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Neutrophils count and associated infections with clozapine treatment in patients diagnosed with Schizophrenia

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A second-generation antipsychotic drug called clozapine is used to treat resistant schizophrenia. However, therapy with clozapine is often complicated by side effects. Clozapine-associated neutropenia (CAN) is most prevalent during the initial month of treatment. This study aimed to detect the association between clozapine treatment, neutropenia and associated infections among patients with schizophrenia admitted to the Eradah and Mental Health Complex - Jeddah, Saudi Arabia. A retrospective cohort study was carried out using medical records. Neutrophil counts calculated, clozapine dose, in addition to infections, social and demographic data on fifty-one patients diagnosed with schizophrenia taking clozapine from 1st July 2018 to 30th June 2021. This paper adhered to the STROBE guidelines. Most cases who developed neutropenia are of a mild type (11%). There is no significant association between the clozapine dose and the occurrence of neutropenia in patients with schizophrenia. However, Clozapine was statistically significantly associated with an increased risk of respiratory, skin, and soft tissue infections. Moreover, age was statistically significantly associated with neutropenia occurrence. However, no statistically significant association was found between neutropenia occurrence and the other sociodemographic or clinical characteristics of the participants. Enforcing the importance of following the treatment protocol of clozapine among patients through periodic lab investigations as preventive precautions is recommended.

Keywords: Schizophrenia, Psychiatric, Clozapine, Neutropenia, Clozapine-associated neutropenia (CAN).

INTRODUCTION

Clozapine is an effective treatment for schizophrenia patients who have failed to respond to other antipsychotic medications. Furthermore, clozapine is an effective treatment for schizophrenia accompanied by suicidal or self-destructive conduct. It is one of the few psychiatric medications with therapeutic effects that can be seen with the naked eye. Despite this, clozapine is still underused, and scientists continue to debate the strength of the evidence for its efficacy compared to other antipsychotics (Bachmann et al. 2017). Of course, clozapine has a dizzying array of side effects, many of which are potentially lethal. It can only be prescribed in most countries after a rigorous blood test regimen. Clozapine is most commonly associated with neutropenia and agranulocytosis, which may lead to severe infections. Therefore, the focus on the safety of the patient and regular monitoring of baseline blood tests are essential and mandatory (Samara et al. 2016; Taylor et al. 2022).

Historically, clozapine has been associated with neutropenia (absolute neutrophil count (ANC) <1500), yet, it is underutilized due to its side effects. Therefore, it is necessary to monitor the white blood cell count and the absolute neutrophil count for its use. However, several side effects must be monitored in clinical practice (de Araujo et al. 2021). Clozapine-associated neutropenia (CAN) is most common within the first month of starting clozapine (Johannsen et al. 2022). Although the pathophysiology of CAN is unknown, it is thought to be either an immunological reaction against neutrophil surface antigens or direct clozapine metabolite toxicity on bone marrow and neutrophils (Myles et al. 2018; Wiciński et al. 2018).

CAN is the most common hematological adverse response that leads to clozapine cessation, according to previous studies (Ucok et al. 2019; Johannsen et al. 2022). Compared to other antipsychotics, clozapine was linked to an increased risk of neutropenia. After medication therapy, the total white blood cells (WBC) and its subtypes, such as neutrophils, basophils, monocytes, and eosinophils, were significantly altered (Xiong *et al.* 2019). On the other hand, CAN could be controlled with different approaches, such as bone-marrow-stimulating medicines such as granulocyte colony-stimulating factor, filgrastim, or lithium (Nielsen et al. 2013).

Schizophrenia is a complex syndrome that usually begins in youth or early adulthood and progresses over time. According to World Health Organization (WHO)

studies, schizophrenia is one of the top ten causes of global disability, with a prevalence rate of 0.2–0.7%, as revealed by community surveys.

It is important to note that there is relatively little research on the prevalence of schizophrenia in Saudi Arabia, with few publications covering schizophrenia-related topics. For example, 22.4% of outpatients receiving mental health care in Saudi Arabia had mental and behavioral disorders brought on by schizophrenia or schizotypal and delusional disorders, according to the Saudi Arabian Ministry of Health 2008. Generally, studies on the prevalence of Schizophrenia in Saudi Arabia have mainly focused on specific problems related to the disease. Approximately 1% of the population is estimated to have schizophrenia. In Saudi Arabia, schizophrenia represents 13% of the patients who are receiving psychiatric outpatient treatment. Additionally, schizophrenia is more common in 50% of patients admitted to inpatient psychiatric facilities (Qureshi et al. 2013). In addition, the Saudi Ministry of Health (MOH) reported data showing that 145,625 frequently and new cases attended mental health outpatients with schizophrenia, schizotypal, and delusional disorders, besides 13,363 frequently and new cases were admitted to psychiatric inpatient departments, indicating a severe public health concern (Al Khani *et al.* 1986; Chaleby *et al.* 1987; WHO, 2015; Alshowkan et al. 2015).

The first objective of this study was to estimate neutropenia among patients diagnosed with schizophrenia under treatment with clozapine. The second objective was to detect the association between clozapine treatment, neutropenia, and associated infections among patients diagnosed with schizophrenia. The significance of this study is to assist healthcare providers in enforcing the importance of following the clozapine treatment protocol among patients with schizophrenia through frequent lab examinations as preventative precautions, as well as ongoing patient education while on treatment.

MATERIALS AND METHODS

Study area

The study was done in the Eradah and Mental Health complex in Jeddah, Saudi Arabia. The hospital facilities consist of psychiatric outpatient, inpatient, home care, and emergency care.

Study design

A retrospective cohort study was carried out in Eradah and Mental Health Complex, Jeddah, Saudi Arabia, from 1st July 2018 to 30th June 2021. The study was conducted using medical records, following (STROBE) statements, which are guidelines for reporting epidemiological observational studies.

Study population

The study subjects were patients diagnosed with schizophrenia who were on clozapine treatment and were admitted to the Eradah and Mental Health Complex between 1st July 2018 to 30th June 2021.

Inclusion and exclusion criteria

In this study, the eligible admissions include both genders aged more than 18 years, Saudi citizens with a principal diagnosis of schizophrenia, and admitted to acute psychiatric wards between 1st July 2018 to 30th June 2021. The exclusion criteria for this study include features or characteristics that disqualify the selected population, such as the patient diagnosis converted to other diagnoses rather than schizophrenia; they were excluded from our study.

Sample size

Fifty-one patients that meet the study inclusion criteria and are admitted to the Eradah and mental health complex with a diagnosis of schizophrenia between 1st July 2018 to 30th June 2021.

Data collection

In this study, the primary source of the data was the patient's medical record. Data on clozapine utilization and demographics, including social and demographic data (gender, age, marital status, living condition, comorbid physical illnesses, employment status, and associated infections), were collected from the patient's medical record, and the patient's family was contacted if there were missing data.

Primary outcome and variables

The primary outcome is estimated neutrophil counts and infections (COVID-19, respiratory infections, gastrointestinal infections, skin, and soft tissue infections) among patients diagnosed with schizophrenia under the treatment of clozapine. Furthermore, social and demographic data (gender, age, marital status, living conditions, and employment status), comorbid physical illnesses, and smoking status were examined.

Data analysis

In this study, the frequency and percentage were used for descriptive statistics to explain the personal characteristic of the patients. The continuous variables were presented in tables, including the mean, standard deviation, minimum, and maximum. Also, the categorical variables were presented with percentages and frequency. Furthermore, a chi-square test and fisher's exact test compared the continuous variables for the analysis. Moreover, the simple logistic regression in multivariate analysis calculated the risk ratios with a 95% confidence interval. Finally, the P-value < 0.05 was considered significant, and the data were analyzed with SPSS version 26.

RESULTS

Sociodemographic and clinical characteristics

Data were collected on fifty-one patients, of which 43 (84.3%) were males while 8 (15.7%) were females. Their median age was 35 ± 9.81 years. Their Marital status was single, married, divorced, and widowed (66.7%, 23.5%, 7.8%, and 2%) respectively. There are differences in their educational level. The outcomes indicate that twenty-two participants (43.1%) have a high school certificate, while Seventeen (33.3%) have below high school certificate, and Twelve (23.5%) are university graduates. On the other hand, the findings revealed that forty-nine (96.1%) were unemployed while two (3.9) were retired. Their median income was 1000 Saudi Arabian Riyal (SAR) monthly. The incidence of neutropenia among the participants was 11.8%.

In addition, skin and soft tissue infections were the most prevalent infection among the participant, including 31.4%. On the other hand, respiratory infections occurred in 17.6% of the participants, including 13.7% common cold, 2% Tuberculosis, and 2% Bronchitis. Besides, Covid-19 occurred in 13.7% of the participants. Comorbidity presents in 29.4% of the participants. Finally, 62.7% of the participants were smokers, versus 37.3% that were non-smokers. Approximately two-thirds (68.6%) of patients have a standard clozapine dose (301 mg/day to 600 mg/day).

Neutropenia and sociodemographic characteristics

Table 1 shows the association between neutropenia occurrence and the patient's sociodemographic characteristics, including Gender, Marital status, educational level, Employment status, Smoking, and age. As indicated in the Table, there was a statistically significant association between neutropenia occurrence and age. The age was significantly lower in the neutropenia group compared with the Non – neutropenia group, P-value <0.05. In contrast, no statistically significant association was found between neutropenia occurrence and other Sociodemographic characteristics, P-value >0.05.

Neutropenia and clinical characteristics

A Fisher Exact test was used to detect the association between neutropenia occurrence and Patients' clinical characteristics, including Clozapine dose (standard and low), Respiratory infections, Covid-19, Tuberculosis, Common cold, Bronchitis, Gastrointestinal infections, Skin and soft tissue infections, and Comorbidity. As shown in Table 2, no statistically significant association was found, P> 0.05.

Table 1: Sociodemographic characteristics and neutropenia among the participants.

Characteristics		Neutropenia group		Non – neutropenia group		P value
		n	%	n	%	
Gender [a]	Male	4	9.3	39	90.7	0.234
	Female	2	25	4	75	
Marital status [b]	Married	0	0	12	100	0.334
	Widowed	0	0	1	100	
	Divorced	0	0	4	100	
	Single	6	17.6	28	82.4	
Educational level [b]	Less than high school	2	11.8	15	88.2	0.290
	High school	4	18.2	18	81.8	
	Graduate	0	0	12	100	
Employment status [a]	Employed	0	0	0	0	0.776
	Un employed	6	12.2	43	87.8	
	Retired	0	0	2	100	
Smoking [a]	Smoker	3	9.4	29	90.6	0.396
	Non - smoker	3	15.8	16	84.2	
Age [c]	Mean	30.67		35.49		0.020*
	SD	2.994		10.23		

n represents the number, % represents the percentage, and SD represents the standard deviation. a, P- value calculated by a Fisher Exact test. b, P- value calculated by a Chi-Square test. c, P- value calculated by an Independent Samples t-test.

Table 2: Clinical characteristics and neutropenia among the participants.

Characteristics		Neutropenia group		Non – neutropenia group		P value
		N	%	N	%	
Clozapine dose	**Low dose**	2	12.5	14	87.5	0.612
	Standard dose	4	11.4	31	88.6	
Respiratory infections	**Yes**	1	11.1	8	88.9	0.716
	No	5	11.9	37	88.1	
Covid-19	**Yes**	1	14.3	6	85.7	0.608
	No	5	11.4	39	88.6	
Tuberculosis	**Yes**	0	0	1	100	0.882
	No	6	12	44	88	
Common cold	**Yes**	1	14.3	6	85.7	0.608
	No	5	11.4	39	88.6	
Bronchitis	**Yes**	0	0	1	100	0.882
	No	6	12	44	88	
Gastrointestinal infections	**Yes**	0	0	1	100	0.882
	No	6	12	44	88	
Skin and soft tissue infections	**Yes**	1	6.3	15	93.8	0.379
	No	5	14.3	30	85.7	
Comorbidity	**Yes**	3	20	12	80	0.234
	No	3	8.3	33	91.7	

n represents the number, % represents the percentage, and P- value is calculated by a Fisher Exact test.

Table 3: The association between the clozapine dose and leukopenia, neutropenia, COVID-19, respiratory infection, gastrointestinal infection, skin, and soft tissue infections occurrence and risk.

Clozapine dose	COVID19		respiratory infection		gastrointestinal infection		Skin and soft tissue infections	
	No	No	No	Yes	No	Yes	No	Yes
low	16 (100)	0 (0)	16 (100)	0 (0)	16 (100)	0 (0)	15 (93.8)	1 (6.3)
standard	28 (80.0)	7 (20.0)	26 (74.3)	9 (25.7)	34 (97.1)	1 (2.9)	20 (57.1)	15 (42.9)
P-value	0.054 [a]		0.025* [a]		0.999 [a]		0.009** [a]	
OR (95% CI)	3.750 (0.421-33.41)		4.444* (1.106-39.02)		0.441 (0.026-7.533)		11.250* (1.334-94.86)	

Values represent the number (percentage). [a], P-value calculated by chi-square test. [b], P-value calculated by fisher's exact test. OR= Odd ratio, CI= confidence interval, both calculated by a simple logistic regression analysis

Clozapine dose and associated infection

As shown in Table 3, there was a significant association between the Clozapine dose and respiratory infection occurrence, p <0.05. The incidence of respiratory infection among the participants was 17.6%, with a percentage of 100% in the standard dose patients compared to the low dose patients. In addition, the respiratory infection risk is 4.44 times more in standard Clozapine dose patients than in low dose Clozapine patients and shows a statistically significant (OR=4.444, 95% CI= 1.106-39.02).

In addition, there was a significant association between the Clozapine dose and the skin and soft tissue infection occurrence, p < .05. the incidence of skin and soft tissue infections was 31.4% among the participants, with a higher percentage in the standard dose patients compared to the low dose patients. in addition, the skin and soft tissue risk are 11.25 times more in standard Clozapine dose patients than in low dose Clozapine patients and show a statistically significant relationship (OR=11.250, 95% CI= 1.334-94.86).

On the other hand, no significant relationship was found between the clozapine dose and COVID-19 and gastrointestinal infection occurrence and risk, p > 0.05.

DISCUSSION

Clozapine is the most effective antipsychotic treatment for resistant schizophrenia (Essali et al. 2009; Li et al. 2015; Wilby et al. 2017). It is effective against the most prominent symptoms of schizophrenia (Leucht et al. 2013; Huhn et al. 2019). The drug can cause serious adverse events (AEs), which can be life-threatening, such as hematological (including neutropenia and agranulocytosis), cardiovascular effects, gastrointestinal, nervous system–related effects, and metabolic side effects (Nielsen et al. 2011; Polcwiartek et al. 2016).

Clozapine-associated neutropenia (CAN) is most common in the first thirty days of treatment (Myles et al. 2018). Recently, The US Food and Drug Administration has revised its guidelines for blood monitoring of the drug to reduce the potential for deadly agranulocytosis and drug interactions (Sultan et al. 2017).

The present study examines the association between neutrophil count and infections with clozapine treatment in schizophrenia patients at Eradah and Mental Health Complex in Jeddah, Saudi Arabia. The patients were grouped based on the Clozapine Dose into low dose group, up to 300 mg, and a standard-dose group, 301 to 600 mg. No significant association was found between neutropenia and sociodemographic characteristics, including Gender, Marital status, educational level, Employment status, and Smoking. These results were consistent with a recent study by (Johannsen et al. 2022) which found no association between gender and clozapine-associated neutropenia. Also, (Moga et al. 2022) did not find a significant association between gender and neutropenia occurrence, P= 0.89, nor between smoking status and neutropenia occurrence, P= 0.53. On the other hand, this study conducted a statistically significant association between neutropenia occurrence and age; the neutropenia group averaged a much younger age than the non-neutropenia group. The relation between age and neutropenia occurrence in this study was inconsistent with previous studies such as (Johannsen et al. 2022; Moga et al. 2022), which found no association between age and neutropenia.

Moreover, the present study did not find a significant association between the clozapine dose and neutropenia, p= 0.612. This result was consistent with (Johannsen et al. 2022) study which did not observe that clozapine exposure was associated with an increased incidence of neutropenia, nor was the duration of a neutropenia episode connected with clozapine discontinuations. In addition, all the neutropenia which developed in the patients of this study was mild at 11.8%. No incidence of moderate or severe neutropenia was found. The result of the current study was inconsistent with a previous large meta-analysis by (Myles et al. 2018) which found that the incidence of severe neutropenia (agranulocytosis) was 0.9%. In contrast, moderate and mild neutropenia incidences were 1.3% and 3.8%, respectively. However, the authors found that about 1 in every 8000 people using clozapine will develop clozapine-associated neutropenia, which can lead to death (Myles et al. 2018).

On the other hand, the current study found no association between neutropenia and some clinical characteristics of the patients, including respiratory infection, Covid-19, Tuberculosis, Common cold, Bronchitis, Gastrointestinal infections, skin and soft tissue infections, and Comorbidity. In a previous study by (Moga et al. 2022), there was no significant association between neutropenia and respiratory, cardiac, neurological, and metabolic diseases in Schizophrenia patients. Conversely, in a previous study by (Torres et al. 2013), several common comorbidities were detected in people with treatment-resistant schizophrenia, which increases the chance of respiratory infections, cardiovascular disease, and diabetes. In addition, clozapine-induced drowsiness and hypersalivation, which raises the risk of aspiration pneumonia, which are proposed explanations for this elevated danger.

Additionally, the correlation between clozapine treatment and infection was reported in several studies; clozapine can cause inflammation, especially during titration, with C-reactive protein (CRP) increases, fever, and myocarditis (Verdoux et al. 2019). Other rare complications have been identified, such as serositis, pneumonitis/alveolitis, hepatitis, pancreatitis, nephritis, colitis, and dermatological problems (Verdoux et al. 2019).

In the present study, the incidence of COVID-19, respiratory, gastrointestinal, skin, and soft tissue infections was 13.7%, 17.6%, 2.0%, and 31.4%, respectively. In addition, clozapine was associated with an increased risk of COVID-19 (OR= 3.75, 95%CI 0.421-33.41), respiratory infection (OR= 4.44, 95%CI 1.106-39.02), skin and soft tissue infection (OR= 11.25, 95%CI 1.334-94.86). In a recent retrospective cohort study in 2021, the incidence of COVID-19 among Clozapine treatment patients was 1.62%, with a hazard ratio of 2.62. Therefore, the researchers conducted that clozapine treatment is associated with an increased risk of Covid-19 infection (Govind et al. 2021). Additionally, Gee et al. 2020, in their examination of the Management of clozapine treatment during the Covid-19 pandemic, found a statistically significant decrease in absolute neutrophil count in the week following a positive SARS-CoV-2 test (Gee et al. 2020).

The current study has results indicating the effect of clozapine exposure on either standard or low doses, which is considered a strength for the given study. On the other hand, the current study has a few limitations and areas for improvement, including a relatively small number of patients.

CONCLUSION

This study can conclude that neutropenia is one of the most significant adverse effects of clozapine medication. The burden of hematological monitoring leads to improper use of the drug, with significant medical consequences. Clozapine-associated neutropenia (CAN) and Clozapine-induced agranulocytosis (CLIA) are far more significant in public health than other drug-induced agranulocytosis. The incidence of neutropenia among the participants was 11.8%. However, all these cases developed mild neutropenia. In addition, clozapine dose was significantly associated with the increased risk of respiratory, skin and soft tissue infection in patients who took a standard dose risked infection more than those who took a low dose.

CONFLICT OF INTEREST

The authors declared that present study was performed in the absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

AMNE conceived the idea, planned and designed the study, collected and analyzed the data, and also wrote the manuscript. MSA and RMA reviewed the manuscript. All authors read and approved the final version.

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