

A COST-ANALYSIS OF RISPERIDONE IN THE TREATMENT OF CHRONIC SCHIZOPHRENIA WITH PREDOMINATING NEGATIVE SYMPTOMS IN HONG KONG

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ABSTRACT

A comparative study of risperidone and conventional anti-psychotic therapy was performed for out-patients with schizophrenia with predominantly negative symptoms. After 3 months, there was a significant change in the Brief Psychiatric Rating Scale, Scale for Assessment of Negative Symptoms and Clinical Global Impression scores in the patients receiving risperidone, together with a better employment status. Both treatments appeared to be cost-beneficial, but risperidone was more cost-effective compared with conventional anti-psychotic therapy for this group of patients. Various limitations of the study are discussed and some clinical implications that warrant further studies to confirm the present findings have been suggested.

Keywords: *Chronic Disorder; Cost-analysis; Negative Symptoms; Risperidone; Schizophrenia*

INTRODUCTION

Patients with schizophrenia exhibit both positive and negative symptoms. The latter appears to be more associated with structural abnormalities,¹ but is not particularly responsive to conventional neuroleptic medications.² Those patients with predominant negative symptoms are particularly difficult to treat,³ and usually experience a chronic deteriorating course with poor prognosis and severe multiple handicaps, creating a burden to their families and society.

The underlying neuro-biochemistry of schizophrenia is quite exciting, with involvement of both the 'dopamine' or DA system⁴ and the 'serotonin' or 5HT system.⁵ Atypical neuroleptic drugs such as clozapine⁶ and risperidone⁷ have recently appeared in the market and the manufacturers claim that they have both DA and 5HT antagonistic properties. However, clozapine has the notorious toxic potential of agranulocytosis and thus requires close white-cell monitoring. This procedure has frightened many potential patients who may benefit from the drug. On the other hand, risperidone appears to be much safer,⁸ even if taken in excessive amounts. Overseas studies show that risperidone has therapeutic effects for both positive and negative symptoms.^{9,10} There are few studies in Chinese populations and, so far, none have been performed in Hong Kong Chinese. Yu *et al.*¹¹ prescribed risperidone to 60 schizophrenic patients in Beijing for eight weeks and found an 88% improvement (with 64% marked improvement) in patients with positive or negative symptoms, with an optimal dosage of 5 to 6.5 mg per day. Zhang

*et al.*¹² compared risperidone with clozapine in a randomised sample of 64 schizophrenic patients in Harbin, Heilongjiang, and found risperidone superior for treating patients with positive or negative symptoms, with minimal side-effects. Besides the cross-cultural or genetic differences between Chinese and non-Chinese schizophrenic patients, it would be useful to conduct a study to assess its efficacy locally, and to look especially on the effects of the medication on negative symptoms and the process of rehabilitation.

OBJECTIVE

An open clinical prospective trial was performed to compare the effects of the atypical neuroleptic, risperidone, with those of conventional anti-psychotic medications in the treatment of chronic schizophrenic patients with predominantly negative symptoms. The study also provided a cost-benefit analysis, modified to a cost-effectiveness comparison between risperidone and conventional neuroleptics. An intent-to-treat approach was used to reflect the actual clinical situation.

METHODOLOGY

SUBJECT SELECTION

Between September and December 1997, all consecutive schizophrenic patients attending the Western Psychiatric Centre in Hong Kong were screened. The eligibility criteria included the following:

- Inclusion criteria
 - schizophrenic patients (diagnosed using International Classification of Diseases/Diagnostic and Statistical Manual of Mental Disorders criteria)
 - taking regular neuroleptic therapy for at least 2 years (criterion for chronicity)
 - a score of at least 35 on the Scale for the Assessment of Negative Symptoms (SANS)¹³
 - informed consent
- Exclusion criteria
 - aggressive, drug-abusing patients
 - co-existing organic disorders or mental retardation
 - those taking other novel anti-psychotics such as olanzapine or clozapine
 - those receiving special treatment regimens such as case management or family therapy
 - in-patients with schizophrenia.

METHODS

Owing to time constraints and difficulty in recruiting sufficient patients to participate in the trial, patients were not randomly assigned to the two treatments. Once an appropriate number of patients consented to participate in the trial, they switched within 2 weeks to the novel anti-psychotic therapy for 3 months. If they showed significant clinical improvement, they would continue to be maintained with this medication. Patients taking conventional anti-psychotic therapy and fulfilling the same criteria were recruited for comparison.

In the experimental treatment group, conventional medications were reduced and stopped within 1 to 2 weeks, and risperidone started instead. The initial dose was low but was increased, depending on improvements, until a maximum of 8 mg per day was reached. Unless there were sufficient clinical reasons, the optimal regimen would be maintained for 3 months.

ASSESSMENT

Besides the essential socio-demographic and clinical data, the following instruments were used for regular assessments:

- The Brief Psychiatric Rating Scale (BPRS),¹⁴ the Scale for Assessment of Positive Symptoms (SAPS)¹⁵ and the SANS

- The Clinical Global Impression (CGI)
 - Employment status and dependency on public assistance.
- These assessments were performed at the beginning and end of the 3-month trial.

RESULTS

In total, 47 patients were recruited into the study, with 22 patients in the experimental treatment group and 25 in the control group. Three in-patients were mistakenly included in the treatment group at the start of the study, however, in order not to bias the cost analysis, they were excluded from the data analysis.

COMPARISON OF BASELINE DATA

Socio-demographic Data

Table 1 shows that there was no difference between the two groups regarding age, sex, or duration of illness. Although the mean duration of illness did not show a statistical significance, subgrouping of the data did show more patients with a duration of illness of 2 to 4 years in the experimental group. Nevertheless, if the subgrouping was structured at intervals of 5 years (≤ 5 , $> 5 - \leq 10$, > 10 years), then the difference became insignificant.

Clinical Assessment

The positive and negative symptoms of the two groups were similar at the start of the trial (Table 2). However, at the end of the study, there were some significant differences in scores in the various instruments used.

All patients in the treatment group with high SAPS scores at the start of the trial now had low scores. However, the changes were not statistically significant owing to the small number of patients involved. Thus, the treatment group fared better only in the BPRS, SANS and CGI scales. Furthermore, since there were no clinical relapses or death during the 3-month trial period, the difference between the two groups in this area could not be considered significant. It is interesting to note that more patients in the treatment group were discharged from the day hospital during the study period, compared with the control group. However, this difference was not statistically significant.

Table 1: Comparison of age, sex, and duration of illness

	Treatment group	Control group	Statistical significance
Age			
Range	17 - 49	21 - 51	$t = 1.50$
Mean (\pm SD)	33.00 (\pm 9.87)	36.80 (\pm 7.39)	$p > 0.05$
Sex			
Male	4	9	$\chi^2 = 1.86$
Female	18	16	$p > 0.1$
Duration of illness			
Mean (months) (\pm SD)	130.86 (\pm 107.4)	130.08 (\pm 75.8)	$t = 0.03; p > 0.1$
Subgrouping			
2 - 4 years	9	2	$\chi^2 = 7.427$
< 5 years	5	11	$p < 0.05$
> 10 years	7	1	

Table 2: Comparison of clinical ratings between the beginning and end of the study

	Treatment group		Control group		Significance
	Baseline	Conclusion	Baseline	Conclusion	
Brief Psychiatric Rating Scale					
Range	8 - 26	5 - 17	1 - 29	2 - 26	
Mean (\pm SD)	14.86 (\pm 6.32)	9.59 (\pm 4.42)	14.16 (\pm 6.34)	13.26 (\pm 5.33)	
ANOVA					
Within groups					F = 15.64 p < 0.001
Between groups					F = 0.63 p > 0.1
Compare treatment group (beginning and end results)					t = 5.49 p < 0.0001
Compare control group (beginning and end results)					t = 0.85 p > 0.1
Scale for Assessment of Positive Symptoms					
Range	0 - 34 [†]	0 - 8	0 - 43 [†]	0 - 35	
Mean (\pm SD)*	5.30 (\pm 10.75)	1.14 (\pm 2.62)	5.00 (\pm 9.91)	4.00 (\pm 8.02)	
* Since SD value > 2 x mean value (a number of subjects had minimal or no positive symptoms) t test was not meaningful. Using non-parametric test by grouping the scores:					
\leq 10	17	22	21	21	
11-20	3	0	2	3	
\geq 21	2	0	2	1	
Compare both groups at the beginning					$\chi^2 = 0.431$ p > 0.5
Compare both groups at the end					$\chi^2 = 3.85$ p > 0.05
Compare treatment group (beginning and end results)					$\chi^2 = 5.64$ p > 0.05
Compare control group (beginning and end results)					$\chi^2 = 0.139$ p > 0.5
Scale for Assessment of Negative Symptoms					
Range	35 - 75	12 - 76	39 - 68	4 - 77	
Mean (\pm SD)	53.82 (\pm 11.62)	39.82 (\pm 16.62)	51.50 (\pm 12.73)	53.14 (\pm 8.98)	
ANOVA					
Within groups					F = 49.71 p < 0.001
Between groups					F = 2.14 p > 0.5
Compare treatment group (beginning and end results)					t = 6.73 p < 0.001
Compare control group (beginning and end results)					t = 0.062 p > 0.05
Clinical Global Interview					
Range	3 - 5	1 - 4	3 - 4	1 - 4	
Mean (\pm SD)	3.95 (\pm 0.64)	1.13 (\pm 1.01)	3.79 (\pm 0.37)	3.63 (\pm 0.57)	
ANOVA					
Within groups					F = 13.88 p < 0.001
Between groups					F = 4.95 p < 0.05
Initial comparison between groups					t = 1.52 p > 0.1
Compare treatment group (beginning and end results)					t = 4.53 p < 0.0001
Compare control group (beginning and end results)					t = 0.83 p > 0.1
Clinical Status					
Day patients	12	5	7	5	
Out-patients	10	17	18	20	
Initial comparison between groups					$\chi^2 = 3.43$ p > 0.05
Compare treatment group (beginning and end results)					$\chi^2 = 4.70$ p < 0.05 [†]
Compare control group (beginning and end results)					$\chi^2 = 0.44$ p > 0.1
[†] If Yates' correction was used					$\chi^2 = 3.45$ p > 0.05

Abbreviation: ANOVA = analysis of variance.

EMPLOYMENT STATUS

The difference between the two groups as regards employment is shown in Table 3. Owing to the small numbers in some subgroups, the full-time and part-time employment status have been combined for statistical analysis. There is no significant difference between the pre-trial employment status, although the treatment group were employed to a lesser extent than the control group. However, the pre- and

post-study comparison for the treatment group showed a statistically significant difference. Comparison of the mean duration of illness between those who became employed and those remaining unemployed did not show any statistical difference ($t = 0.76$; $p > 0.5$), suggesting that employment success was not affected by the chronicity of the disorder.

There are two forms of public assistance given to psychiatric patients. If their families are significantly disrupted

Table 3: Comparison of employment status and dependence on public assistance

	Treatment group		Control group		Significance	
	Baseline	Conclusion	Baseline	Conclusion		
Employment status						
Full-time	1	5	3	4		
Part-time	5	12	9	9		
Unemployed	16	5	13	12		
Initial comparison between groups					$\chi^2 = 2.26$	p > 0.05
Compare treatment group (beginning and end results)					$\chi^2 = 9.11$	p < 0.01
Compare control group (beginning and end results)					$\chi^2 = 0.18$	p > 0.1
PA dependence						
DSA	8	6	3	2		
CSSA + DSA	5	4	7	7		
No PA	9	12	15	16		
Initial comparison between groups					$\chi^2 = 3.93$	p > 0.1
Compare treatment group (beginning and end results)					$\chi^2 = 0.82$	p > 0.1
Compare control group (beginning and end results)					$\chi^2 = 0.23$	p > 0.1

Abbreviations: PA = public assistance; DSA = disability allowance; CSSA = comprehensive social security assistance.

by their disorders, they could receive a disability allowance (DSA) currently worth HK\$1,200 (US\$150) per month. However, if their families are sufficiently poor, they could be granted the additional comprehensive social security assistance (CSSA) which is a monthly allowance of HK\$3,140 (US\$400). Table 3 shows that at the end of the study, 3 fewer patients in the treatment group were dependent on social allowances compared with only 1 fewer in the control group, although the numbers are too small to be statistically significant.

ECONOMIC ANALYSIS

The cost-benefit analysis was obtained by calculating the various costs involved in the consumption of services. Direct costs can be clinical or social, whereas the indirect costs were negligible as no obvious mortality or morbidities occurred. Intangibles are not included here because of uncertain accounting value. The benefits can be calculated from the employment earnings and the decreased dependence on public assistance (Table 4).

There was an increase in the number of patients in the treatment group discharged from the day hospital to the out-patient unit. In the control group, the number was smaller, however, there was no statistically significant difference between the two groups. Comparison of patients who remained in the day-hospital and those discharged from the day-hospital did not show any statistical difference in the mean duration of illness ($t = 0.45$; $p > 0.5$). There was an increase in the actual number of out-patient attendances in the treatment group because of the necessity of close drug titration when risperidone was increased. However, the number of attendances per patient was similar for the two groups after stabilisation.

Patients in the treatment and control groups showed a positive balance, meaning that both treatments were cost-beneficial. However, risperidone appeared to be more cost-effective, with a possible improvement in the quality of life. It should be noted that there was an uneven number of patients initially attending the day hospital, which favoured

the risperidone group. If the two items of day hospital and out-patient attendance were not calculated, the gain would then be greater for the control group (by HK\$150 per patient per month).

DISCUSSION

The improvement with risperidone in patients with negative symptoms was remarkable. This was consistent with the meta-analysis of six double-blind trials by Carman *et al.*,¹⁶ which showed that risperidone had a significantly higher response rate for patients with negative symptoms compared with haloperidol, perphenazine, or zuclopenthixol. However, the response rate differed from the study by Claus *et al.*⁹ (1992) which showed a similar improvement in chronic schizophrenics with negative symptoms for risperidone and haloperidol after 12 weeks, using the Positive and Negative Symptom Scale.¹⁷ Another meta-analysis, including Claus *et al.*'s study,⁹ concluded that risperidone had a better response in chronic schizophrenia than conventional neuroleptics, especially for patients with negative symptoms and symptoms of general psychopathology.¹⁸

For schizophrenia with positive symptoms, this study showed a non-significant decrease in scores for the treatment group, perhaps due to the fact that the patients were not really psychotic when they were recruited and therefore had a low baseline SAPS score. Unless there was an extremely marked improvement for a large proportion of patients, any difference in the scores would not be statistically significant. Unfortunately, there was no specific measure of extra-pyramidal side-effects for the two groups. Nevertheless, the clinical impression was that risperidone did have some mild effects but not serious enough to merit anti-cholinergic medications.

Besides the clinical improvement, the employment status showed a more favourable result with risperidone. Whereas the treatment group showed a significantly higher number of patients gaining employment, the control group remained static. The latter result was not unexpected, as another study

Table 4: Cost-effective analysis between patients receiving risperidone or conventional therapy (1997/1998 rate in HK\$*)

Items	Mean unit cost (month)	Treatment group				Control group			
		Baseline	Conclusion	Difference	Saving	Baseline	Conclusion	Difference	Saving
Clinical costs									
Day hospital [†]	14,680	12	5	7	102,760	7	5	2	29,360
OPD [‡]	623	10	17	-7	-4,361	18	20	-2	-1,246
CPNS [‡]	767	8	9	-1	-767	4	3	1	767
MSW [‡]	100	19	19	0	0	13	13	0	0
Medication [§]	969	0	22	-22	-21,318	0	0	0	0
Risperidone	141	22	0	22	3,102	25	25	0	0
conventional									
Social costs									
Half-way house	6,000	2	2	0	0	5	5	0	0
Shelter workshop	1,950	5	12	-7	-13,650	9	9	0	0
Public Assistance									
CSSA	3,995	5	4	1	3,995	7	7	0	0
DA	1,200	8	6	2	2,400	3	2	1	1,200
Earnings									
Full-time	5,000	1	5	4	20,000	3	4	1	5,000
Part-time	1,300	5	12	7	9,100	9	9	0	0
Balance					101,261				
Average/patient		22 patients			4,602	25 patients			1,403

* US\$1 = HK\$7.8.

[†] Cost of the district general hospital where the study was performed.[‡] Mean salary scale divided by contact working hours.[§] Mean costs of all the patients involved.^{||} Social Welfare Department standard rate.

Abbreviations: OPD = out-patient department; CPNS = community psychiatric nursing service; MSW = medical social worker; CSSA = comprehensive social security allowance; DA = disability allowance.

on the use of risperidone also showed a negative result for the control group.¹⁹

It should be noted that the very low unemployment rate in Hong Kong at the time of the study (less than 2.5%) and the rehabilitation of some patients at the day hospital could have played a part in this positive outcome for the treatment group. Unfortunately, cognitive deficits, mood change, and other psychosocial functioning or quality of life have not been explored in this study. The clinical impression so far seems to favour risperidone over conventional neuroleptics.

It appeared that both treatments were cost-beneficial for these patients, but that risperidone was more cost-effective compared with conventional anti-psychotics (by HK\$3,200 per patient per month). Although risperidone is more expensive per dosage than conventional medications, this increase in direct costs could almost be offset by the savings from increased earnings and the decreased consumption of day hospital care. Given a longer period, the costs for risperidone could perhaps decrease as the dosage is reduced. However, if day hospital costs were not considered, then there would be a slightly higher benefit for the conventional drug regimen. In the USA, Schiller *et al.*²⁰ found that total treatment costs for risperidone and standard antipsychotic medication were similar in the out-patient setting. Likewise, Nightingale *et al.*²¹

compared traditional agents with risperidone and concluded that the use of risperidone has an economic impact beyond that of the drug costs, as evidenced by a significant decrease in in-patient care. In Canada, Albright *et al.*²² found a reduction of health care resource utilisation and costs following the use of risperidone for schizophrenic patients previously treated with standard medications. Applying the UK costs and resources to the findings of a Swedish trial with risperidone, Guest *et al.*²³ found that increased costs of risperidone and residential accommodation could be offset by decreased hospitalisation. If there were similar results for in-patients in Hong Kong, then the savings from hospital care would be very substantial (as is the impression of the authors for some in-patients).

STUDY LIMITATIONS

This study was nevertheless affected by the following problems. Firstly, owing to lack of time of the qualified psychiatrists, only the BPRS was rated blindly, and there may be a subjective bias for the SANS and SAPS scales. The CGI was rated by the patients' doctors, and could be considered relatively blind. Fortunately, the various scales matched closely, and their clinical judgement was closely correlated with the employment outcome, which should be very objective, for the two groups.

Secondly, in order not to delay the study, and with the stringent admission criteria, the number of eligible patients at the Western Psychiatric Centre was limited, and it was not possible to randomly assign patients to either group. Since patients with chronic and severe negative symptoms could not be recruited into this study (explaining the relatively low cut-off score for SANS in the inclusion criteria), the present findings could not be generalised to those with very serious negative symptoms.

Thirdly, even though the two groups were similar in age, sex, and duration of illness, they were not matched for other variables such as educational level, marital status, family support, etc. However, there was an unintentional recruitment of a larger number of patients with a lower duration of illness in the treatment group, although this was not significant. This could bias the results and affect the true response to treatment in the day hospital and perhaps the outcome of employment, thereby affecting the economic balance. In future, there should be more exact matching of the duration of the disorder. Likewise, there was an apparent excess of day patients in the treatment group (although again this was not statistically significant), but this difference should be reduced in future studies.

Fourthly, since only the treatment group switched medication, there could be a 'halo' effect in favour of this group. However, it is ethically difficult to switch patients in the control group to another conventional medication of no clinically suggested superiority, and perhaps a placebo drug could be added for the control group to balance the halo effect. Further studies in this area should perhaps explore these areas. Indeed, quality of life, social support, patient satisfaction, and that of their carers could also be studied.

Fifthly, the duration of the trial was short (3 months) and thus long-term outcome was not examined. It appears that some patients with chronic disease may need a longer treatment period for obvious changes to occur, especially in the process of rehabilitation.¹⁹ Unfortunately, owing to the cost of this medication, even in the public health sector, a longer trial was not feasible.

Last but not least, the balance sheet was performed rather arbitrarily, based on some general assumptions such as the mid-point salary of staff (disregarding their grading and actual salaries), and that patients would retain the status quo throughout the year. More details were required, and there should also be some estimation of the costs to family members in future studies.

CLINICAL IMPLICATIONS

These results imply that risperidone could be a remedy for quite a number of chronic schizophrenic patients. Despite the limitations described above, it follows that those schizophrenic patients with predominantly negative symptoms and characteristics similar to that of the treatment group should be given the benefit of a trial of this medication for 3 months. Those who respond well should be maintained by the drug for as long as the clinical conditions require, while those who fail to respond should be given conventional treatment.

Since this study was the first of its kind for this group of patients in Hong Kong, further research is much needed to find out which particular group of chronic schizophrenic patients would best benefit from the novel antipsychotic and who would not, and to determine the optimum dosage. To extend these principles further, similar trials should be performed, preferably a randomised, double-blind, controlled trial with better matched subjects. The trials could be conducted for varying periods of treatment, and for schizophrenic patients with different degrees of illness severity. If resources are available, there should be a more comprehensive assessment of other outcomes such as cognitive dysfunction, patient satisfaction, and quality of life.

CONCLUSION

This study suggests that within a period of 3 months, risperidone was more cost-effective than conventional medications in the short-term treatment of chronic stabilised schizophrenic patients with predominant negative symptoms, and could improve the social employment status for these patients. However, with the various inherent and incidental limitations of the study, more refined and long-term studies should be performed to ascertain the clinical and economic significance of these findings.

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