ORIGINAL ARTICLE

A RANDOMIZED TRIAL OF ORAL RISPERIDONE VERSUS INTRAMUSCULAR HALOPERIDOL IN THE EMERGENCY TREATMENT OF ACUTE PSYCHOTIC AGITATION

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Abstract

Objective: **The study aimed to compare the efficacy and tolerability of oral risperidone and oral clonazepam with intramuscular haloperidol and oral clonazepam in Filipino patients with acute psychotic agitation.** ***Methods:*** **This study used a prospective randomized design targeting patients who were referred to the emergency department or hospital inpatients exhibiting both psychosis and agitation. Patients were randomized into oral risperidone group or intramuscular haloperidol group. Both groups received oral clonazepam as part of treatment. Patients were observed for 24 hours. The main efficacy parameter was the PANSS agitation cluster score. Other parameters were total PANSS, other PANSS subscale scores, time and incidence of additional clonazepam usage. The safety parameter measured as incidence of adverse events.** ***Results:*** **There were 99 subjects enrolled in the study: 49 in the oral risperidone arm and 50 in the intramuscular haloperidol arm. There were significant reductions in the mean PANSS agitation cluster scores for both groups: -7.6±4.7 for oral risperidone group ($p<0.0001$) and -6.7±5.0 for intramuscular haloperidol group ($p<0.0001$). There was no statistical difference observed in the mean change in PANSS agitation cluster scores among the two groups ($p=0.3928$). Similar trends were observed in the total PANSS and other subscale scores. The incidence of additional clonazepam use is numerically higher in the oral risperidone arm than the intramuscular haloperidol arm (33% vs. 20%), but the difference did not attain statistical significance ($p=0.1370$). At the end of the study, 17 (33 %) and 18 (36%) of patients in the risperidone and haloperidol groups experienced varying degrees of sedation. No serious adverse event was reported.** ***Conclusion:*** **Oral risperidone is comparable to intramuscular haloperidol in the treatment of acute psychotic agitation in terms of efficacy and safety.** ***ASEAN Journal of Psychiatry, Vol.12(1): Jan – June 2011: XX XX***

Keywords: Risperidone; Haloperidol; Clonazepam; Agitation.

Introduction

Acute agitation secondary to an underlying psychotic condition is a common presentation in the psychiatric emergency room [1,2]. Standard treatment of acutely agitated psychotic patients involves parenteral administration of an antipsychotic and a benzodiazepine. Intramuscular (IM) Haloperidol is the antipsychotic preferred by most clinicians because of its reliable drug delivery, rapid onset and sedating effect. However, the use of IM neuroleptics has several drawbacks. The route of administration is perceived by some patients as coercive and abusive, thus oral medication is preferred. Furthermore, staff members are exposed to the risk of accidental needle pricks and blood borne pathogens. Increased risk of extrapyramidal symptoms (EPS) at the doses used, pain and bruising at the injection site, and other adverse physical effects such as confusion, disinhibition, ataxia and prolonged sedation are associated with standard IM treatment of acute psychotic agitation [3,4].

Various expert treatment guidelines recommend the use of oral therapy over parenteral treatment for behavioral emergencies. The American Association for Emergency Psychiatry has recommended the preferential use of oral over IM antipsychotics whenever possible.

The advantages and disadvantages of choosing the IM route need to be evaluated in terms of how they influence rapid behavioral control of agitation. Compliance with treatment, for example, may be influenced by patient's experience in emergency settings. The alternative oral antipsychotics have been proven just as effective as the intramuscular ones for first intervention in several studies. A survey also showed that most medical directors of psychiatric emergency programmes would prefer to use oral agents if they were proven to be effective, safe, reliable, and practical to use [5].

Risperidone, a benzisoxasole derivative, is available in liquid form and is an effective antipsychotic, ameliorating both positive and negative symptoms of schizophrenia and exhibiting a low rate of EPS. It is rapidly absorbed and reaches peak plasma concentration in one hour. At dosages of 4-6 mg/day, risperidone does not differ from placebo in producing EPS in subjects with psychosis [4]. Placebo-controlled prospective studies suggested risperidone is efficacious in controlling psychosis, aggression, and agitation associated with dementia and is more effective than haloperidol in controlling hostility associated with schizophrenia [6]. Several other studies displayed the superiority of risperidone over haloperidol. In a randomized controlled trial that compared efficacy and extrapyramidal symptoms with risperidone and haloperidol, there was less antiparkinson drug use and fewer dropouts for treatment failure with risperidone than with haloperidol [7].

In a pilot study, 60 agitated psychotic patients admitted to a large emergency hospital were given either risperidone (2 mg liquid concentrate) and oral lorazepam (2 mg) or haloperidol (5 mg IM) and lorazepam (2 mg IM). Both groups exhibited similar improvement in the 5 agitation subscales of PANSS, the Clinical Global Impressions Scale and time to sedation. Patients receiving risperidone experienced no adverse events while 1 patient receiving haloperidol developed acute dystonia [8]. However, this study did not randomly select patients into treatment groups, followed up subjects only during the initial emergency

period, and did not have enough statistical power [4].

A prospective, parallel-group, randomized, rater-blinded non-inferiority study compared oral treatment with risperidone and lorazepam versus IM treatment with haloperidol and lorazepam. Results showed that the oral regimen is an acceptable alternative to IM treatment. Mean acute-agitation cluster scores were similar at baseline. Mean score improvements were significant at 30, 60, and 120 minutes from baseline in both groups ($p<0.0001$) and were similar in both groups ($p>0.05$). Both treatments were also well tolerated [3].

Although data coming from initial studies are encouraging, there is a prevailing, unfortunate clinical impression that atypical antipsychotics are not as effective as the traditional antipsychotics like haloperidol in acutely agitated and psychotic patient and the IM route of administration is absolutely necessary in emergencies. Without evidence of necessity, this practice of overreliance on IM antipsychotics put the patients at risk of adverse effects of these agents and delays the start of treatment with novel antipsychotics with superior efficacy and safety profile [5].

Methods

This study used a prospective, randomized design. The primary aim of the study was to compare the efficacy and tolerability of oral risperidone with oral clonazepam and IM haloperidol with oral clonazepam in Filipino patients with acute psychotic agitation. Patients were included if they (1) were admitted to an emergency setting experiencing agitation associated with active psychosis or inpatients experiencing exacerbation or agitation with active psychosis (2) were aged 18 to 65 years old (3) had $\geq$ 14 on 5-item acute-agitation cluster PANSS and (4) had $\geq$ 3 CGI-S. Patients were excluded if (1) they had delirium, epilepsy or mental retardation (2) were intoxicated or had symptoms of withdrawal from CNS depressants, alcohol, benzodiazepines, narcotics or stimulants (3) had any serious unstable medical condition or (4) had a history of neuroleptic malignant syndrome.

Subjects were randomized into 2 groups: risperidone group and haloperidol group. Subjects received single doses of either oral 2 mg risperidone (1 mg/mL) and 2 mg clonazepam tablet or 5 mg IM haloperidol (5mg/mL) and 2 mg clonazepam (2 mg/mL). Risperidone and haloperidol were given every 8 hours, if necessary, depending on the patient's condition and investigator's discretion. A maximum of 8 mg of clonazepam were given, if necessary, depending on the patient's condition and the investigator's discretion.

Subjects were observed for 24 hours for changes in PANSS cluster scores and total PANSS scores. Time and frequency of clonazepam use were also analysed.

Results and Discussion

A total of 99 patients were enrolled in the study. There were 49 (49.5%) patients enrolled in the Risperidone arm and 50 (50.5%) enrolled in the Haloperidol arm. Demographic profile is summarized in Table 1. Mean age, gender distribution, mean weight and civil status distribution did not significantly differ in both arms ($p > 0.05$). Mean height was slightly higher in the risperidone arm (162.9cm vs. 159.2 cm, $p = 0.038$).

Table 1. Demographic Data

	Risperidone		Haloperidol		*p*-value
Age (years)					
Mean ± SD	32.837 ± 9.951		32.000 ± 8.106		0.647
Gender	No.	%	No.	%	
Female	23	46.9	20	40.0	0.488
Male	26	53.1	30	60.0	
Total	49	49.5	50	50.5	
Weight (kg)					
Mean ± SD	56.667 ± 10.783		56.447 ± 10.340		0.925
Height (cm)					
Mean ± SD	159.211 ± 7.984		162.921 ± 7.302		**0.038**
Civil Status	No.	%	No.	%	
Single	39	79.6	29	60.4	0.089
Married	9	18.4	17	35.4	
Widow	1	2.0	1	2.1	
Annulled	0	-	1	2.1	
Total	49	50.5	48	49.5	

(SD = Standard Deviation)

The PANSS baseline agitation cluster scores are presented in Table 2 and Figure 1. Mean scores were comparable for the risperidone and haloperidol groups (21.9 vs. 22.5, respectively; p=0.526). The end-study scores for risperidone and haloperidol groups were 14.3 ± 4.9 and 15.8 ± 5.3 respectively (p=0.161). There were significant changes for the risperidone group (-7.6 ± 4.7) and haloperidol group (-6.7 ± 5.0) from baseline to end-visit (p<0.0001) for both groups, however there was no significant difference in the magnitude of change between the two groups (p=0.393).

The mean total PANSS scores, PANSS disorganized thoughts cluster scores, PANSS uncontrolled excitement /hostility cluster scores and PANSS anxiety / depression cluster scores at baseline and end follow-up per treatment are presented in Table 2 and Figure 1. Baseline values were comparable for both groups on all parameters. Changes from baseline to end follow-up for both treatment arms on all parameters showed significant (p<0.0001). There were no significant differences in the magnitude of change between the two groups for all parameters observed.

Figure 1. PANSS scores

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Figure 1. PANSS scores

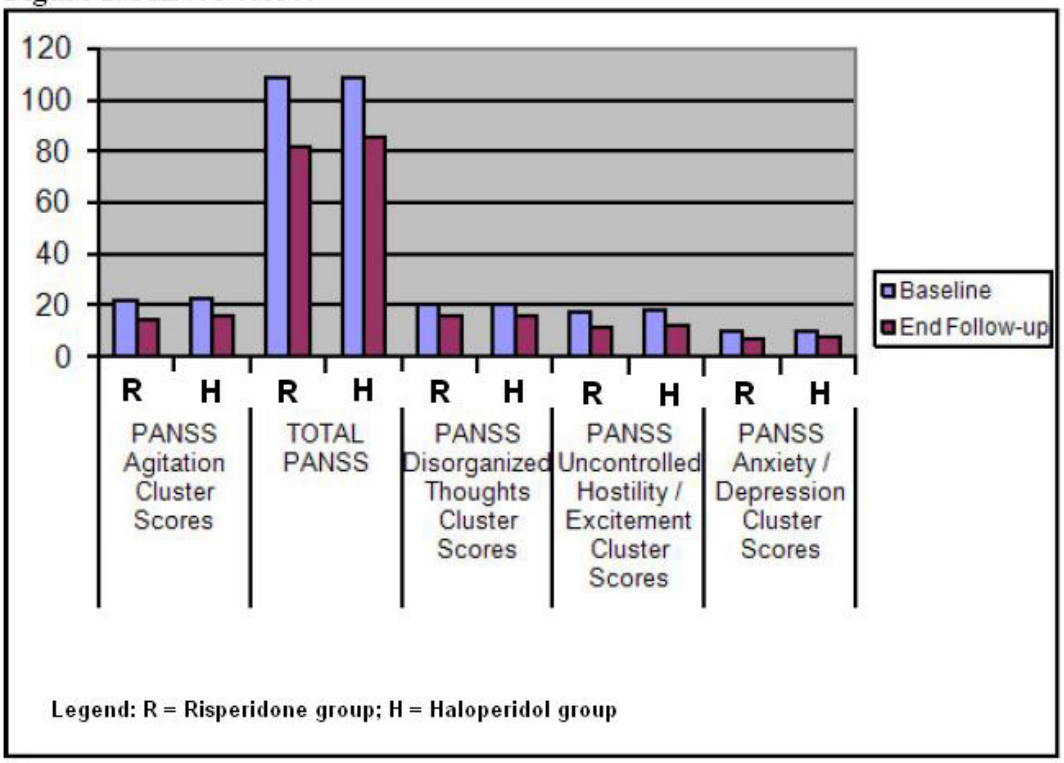


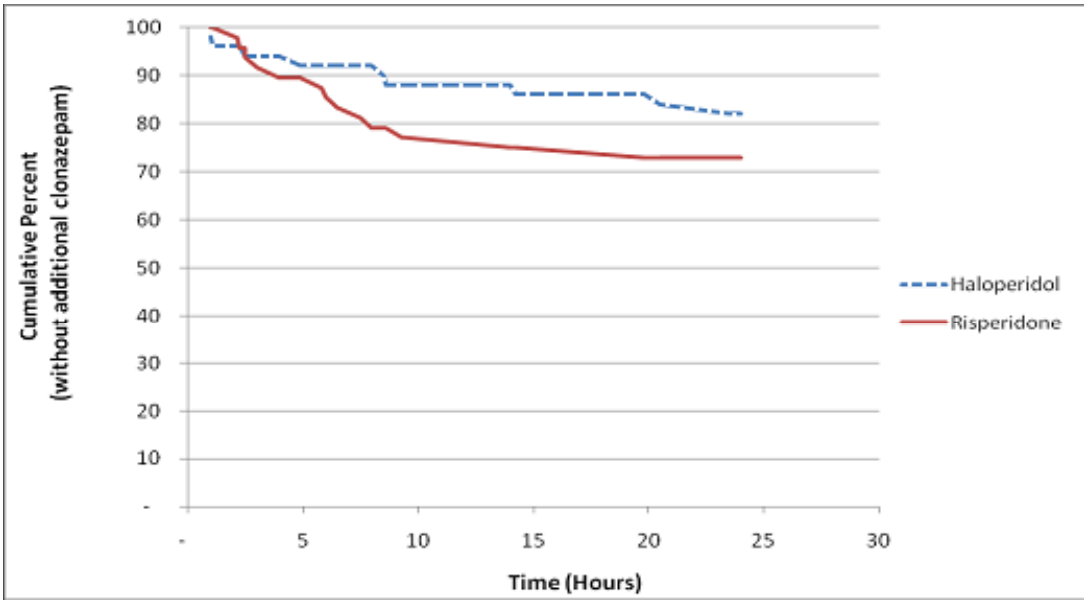
Table 2. PANSS scores

Mean ± SD	Baseline	End Follow-up	Change[1]	*p*-value (R vs. H)
PANSS Agitation Cluster Scores				
Risperidone	21.917 ± 4.068	14.333 ± 4.861	-7.583 + 4.708	0.393
Haloperidol	22.520 ± 5.215	15.780 ± 5.254	-6.74 + 5.005	
TOTAL PANSS				
Risperidone	108.479 ± 13.576	81.500 ± 20.012	-26.979 + 16.142	0.264
Haloperidol	108.820 ± 21.125	85.820 ± 21.710	-23 + 18.774	
PANSS Disorganized Thoughts Cluster Scores				
Risperidone	19.875 ± 3.728	15.750 ± 4.008	-4.125 + 3.133	0.827
Haloperidol	20.080 ± 4.948	16.120 ± 4.698	-3.96 + 4.228	
PANSS Uncontrolled Hostility / Excitement Cluster Scores				
Risperidone	17.167 ± 3.417	11.042 ± 4.016	-6.125 + 4.155	0.441
Haloperidol	17.640 ± 4.615	12.180 ± 4.341	-5.46 + 4.343	
PANSS Anxiety / Depression Cluster Scores				
Risperidone	9.958 ± 3.439	6.979 ± 2.436	-2.979 + 3.179	0.090
Haloperidol	9.460 ± 3.553	7.500 ± 2.873	-1.96 + 2.695	

[1] all change from baseline to end follow-up; $p<0.0001$; R vs. H = Risperidone vs. Haloperidol.

Figure 2 presents the time to additional clonazepam use as a survival curve. The mean time to additional clonazepam use for risperidone group is 19.39 hours and 21.38 hours for haloperidol group (p=0.2670).

Figure 2. Survival Curve of time to additional clonazepam use by treatment group



Log ranks test, p=0.2670

Table 3 presents the frequency of additional clonazepam use in both groups. The Table presents the clonazepam usage per treatment group. The proportion of at least one additional clonazepam dose as well as the incidence of additional clonazepam use is numerically higher in the risperidone group, but this has not achieved statistical significance (27% vs. 18%, p = 0.2818 and 33% vs. 20%, p=0.1370, respectively).

Table 3. Additional clonazepam use per treatment group

	Risperidone		Haloperidol	
	No.	%	No.	%
At least one additional dose of Clonazepam[1]	13	27.1	9	18.0
Incidence of Clonazepam use[2]	16	33.3	10	20.0

[1] p=0.2818, RR=1.50 (0.71 – 3.19)
[2] p=0.1370, RR=2.00 (0.80 – 5.00)

Efficacy wise, the results of the study indicates that use of risperidone oral solution coupled with clonazepam tablets improves not only the PANSS agitation cluster scores but the total PANSS scores and the other PANSS subscale scores of patients in the same degree as IM haloperidol. This confirms that what was observed in other studies with lorazepam as adjunct drug. [3-5,9].

The time to clonazepam use, the proportion of at least one additional dose of clonazepam and the incidence of clonazepam use was stistically similar in both groups. However, there seems to be a trend toward a higher incidence of total additional clonazepam use (33% vs. 20%, p=0.1370). A larger sample size would be necessary to establish if there is indeed a higher incidence of additional clonazepam use with oral risperidone in these patients. However, the magnitude of the difference is small and this should be seen in the light of the multiple benefits of oral administration vs. IM administration of antipsychotics in these patients. Achieving the same PANSS improvement, even at the expense of a slightly higher additional clonzepam use is clearly preferable considering that the risks associated with needle pricks and the perception of a coercive and abusive treatment modality are eliminated.

There was no serious adverse event reported in this 24-hour study. The only non-serious adverse event noted in both groups was sedation. At baseline, none of the risperidone group experienced sedation while 2 (4%) of the haloperidol group experienced slight sedation (p=0.495). At the end of follow-up, 33% of the risperidone group and 36% of the haloperidol group experienced at least slight sedation. The distribution of the proportion of slight sedation (21% vs. 22%), moderate sedation (8% vs. 10%) and fallen asleep (4% vs. 4%) did not significantly differ between both groups (p= 0.990).

Discussion

Oral risperidone was shown to be comparable to intramuscular haloperidol in the treatment of acute psychotic agitation in terms of efficacy and safety. Mean PANSS agitation cluster scores and total PANSS scores were similar at baseline and significantly improved in both groups. The magnitude of improvement were similar in both groups. The same is true for the other PANSS subscale cluster scores (disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression subscales) and clinical global impression. Mean time to clonazepam use and proportion of at least one additional dose of clonazepam, as well as the incidence of additional clonazepam use were also not statistically different between the two groups. No serious adverse event was reported in the 24-hour study and sedation was the only non-serious adverse event noted, the frequency of which also did not differ in both groups.

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