ORIGINAL ARTICLE

COMPARISON OF EFFECTIVENESS OF ANTIPSYCHOTICS IN SCHIZOPHRENIA: SECOND-GENERATION VERSUS THE FIRST-GENERATION

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Background: The choice of the antipsychotic medication is based upon the risks, benefits and the cost. There has been still a debate that which group of antipsychotics is overall better amongst the two so we planned this study with the objective to compare the efficacy of the 1st & 2nd generation antipsychotics for the treatment of schizophrenia. **Methods:** This RCT was conducted at in/out patient department of Psychiatry at a tertiary care hospital of Pakistan over the time period of six months. All the patients of schizophrenia between 18–50 years of age of either gender and all the socioeconomic groups were included in the study. Each patient was assessed with the Simpson-Angus Scale (SAS) for the EPS and the Positive and Negative Syndrome Scale (PANSS) for the schizophrenia at the baseline, 6 weeks and 12 weeks after starting the designated medication. **Results:** The mean age of the 350 patients included in the study was 34.25±16.74 years. One hundred and forty-eight (42.3%) patients were female and 202 (57.7%) were male. The overall response of 1st Generation & 2nd Generation antipsychotics was 51 (140) 36% and 135 (210) 64% respectively (*p*-value=0.00024). Sixty-three (45%) patients who were taking 1st Generation Antipsychotics had relapse of the disease as compared to the 29 (13.7%) patients who were taking the 2nd Generation antipsychotics. Dryness of mouth, sedation and EPS were the common side effects with the 1st generation antipsychotics while dryness of mouth, cardiac arrhythmias, and sexual dysfunction were the common side effects with the 2nd generation antipsychotics. **Conclusion:** This study concluded that the 2nd generation antipsychotics were superior to the 1st generation antipsychotics among the patients of schizophrenia in terms of the success rate, relapse rate and the tolerability.

Keywords: Effectiveness; Antipsychotics; Schizophrenia

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INTRODUCTION

Schizophrenia includes the delusions, disorganized thinking, hallucinations and the abnormal motor behaviour which are regarded as the positive symptoms. Negative symptoms include lack of eye contact, lack of emotion, decreased talking, flat effect, loss of interest and decreased self-care.[1] Antipsychotic medications are the first line treatment for the schizophrenia that reduces the positive symptoms of this disease in 8–15 days.[2] However cognitive dysfunction and negative symptoms does not respond well to these medications.[3,4]

Traditional antipsychotics were first developed in the 1950's. They have been effective in reducing the positive symptoms, but usually did not cater for the negative symptoms.[3] Newer or 2nd generation antipsychotics have been in practice for almost a decade now. The choice of the antipsychotic medication is based upon the risks, benefits and the cost.[5] There has been still a debate that which group of antipsychotics is overall better amongst the two.[6] Various meta-analysis done in the past were unable to prove any statistically significant differences between the typical and the atypical antipsychotic drugs in acute symptomatic effect or in discontinuation rates but side-effect profile was different for both the classes.[7,8] Crespo *et al* conducted a RCT to compare the haloperidol, risperidone and olanzapine and found that there was no difference in remission attainment or relapse prevention during the first year of treatment.[9]

However, in one meta-analysis, the atypical antipsychotic drugs, i.e., olanzapine, amisulpride and risperidone were found to be better than the typical antipsychotics.[10] Leuchdt *et al* reported that treatment failure was found in 53% cases with second generation and 70% with the first-generation antipsychotics. The relapse rate was 14% and 23% respectively.[11] Extra pyramidal motor control disabilities are less encountered among the patients using the newer antipsychotics as compared to the commonly used older antipsychotics but less frequently used older antipsychotics were not studied to generalize this finding.[12,13]

As far as side effect profile is concerned, insulin resistance, dyslipidaemias and weight gain were the common metabolic disorders found among the patients suffering from the schizophrenia using the antipsychotic medications.[14,15] Both typical and atypical antipsychotics were associated with the hyperlipidaemias, especially the typical ones.[15]

We planned to conduct a randomized controlled trial of the two therapeutic options to determine the effectiveness of the interventions in terms of the treatment success and relapse after the twelve weeks of the therapy. The evidence will provide a base to the healthcare professionals dealing with the schizophrenic patients not only in the better management but also to assess the safety profile of the treatment.

MATERIAL AND METHODS

This randomized controlled trial was conducted at the psychiatry department of a tertiary care hospital of Pakistan between June–November 2015. A total of 350 patients of schizophrenia with the age between 18 and 55 years, who could take the oral medication were included in the analysis. Patients were divided into two groups A and B. One hundred and seventy-five patients were allocated to each group via lottery method. This method was adopted to ensure randomization. Group A received the haloperidol while group B received the olanzapine. One hundred and seventy-five patients were allocated to each group via lottery method. Exclusion Criteria were the patients hypersensitive to the study drugs or those with coexisting severe organic illness or depression. Patients who were pregnant or lactating or those who had mental retardation were also excluded. Patients with illicit substance abuse or those required parenteral medication or ECT were also not included in the study. We used the Positive and Negative Syndrome Scale (PANSS) which is a validated tool to study the severity of the symptoms among the patients of schizophrenia. It has been used successfully to see the response of antipsychotic medications for the treatment of schizophrenia.[16]

It is a standardized psychometric tool for evaluating the drug related extra pyramidal syndromes (EPS). It is 10-item rating screening instrument with a range of score between 0-40. Increased score indicates the severity of the EPS. Ethical approval was obtained from the ethics committee prior to the start of the study. Schizophrenia was diagnosed according to the ICD-10 DCR criteria. After applying the inclusion and exclusion criteria patients were selected and randomized by the lottery method with equal chance to receive either the typical antipsychotic haloperidol (Group A) or the atypical antipsychotic olanzapine (Group B) for a period of twelve weeks. Written informed consent was obtained from each patient/guardian before their inclusion into the study. Detailed base line haematological, clinical and biochemical investigations were performed on the patients who were found eligible for the final participation.

A proforma containing the demographic details was filled at the start and at the end of the study. PANSS and the SAS were used to assess the patients for the schizophrenia and the EPS respectively at the baseline, six weeks and 12 weeks after the start of the designated medication. Monitoring of the vital signs, physical examination, ECG and the relevant safety laboratory investigations were done at each visit according to the international guidelines. The study outcome was measured as the efficacy and safety of the interventions after 12 weeks of the treatment.

Data was analysed using the SPSS 21.0. Descriptive statistics were used to calculate the mean and standard deviations from continuous variables like age, duration of illness, PANNS score and SAS scale. Frequencies and percentages were calculated for the categorical variables like gender, occupation, education, socioeconomic status, marital status, efficacy and PANNS score (mild, moderate, severe). Efficacy was compared using the chi-square test between the two study groups and p-value <0.05 was considered as significant.

RESULTS

Final analysis included a total of 350 patients. The mean age of the patients was 34.25±16.74 years [range 18–50 years]. General characteristics of the patients participating in the study are given in the Table-1. The overall response of 1st & 2nd Generation Antipsychotics was 51 (140) 36% and 135 (210) 64% respectively (p-value = 0.00024). Sixty-three (45%) patients who were taking 1st Generation Antipsychotics had relapse of the disease while the relapse rate in patients who were taking 2nd generation antipsychotics was 13.7% (p-value = 0.002160). Thirty-six (41%) patients who were taking 1st Generation Antipsychotics had good tolerability, while tolerability rate in the patients who were taking 2nd generation antipsychotics was 37% (p-value=0.00560). Efficacy of the first generation was much less than the efficacy of 2nd generation antipsychotics (Table-2). The major adverse effects observed with the use of typical antipsychotics were dryness of mouth 30.7%, sedation 30%, EPS 7.1% and the NMS 2.9%. Major adverse effects observed with the use of newer antipsychotics were dryness of mouth 56.6%, cardiac arrhythmias 8%, sexual dysfunction 6.3%, sedation 21%, weight gain 13.3%, hyperglycaemia 09% and the NMS 0.4% (Table-3).

Table-1: Baseline characteristics of the study patients (n= 350)

Age (years)	
Mean±SD	40.5±20.46
Range (min-max)	18–60 years
PANS Score	
Mean±SD	31.0±19.0
Range (min-max)	7–49
Duration of Illness months)	
Mean±SD	3.5±2.5
Range (min-max)	0-6

Age (years)	Group A n= 175	%age of Patients	Group B n= 175	%age of Patients
18–20	16	9.1	21	12
21–30	72	41	54	31
31–40	57	32.5	68	39
41–50	30	17	32	18

Table-2: Efficacy of the 1st generation & 2nd generation antipsychotics (n= 350)

	1st Generation n= 175		Total Number of patients	2nd Generation n= 175		Total Number of patients	*p*-value
	Yes	No	175	Yes	No	175	0.00601
Efficacy	41	134		135	40		
Relapse	63	112	175	29	146	175	0.00216
Tolerability	36	139	175	46	125	175	0.00560

Table-3: Side effects of the 1st generation & 2nd generation antipsychotics among the study participants (n=350)

Side Effects	1st Generation (n=140)	%Age of patients	2nd Generation (n=210)	%Age of patients
Tremors	11	7.8	09	4.30
Diarrhoea	06	4.2	15	7.1
Tardive dyskinesia	08	5.7	03	1.4
Prolong QT interval	01	0.7	17	8
Sexual dysfunction	01	0.7	13	6.2
Dryness of Mouth	43	30.7	47	56.6
Dyslipidaemias	03	2.10	13	6.20
Sedation	42	30	45	21.4
Weight Gain	11	7.8	28	13.3
Hyperglycaemia	00	00	19	09
NMS	04	2.9	01	0.4
EPS	10	7.1	00	00

EPS: Extrapyramidal side effects NMS: Neuroleptic malignant syndrome

DISCUSSION

Antipsychotic drugs have been the mainstay of treatment for schizophrenia for almost 50 years. Superiority upon the basis of efficacy between two groups of antipsychotics is still debatable. Two large systematic reviews concluded that positive symptoms of schizophrenia respond equally to both newer and older antipsychotics[7,8], whereas another study proved the superiority of the newer drugs[10]. Improvement in the negative symptoms, fewer EPSs, improved cognition and good tolerability were claimed for the SCA's which have reduced the use of FGAs in the treatment of schizophrenia worldwide. Various questions have been raised in met analysis about the size and significance of these effects. Like FGAs, SGAs (apart from clozapine) are usually grouped as a class in clinical guidelines, despite pharmacologic heterogeneity. Older drugs are also cost effective when compared with the SGA's.[17]

In our study 63 (45%) patients who were taking the 1st Generation Antipsychotics had relapse of the disease whereas relapse rate among the patients who were taking 2nd Generation antipsychotics was 13.7%. This was contrary to the findings of the famous CUtLASS (Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study) trail in which both the classes of antipsychotics had the equal efficacy.[18]

Meta-analysis of Leucht *et al* concluded the similar findings, as of our trial. Olanzapine was among those antipsychotics which was superior to the first-generation antipsychotics. Side effect profile was also similar to that of our study.[10] In our RCT the dropout rate of 1st Generation Antipsychotics was 28% while in 2nd generation antipsychotics, dropout rate was 22%. This was in contrast to a non-commercially funded, multisite, pragmatic RCT in which there was no difference in the efficacy of both groups and discontinuation rate was also similar among the two groups.[19] University of Maryland conducted a detailed review by the Schizophrenia Patient Outcomes Research Team (PORT). They concluded that newer and older drugs have similar efficacy in acute illness and early treatment causes marked reduction in the positive symptoms of the disease. Clozapine and Olanzapine were discouraged for the first line use due to their adverse effect profile.[20] Findings of our trial were similar to that of PORT in terms of early treatment and symptoms reduction but differ in terms of the side effect profile as in our study typical drugs were associated with more adverse effects than the atypical ones.

Olanzapine was proved to be better in terms of reduction in hospital admission frequency and patient tolerability in the Phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. It was a large nationwide trial that compared the efficacy of the typical and the atypical antipsychotics. Major side effect with this drug was the weight gain.[21] Our study showed the similar results, where the drop-out rate of 1st generation antipsychotics was 28% while in the olanzapine group, the dropout rate was 22%. Weight gain was found in 13% of our patients using the olanzapine.

In 2009, NICE updated their guidelines which were issued in 2002. In the previous guidelines, second generation antipsychotics were recommended as the first line treatment of acute psychosis/schizophrenia. After 2009 they no longer recommend second generation antipsychotics as the first line treatment, rather decision should be made by weighing the side effects of both the groups (EPS vs metabolic side effects).[22] This shows that the formulation of the guidelines and choice of the right treatment is a dynamic process and more trials based upon different group of populations will add to the knowledge about the safety and efficacy of the antipsychotic drugs among various population groups.

This study has some limitations. The randomization procedure and its results were revealed to the researchers and the participants. There was no placebo control group, and many side effects were subjectively reported. Both the groups were not matched fully at the baseline in terms of the PANSS scores. The design of the study, comparing the individual drugs, will not help in the generalization of the efficacy or tolerability advantage as a group. Many outcomes and adverse effects reported in this study might be caused by the small sample size. We suggest further trials on a broader based and a more representative sample size using locally developed and standardized psychometric tools with a long follow-up period.

CONCLUSION

This study concluded that 2nd generation antipsychotics were superior to the 1st generation antipsychotics among the patients of schizophrenia in terms of the success rate, relapse rate and the tolerability.

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AUTHORS' CONTRIBUTION

UBZ: Analysed the data and wrote the final manuscript. SAA: Designed the study and collected data. RT: Supervised the study from conception till manuscript writing. SMB: Analysed the data and reviewed the final manuscript

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