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The Use of Risperidone-combination and Haloperidol-combination in Schizophrenia Patients; a Cost Utility Analysis in Psychiatric Hospital of Prof. V. L. Ratumbuysang

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ABSTRACT

Introduction: Various clinical factors related to the life quality of schizophrenic patients have been reported.

Objective: This research aims to evaluate the cost and utility of the use of risperidone or haloperidol combinations on schizophrenic patients in the cases at Prof. V. L. Ratumbuysang Psychiatric Hospital North Sulawesi Province of Indonesia.

Methods: This is an observational study with a Cohort design. Sampling was done using a purposive sampling method for all 82 patients and finally obtained 22 patients for the risperidone-combination group and 28 patients for the haloperidol-combination group. Data were collected from patient's medical records by using retrospective approaches from April to July 2018 and prospectively by using a short-form questionnaire. The utility based on the quality of life was assessed by the 36-item Short Form (SF-36) questionnaire. The quality-adjusted life years (QALY's) for haloperidol-combination were recorded as 0.433 which more high than the risperidone-combination group, which recorded as 0.423 Average cost-effectiveness ratio (ACER) for the risperidone-combination group was IDR 5.813.716,13/QALY's, which more cost-effectively than the haloperidol-combination group of IDR 6.454.822,17/QALY's with the record of incremental cost-effective ratio (ICER) of IDR 33.573.600/QALY.

Results: The result of sensitivity test to 25% total cost increase for the risperidone-combination group (IDR 7.267.145) and the 25% total cost decrease for the haloperidol-combination group has changed in ACER values with compared to the baseline of the risperidone-combination group.

Conclusion: Risperidone-combination is the dominant therapeutic choice related to cost and QALY's in the treatment for schizophrenic patients.

Key Words: Cost-utility, Schizophrenia, Risperidon-combination, Haloperidol-combination

INTRODUCTION

Schizophrenia is a chronic mental disorder that affects more than 21 million people worldwide, and changes the way people think, feel, and act.[1,2] The incidence of schizophrenia is 2 to 5 cases per 1000 population per year, and its prevalence is 1% of the world's population. In Indonesia, especially in North Sulawesi Province, the prevalence of schizophrenia is about 0.8 per 1000 populations.[3] Pharmacotherapy by using antipsychotics is the first-line choice in schizophrenia therapy.[4,5] Meta-analysis studies showed that atypical-antipsychotics like risperidone is more effective than typical-antipsychotic like haloperidol.[6] But there is a risk of side effects for either haloperidol or risperidone, thus in the practice, those antipsychotics were combined trihexyphenidyl.[4] As a chronic disease, schizophrenia is associated with a decrease in productivity and a low quality of life.[7] Various clinical factors related to the life quality of schizophrenic patients have been reported. A *cross-sectional* study stated that psychopathological symptoms have a stronger correlation with a community function.[8] Correlation between atypical antipsychotic with cognitive function also revealed there is a significant improvement.[9] Even though atypical antipsychotic (risperidone) has been recognized as the first-line choice for schizophrenia therapy in the real clinical practice, the typical antipsychotic is still given to schizophrenia patients (Fujimaki 2012),[10] similar to the practice in Prof. Ratumbuysang

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Hospital where the typical antipsychotic is still the choice of clinician. This is associated with the high financial burden in the treatment of schizophrenia,[11] the cost of risperidone relatively higher than haloperidol. Hence, a pharmacoeconomic study related to the quality of life is important. Using the cost-utility analysis (CUA) method, this study aims to assess the cost-utility of using risperidone-combination and haloperidol-combination in the Prof. Ratumbuysang Psychiatric Hospital, North Sulawesi Province of Indonesia.

MATERIALS AND METHODS

Study Design

The design of this study was a non-experimental or observational with a cohort study design. Data were obtained retrospectively from the patient's medical record as a secondary data and prospectively by the assessment of the patient's quality of life by using the 36-item Short Form (SF-36) as a primary data. Interviews for patients were conducted in two stages to obtain initial and final scores with two months interval. The design of this study is approved by the ethical consideration related toward all subjects were willing to fill the informed after received an explanation from the researcher.

Subjects of Study

The Subjects of this study were schizophrenic inpatients in Prof. Ratumbuysang Psychiatric Hospital in North Sulawesi Province of Indonesia, started from April to late July 2018. The number of subjects was obtained by using the *role of thum* method accompanied by *purposive sampling* technique. Total subjects which obtained were 50 samples, 22 patients were using risperidone-combination and 28 patients using haloperidol-combination. Patients matched to the inclusion category were the patients diagnosed with schizophrenia and had been received risperidone-combination and haloperidol-combination for at least 2 months or 8 weeks. Haloperidol dose is 4-6 mg/day, and risperidone dose is 5-15 mg/day. Every patient also treated with anticholinergic trihexyphenidyl in dose 5-15 mg/day as the combination for antipsychotics. Patients with the incomplete medical record refused to fill the informed consent and included in default criteria categorized in exclusion criteria in this study. The use of other medicines for agitation or insomnia (diazepam 2-10 mg/day and lorazepam 1-10 mg/day); mood stabilizer (lithium carbonate 200-400 mg/day); and vitamin (folic acid 0.4 mg and vitamin B complex) also included in this study without interfering the effectivity of antipsychotic.

Assessment of the Quality of Life

The quality of life of patients was assessed by an international standard of Short Form 36 (SF-36) instrument.[12] The SF-36 form has been widely used to assess function and health generally to the improvement of schizophrenic patient symptoms. The SF-36 form consists of 36 questions that covered 8 domains: physical function, physical role, emotional role, vitality, pain, mental health, general health and social function.[12] Furthermore, these 8 domains grouped into 2 assessment components, such as mental component (consists of vitality, emotional role, social role, and mental health) and physical component (consists of physical function, general health, pain, and physical role).[13] The SF-36 form assessment is done through two stages: the first stage is converted to the value into 0-100; the second stage is averaging convention values of every domain.[13] Score above 50 is interpreted as good quality of life and score under 50 is interpreted as poor quality of life.[14]

Drugs

Drugs (risperidone-trihexyphenidyl and haloperidol-trihexyphenidyl combinations) and other drug supplements, hospitalization, clinician visit, treatments, administration, and other supported, like laboratory costs were cost components measured in this study. The drug costs were obtained from The 2018 Drug e-catalogue which has been set by the government through the department of LKPP. The costs of hospitalization, clinician visits, treatment and administration were based on the BPJS insurance perspective. The cost of laboratory included in support cost which has been set by the North Sulawesi Local Regulation No. 2 the Year 2016.

Utility

Utility unit used in this study was the quality-adjusted life years (QALYs) score. Utility score illustrates by the assessment of the patient's quality of life set by The Ministery of Health of Indonesia.[15] The assessment was carried out subjectively based on patients quality of life score associated with their health, which is, in this case, the quality of life score was obtained from the percentage of score increasing from the initial to the final treatments by using the SF-36 questionnaire.

Cost-Utility Analysis

In every group, the average cost-effectiveness ratio (ACER) is calculated by using a standard formula from the ministry of health of Indonesia as follows[15] :

$$\text{Cost-effectiveness ratio} = \frac{Cost}{Utility}$$

Furthermore, the alternative positioning of schizophrenia treatment based on cost-utility diagram was conducted (Figure 1). If the treatment position was located in column A and column I then it was necessary to calculate incremental cost-effectiveness ratio (ICER) with the standard formula from the ministry of health of Indonesia as follows[15] :

$$ICER = \frac{Cost\ drug\ A - Cost\ drug\ B}{Utilities\ drug\ A - Utilities\ Drug\ B}$$

Cost-Utility	Lower cost	Equal cost	Higher cost
Lower utility	A (need ICER calculation)	B -	C Dominated
Equal utility	D	E Midst	F
Higher utility	G Dominant	H -	I (need ICER calculation)

Figure 1: Diagram of alternative groups based on cost utilities.

Sensitivity Analysis

Sensitivity analysis is conducted to find out how the extent of change in cost or utility value was used to calculate the cost-effective ratio and could affect the conclusion. Sensitivity analysis was carried out by varying 25% of increase and decrease of the cost-utility analysis of antipsychotic to the total cost.[16]

Statistical analysis

The patient's demographic data was shown in the form of a percentage (frequency), and the age of patients was analyzed by using *Chi-Square Test*, while the patient's gender, occupation, and education were analyzed by *Independent Sample T-Test* as well. If the value of $p > 0.05$ it was interpreted as not significantly different. The quality of life value based on SF-36 also processed by using *Paired Sample T-Test* when data distributed normally and *Wilcoxon* test was used if the data were not distributed normally. If the value of $p < 0.05$, it was interpreted as significantly different.

RESULTS

Demographic Characteristic of Sample

Demographic characteristics of the two groups of patients, namely 22 patients with risperidone combination and 28 patients haloperidol combination, could be seen in detail in table 1. The average age of group risperidone-combination was 43.77 years (±10.94) and the group of haloperidol-combination was 39.86 years (±7.75). The group of risperidone-combination consisted of 63.6% female and 36.4% male, while in the group of haloperidol combination consisted of 57.1% female and 42.9% male. The occupation characteristics of the group risperidone combination were 81.8% unemployment and in the group of haloperidol combination was 96.4% unemployment. In the Education, sector shows that 50.0% in the group of risperidone combinations were high school graduates, and 53.6% of the group haloperidol combination were high school graduates. Each variable from the two groups was compared to each other than statistically analyzed. There is no significant difference between the two groups based on age, sex, occupation, and education characteristics.

Table 1: Demographic characteristic of patients.

Characteristic	Risperidone-combination (n=22)	Haloperidol-combination (n=28)	p
Age (year)	43.77(±10.94)	39.86(±7.75)	0.145[b]
Sex			
Male	8 (36.4%)	12 (42.9%)	0.861[a]
Female	14 (63.6%)	16 (57.1%)	
Occupation			
Unemployment	18 (81.8%)	27 (96.4%)	0.210[a]
Farmer	1 (4.5%)	0	
Civil servant	0	0	
Private sector	0	0	
Odd jobs	3 (13.6%)	1 (3.6%)	
Education			
Elementary	5 (22.7%)	1 (3.6%)	
Middle School	6 (27.3%)	12 (42.9%)	0.099[a]
High school	11 (50.0%)	15 (53.6%)	

a: Chi-Square Test; b: Independent Sample T-Test

Quality of life assessment using the SF-36 questionnaire

The result of initial and final scoring by using the SF-36 questionnaire to each domain and component from both groups was presented in table 2. In a risperidone-combination group, the final scores which were shown mean scores below to the normative score could only be found in physical role (19.32 ± 24.31), emotional role (25.50 ± 22.61) and social function domains (45.68 ± 21.29), while other domains and components shows mean scores were above to normative score. These mean that there was a significant improvement in quality of life in each domain and component in the risperidone-combination group with p-value < 0.05. It was different result found on the haloperidol-combination group which was the final scores shown mean scores to above normative score was the physical role (6.25 ± 12.95), emo-

tional role (14.14 ± 24.47), social function (46.64 ± 21.56), general health (49.57 ± 12.7), a physical component (43.07 ± 16.69) and mental component (44.78 ± 13.15), while other domains were above to the normative score (Table 2). These mean that there was a significant change in the physical function domain (p=0004), pain (p=0.038), and mental component (p=0.033).

Table 2: SF-36 Scores.

Domain	Risperidone-Combination		p-value	Haloperidol-Combination		p-value
	Initial	Final		Initial	Final	
Score Scale						
Physical Function (0-100)	65.68±(14.90)	73.14±(16.7)	0.001[b]	60.36±(20.50)	71.07±(16.35)	0.004[b]
Physical role (0-100)	6.82±(22.06)	19.32±(24.31)	0.005[b]	5.36±(15.74)	6.25±(12.95)	0.739[b]
Emotional Role (0-100)	4.50±(11.59)	25.50±(22.61)	0.000[b]	10.68±(28.70)	14.14±(24.47)	0.723[b]
Vitality (0-100)	40.91±(19.85)	58.64±(20.12)	0.000[a]	49.64±(20.68)	55.00±(15.51)	0.123[a]
Mental Health (0-100)	40.00±(20.05)	62.55±(16.54)	0.000[b]	50.43±(17.43)	56.14±(15.18)	0.084[a]
Social Function (0-100)	30.91±(18.44)	45.68±(21.29)	0.001[b]	39.04±(18.93)	46.64±(21.56)	0.067[b]
Pain (0-100)	41.91±(21.12)	59.50±(17.20)	0.000[b]	43.64±(19.35)	51.64±(19.34)	0.038[b]
General Health (0-100)	46.55±(18.77)	56.5±(16.2)	0.003[a]	47.50±(15.37)	49.57±(12.70)	0.328[b]
Group Scores						
Physical Components (0-100)	40.36±(14.72)	52.36±(15.06)	0.000[a]	37.6±(18.56)	43.07±(16.64)	0.092[b]
Mental Components (0-100)	29.23±(14.42)	48.273±(16.57)	0.000[a]	39.32±(15.24)	44.79±(13.12)	0.033[b]

SF-36, 36-item Short From the questionnaire
Data are rounded mean ± SD. a: Paired Sample T-Test, b: WilcoxconTest

Determination of utility cost was based on the increase in the percentage of SF-36 which result could be seen in table 3. There was no significant difference in the SF-36 average increase of value (p=0.681) between the two groups.

Table 3: Mean/Average of initial, final, and increase the value of SF-36.

SF-36	Risperidone-combination (n=22)	Haloperidol-combination (n=28)	p-value
Initial	0.413	0.430	0.739
Final	0.553	0.580	0.73
Increase	0.423	0.433	0.681

SF-36, 36-item Short Form questionnaire Statistical tested by using independent sample T-Test

The Average Cost-Effectiveness Ratio (ACER) for both groups could be seen in table 4. Risperidone-combination group yielded a lower ACER (IDR 5.813.822,13.-per-QALY) compared to haloperidol-combination group (IDR 6.454.822,17.-per-QALY). By placing the ACER alternative position of these two groups into the diagram of alternative based on cost-utility, (Figure 1), it was noted that risperidone-combination group was into column A which mean the column for low cost and low utility and haloperidol-combination group was into column I which mean column for high cost and high utility, thus an Incremental Cost-Effectiveness Ratio (ICER) calculation was necessary to proceed.

Table 4: The result of the average cost-effectiveness ratio (ACER).

Drugs	Utility (U)	Total Cost (B)	ACER (B/U)
Risperidone-combination	0.423	Rp. 2,459,202,-	Rp. 5,813,716.31,-
Haloperidol-combination	0.433	Rp. 2,794,938,-	Rp. 6,454,822.17,-

The result of Incremental Cost-Effectiveness Ratio (ICER) calculation could be seen in table 5 as follows;

Table 5: The result of ICER calculation for two months period of therapy to schizophrenic patients in Prof. DR. V. L. Ratumbuysang Psychiatric Hospital.

Antipsychotic Therapy	Cost (C) (IDR)	Utility (U)	ΔC	ΔU	ICER ΔC/ΔU
Risperidone-combination	2,459,202	0.423	-335,736	-0.01	33,573,600
Haloperidol-combination	2,794,938	0.433			

Sensitivity Analysis

A Sensitivity Analysis has been done for both groups, as shown in table 6. The results show that the risperidone-combination was sensitive to the 25% of cost-increase, and was also sensitive to the 25% of cost-decrease into the haloperidol-combination group.

Table 6: Sensitivity analysis of the risperidone-combination and haloperidol-combination to schizophrenia patients in Prof. DR. V. L. Ratumbuysang Psychiatric Hospital.

Sensitivity	Cost (B)	Utility (U)	REB (B/U)
Risperdione-Combination			
0% Decrease	IDR 2,459,202	0.423	IDR 5,813,716
25% Decrease	IDR 1,844,402	0.423	IDR 4,360,287
50% Decrease	IDR 1,229,601	0.423	IDR 2,906,858
25% Increase	IDR 3,074,003	0.423	IDR 7,267,145
50% Increase	IDR 3,688,803	0.423	IDR 8,720,574
Haloperidol-Combination			
0% Decrease	IDR 2,794,938	0.433	IDR 6,454,822
25% Decrease	IDR 2,096,204	0.433	IDR 4,841,117
50% Decrease	IDR 1,397,469	0.433	IDR 3,227,411
25% Increase	IDR 3,493,673	0.433	IDR 8,068,528
50% Increase	IDR 4,192,407	0.433	IDR 9,682,233

DISCUSSION

Several studies reported that schizophrenic patients obtain a better quality of life when using atypical antipsychotics than when they are using typical antipsychotics.[17,18] In this study, the result of SF-36 score for both groups of the patient, shows final score is below the normative score were the domain of physical role, emotional role, social function and physical component associated with an activity factor, and the side effect of therapy as well. The lack of activity and the utilization of free time to do activities in schizophrenic patients was lead to the poor quality of life, as well as the side effects of the therapy, like tardive dyskinesia, pseudo-parkinson symptoms and akathisia that interfere the physical and social comforts of schizophrenic patients, and affected the quality of life of schizophrenic patients.[4,19] The interesting fact, that the lowest scores on initial and final assessment were domain in the physical role and emotional role. Previous studies reported that physical role and emotional role are interrelated with each other, and the patient usually unable to distinguish where the source of his/her limitation is physically or mentally.[20] Furthermore, this study showed that risperidone-combination group was significantly exhibited an increase in quality of life compared to the haloperidol-combination group. This is associated with the response of patients to the given therapy which the effect of risperidone therapy was already seen in the fifth to eighth week of therapy,[4] while the significant final result also indicated that the result could be maintained during therapy and there was an improvement in the symptoms of mental health.[17,19]

Previous studies also indicated that the atypical antipsychotic (risperidone) was more cost-effective than the typical antipsychotics (haloperidol), and it was an expectation that by using the second generation of antipsychotic there will be decreased in the cost of every component related to schizophrenia therapy.[21,22] This study showed that the average cost-effectiveness ratio (ACER) value of risperidone-combination was lower than the haloperidol-combination. This indicated that risperidone-combination was more cost-effective compared to haloperidol-combination, which means that it is needed a cost of IDR 5,813,716.13 per quality-adjusted life-year (QALY). Based on the position resulted in Diagram of Alternative Groups Based on Cost Utilities, an incremental cost-effectiveness ratio (ICER) calculation is also necessary to be done. The ICER value obtained is the additional cost required per QALY in therapy, and in this case, it was required an additional cost of Rp. 33.573.600,- per QALY for the risperidone-combination group, but the patients in this group gained 0.423 additional times (survival years) or equally 5.08 months. Based on the result of sensitivity analysis, it was noted that in the change of 25% total cost-increase for risperidone-combination and 25% total cost-decrease for haloperidol-combination and causes a significant change in

ACER values. A meta-analysis study in France showed that risperidone is the dominant choice compared to the use of haloperidol, and the use of risperidone saved $6.510 (CAN$) and yielded more than 0.04 QALYs than haloperidol.[21] Risperidone also became a dominant choice for antipsychotic therapy, compared to haloperidol, in Spain.[22]

CONCLUSION

Risperidone-combination is the dominant antipsychotic therapy choice compared to the haloperidol-combination. But the result of the sensitivity test of the 25 % total cost decrease for the risperidone-combination group and the 25 % total cost decrease for the haloperidol-combination group will affect the result of cost-utility.

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