3)	0.672
Arrhythmia	1 (9.1)	1 (7.1)	0 (0.0)	0.267

MDAS = Memorial Delirium Assessment Scale; EPS = extrapyramidal symptom

* One-way ANOVA of between group difference

Table 3. Multilevel mixed-effects linear regression model

Score	Coefficient (95% CI)	*p*-value
Quetiapine	-	-
Risperidone	-0.20 (-1.42 to 1.02)	0.750
Haloperidol	-0.68 (-1.94 to 0.59)	0.254
Age	-0.01 (-0.05 to 0.03)	0.571
Gender (female)	-0.29 (-1.36 to 0.78)	0.593
Preexisting dementia	0.87 (-0.44 to 2.18)	0.192
Previous confusion	-0.48 (-1.36 to 0.78)	0.426
Visit (T1, T2, T3)	-3.39 (-4.13 to -2.65)	<0.001
Baseline T1	0.94 (0.86 to 1.03)	<0.001
Constant	2.28 (-0.77 to 5.33)	0.143

LR test vs. linear model: Chi-square (2) = 72.20

antipsychotics in the treatment of delirium[8,12,13,17]. The findings indicate that atypical antipsychotics, which are risperidone and quetiapine, and the typical antipsychotic, which is haloperidol, were both effective in the management of the symptoms of delirium caused by multiple etiologies, as confirmed by the same pattern of MDAS effects. Resolution rates at the seventh day were also comparable among groups.

Although the findings indicated similar efficacy of the three medications, the crude data showed that MDAS score improved the most in risperidone group (-8.3) followed by haloperidol (-7.3), and quetiapine group (-5.9). The coefficient in multivariate analysis also showed the least reduction of the MDAS score in quetiapine group. The delirium resolution rates at T3 were 72.7% in haloperidol-treated patients, 50% in risperidone-treated patients, and 48.4% in quetiapine-treated patients. Quetiapine seemed to be the least effective among the three medications from both measures. This event may be explained by the fact that patients with previous confusion and preexistent dementia were found mainly in the quetiapine group. Dementia may be reducing the response rates in the observation period.

In the present study, the average doses of antipsychotics in the management of delirium were low to moderate[15], and relatively low compared with those applied in previous studies[8,12,13]. Data indicated that low dose antipsychotics, similar to the present study, were also effective for the treatment of delirium. The small body size of Asian patients and advanced age might be reasons for the lower dose administration.

From the standpoint of safety, the adverse events observed in the present study were found in about 30% of patients, a higher rate compared to other studies. This is not particularly surprising as advanced age and comorbid dementia makes the group of patients vulnerable to medication side effect by the changes in drug pharmacokinetics and pharmacodynamics[14,16]. In our findings, most common side effects were sedation and EPS. Sedation may have clinical utility in delirious patients with insomnia and aggressive behavior.

EPS associated with antipsychotic medications, occur more often in the patients treated with haloperidol in most previous studies[12,13,17]. In contrast, the author's finding indicated similar side effect profile of the three medications. Both the low-dose administration and the small number of patients in haloperidol group in our study perhaps produced the statistically insignificant outcome.

Limitation

The data collection procedure had strengths, which are the one week prospective that was appropriate to observe the course of delirium and the optimal measures that were used for determining the outcomes. However, several important limitations have to be

noted. First, the study was observational in nature. These results were prone to bias because the selection of antipsychotic intervention was not random and was based on the treating physicians' preferences. The patients might have been receiving other drugs apart from the study's medications that could have interfered with the results. The sample size was small. Additionally, self-improvement of delirium after underlying causes were removed cannot be ruled out.

Nevertheless, the setting in our study was naturalistic. These kinds of treatments are normally used in clinical practice. The characteristic of patients, as vulnerable subjects, in our study, are usually found in the general hospital setting.

Further research, particularly larger, double-blind, randomized controlled trials in groups of patients who are a good representation of the true delirium population, will be needed to confirm the findings and to determine recommended dosing and titration schedules.

Conclusion

In summary, the present analysis has provided further results supporting that the typical antipsychotic, haloperidol and the atypical antipsychotics, risperidone and quetiapine are similarly effective in the management of delirium. No different side-effect profiles were found in the present study.

What is already known in this topic?

To our knowledge, the medications mentioned above, appear to be effective and tolerable in the management of delirium. Low doses of typical and atypical antipsychotics may be effective. The evidence so far also suggests that haloperidol may be associated with EPS.

What this study adds?

Currently, there is no evidence supporting the superiority in efficacy of any antipsychotics. Most of the patients have delirium resolution after treatment with either typical or atypical antipsychotics, but there are many patients who experience the side effects. As a consequence, the choice of antipsychotics for the management of delirium may be more determined by the profile of risk of side-effect, as well as the potentially desirable side effect of sedation, than efficacy. In the future, skill training for managing delirium and standard clinical practice guideline should be established in the hospital to reduce the side effects and improve patient care.

Authors' contribution

Charoenporn V designed the study, collected, and analyzed the data, and wrote the manuscript.

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Potential conflicts of interest

The author declares no conflict of interest.

References

1. Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly hospitalized patients. J Gen Intern Med 1998;13:204-12.
2. Burns A, Gallagley A, Byrne J. Delirium. J Neurol Neurosurg Psychiatry 2004;75:362-7.
3. Bucht G, Gustafson Y, Sandberg O. Epidemiology of delirium. Dement Geriatr Cogn Disord 1999;10: 315-8.
4. Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. Age Ageing 2009;38:19-26.
5. Blumenfield M, Tiamson MLA. Delirium. In: Leigh H, Streltzer J, editors. Consultation-Liaison of psychiatry: A practical guide. San Francisco: Springer; 1999:117-29.
6. American Psychiatric Association. Practice guideline for the treatment of patients with delirium. Am J Psychiatry 1999;156:1-20.
7. Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics 2004;45:297-301.
8. Maneeton B, Maneeton N, Srisurapanont M. A double-blind, randomised, controlled trial of quetiapine versus haloperidol for the treatment of delirium: a preliminary report. Eur Neuropsychopharmacol 2011;21(Suppl 3): S557.
9. Lawlor PG, Nekolaichuk C, Gagnon B, Mancini IL, Pereira JL, Bruera ED. Clinical utility, factor analysis, and further validation of the memorial

delirium assessment scale in patients with advanced cancer: Assessing delirium in advanced cancer. Cancer 2000;88:2859-67.
10. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11-9.
11. Sadock BJ, Sadock VA, Pedro R. Delirium. In: Sadock BJ, Sadock VA, editors. Kaplan & Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:351-62.
12. Boettger S, Breitbart W, Passik S. Haloperidol and risperido ne in the treatment of delirium and its subtypes. Eur J Psychiatry 2011;25:59-67.
13. Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: A comparison of efficacy, safety, and side effects. Palliat Support Care 2015;13:1079-85.
14. Fosnight SM, Holder CM, Allen KR, Hazelett S. A strategy to decrease the use of risky drugs in the elderly. Cleve Clin J Med 2004;71:561-8.
15. Meagher D, Leonard M. The active management of delirium: improving detection and treatment. Adv Psychiatr Treat 2008;14:292-301.
16. Pariwatcharakul P. Psychiatric drug use in elderly patients. In: Udomratn P, Wongpakaran N, editors. Psychotropic drug use in elderly patients. Chiang Mai: Klangwieng Printing; 2012:25-7.
17. Maneeton N, Maneeton B. Management in delirium. In: Woolfolk R, Allen L, editors. Mental and behavioural disorders and diseases of the nervous system [Internet]. 2013 [cited 2017 Jan 11]. Available from: https://www.intechopen.com/books/mental-disorders-theoretical-and-empirical-perspectives/management-of-delirium.