Long-lasting leukocytosis in patients with schizophrenia treated with clozapine after electroconvulsive therapy

ECT stabilizes white blood cell count

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Abstract

Introduction The present study was conducted to investigate the possible hematologic impact of long-term electroconvulsive therapy (ECT) in patients with drug-resistant schizophrenia and receiving clozapine therapy.

Subjects and Methods In this retrospective study, clinical charts of 57 hospitalized patients with schizophrenia who required clozapine therapy because of active psychotic symptoms resistant to other antipsychotics were examined. For 18 who underwent ECT, the first assessment was conducted at the end of that therapy (average two months after start, 7.68 sessions) and the second two months later. As for the 39 patients who did not undergo ECT, the first and second assessment points were at two and four months, respectively, after a randomly chosen time point.

Results Multiple regression analysis revealed that modified ECT (m-ECT) (β = 0.346, p = 0.005), gender (males showed greater increase) (β = 0.273, p = 0.023), and disease duration (longer associated with greater increase) (β = 0.258, p = 0.033) were correlated with a change in white blood cell (WBC) count (ΔR2 = 0.277, p < 0.001) at the first assessment point. At the second assessment point, multiple regression analysis showed that m-ECT (β = 0.262, p = 0.039), gender (males showed greater increase) (β = 0.264, p = 0.036), and disease duration (longer associated with greater increase) (β = 0.234, p = 0.068) were again correlated with changed WBC count (ΔR2 = 0.203, p < 0.007).

Discussion An increase in leukocytes may have a protective influence against the adverse myelo-suppressive effects of clozapine. However, a simple mobilization of leukocytes from bone marrow

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to peripheral circulation may not enhance the immune system, leading to only a masking of the effects of a potential immuno-insufficient state in the treated patient. In either case, should leukocytosis be induced and then remain for an extended period, hematologists, as well as psychiatrists involved in electroconvulsive intervention for clozapine-treated patients, must keep this factor in mind.

**Keywords**
Clozapine therapy, Electroconvulsive therapy, Schizophrenia, white blood cell count, leukocytosis

### Introduction

Electroconvulsive therapy (ECT) has been shown effective for a wide range of psychiatric illnesses, including depression, bipolar disorder, catatonia, and psychosis.\(^1\)–\(^4\) In patients with schizophrenia as well, ECT is now well recognized as an effective countermeasure against drug-resistant psychosis.\(^5\)–\(^7\) Nevertheless, while several papers regarding the effects and side-effects of ECT on schizophrenia have been published,\(^8\)–\(^9\) its hematologic impact has only scarcely been elucidated. Furthermore, the results presented in two notable exceptions are mutually contradictory. While Asoglu et al. reported that ECT negated an increase in leukocytes and suggested that it instead caused a decrease in red erythrocytes,\(^10\) Chaturvedi et al. emphasized findings showing an increase in leukocytes.\(^11\) Both of those studies compared hematologic parameters immediately before and after ECT, and the potential long-term impact of that therapy on those factors has yet to be reported.

Clozapine was synthesized in 1956 and then later released in 1975 in Europe.\(^12\) However, development was halted in the United States and actual use was virtually stopped in Europe in response to reports from Finland of agranulocytosis leading to death.\(^13\) The role of clozapine in treatment-resistant schizophrenia was then re-evaluated by the landmark Clozaril Collaborative Study Group Study #30, which showed marked benefits as compared to chlorpromazine for patients with protracted psychosis who had already shown an inadequate response to other antipsychotics.\(^12\)–\(^14\) Most subsequent studies supported those results, leading to a re-positioning of clozapine to be considered effective for drug-resistant schizophrenia.\(^15\)–\(^16\) As a result, both clozapine and ECT are now generally recognized as powerful alternatives for drug-resistant schizophrenia.\(^3\)\(^,\)\(^4\)\(^,\)\(^17\)

In Japan, the minimum number of leucocytes in the body for starting and maintaining clozapine therapy is strictly regulated.\(^18\) In our previous study of drug-resistant schizophrenia, patients administered clozapine and who underwent ECT because of acute exacerbation despite clozapine treatment were found to have an increase in leukocytes for at least a few months or even longer after therapy.\(^19\) In the present study, we attempted to confirm the possible hematologic impact of ECT over the long term in patients with drug-resistant schizophrenia who were receiving clozapine therapy.

### Subjects and methods

In this retrospective study, clinical charts of patients with schizophrenia diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
(DSM-V), criteria were reviewed. They were hospitalized at Sugita Hospital between 2017 and 2020 and required clozapine therapy because of intractable active psychotic symptoms. Intractable was defined as a PANSS score >100 and/or global assessment of functioning scale (GAF) score <40 despite administration of at least two types of atypical antipsychotics for more than one month at a dose equal to or greater than that equivalent to chlorpromazine at 600 mg/day. Patients older than 65 years were excluded. Finally, of 220 hospitalized patients with schizophrenia, the clinical charts of 57 were chosen for this analysis. Clinical and demographic data of the enrolled subjects are shown in Table 1. According to the official guidelines in Japan for clozapine therapy, white blood cell (WBC) count in all patients given clozapine was regularly determined at intervals of 7 days for at least the first six months after starting administration of the compound.

Prior to undergoing ECT, the patients underwent an electrocardiogram (ECG) examination (normal, 12 leads), and blood tests for liver and/or kidney functions. All who received ECT had been fasting for at least four hours. Under titration with saline, relaxation was achieved by anesthesia using intravenous propofol (0.05 ml/kg) and suxamethonium (2 ml, 44 mg). With oxygen supplied and continuous titration, bilateral modified ECT (m-ECT) was performed with a voltage of 450 V and maximum energy of 504 mC. The electric shock was given in a range from 50% to 100%, then 10% higher at the next session if convulsions did not continue for more than 60 s. Seizure induction was assessed by a combination of the cuff limb method and determination of seizure quality, as previously described.20

Demographic and clinical variables analyzed were age, gender, duration of psychosis, dose of concomitant psychotropic drugs including lithium carbonate, valproate, and other antipsychotic drugs, presence or absence of ECT therapy, and WBC count. The dose of antipsychotic drugs was converted to that of the equivalent chlorpromazine dose.

Multiple regression analysis was performed using change in WBC count as a dependent variable, with the other demographic and clinical variables at the two assessment points used as independent variables. Independent variables that showed a $p$-value <0.10 were subjected to analysis. In patients who underwent ECT, the first assessment was conducted at the end of therapy (average two months after start of ECT, number

Table 1. Subjects (n = 57).

| Variable                                      | Value                  |
|-----------------------------------------------|------------------------|
| Average age at the examination, years         | 44.5 (42.0–47.0)       |
| Presence/absence of ECT therapy, Yes/No       | 18/39                  |
| Gender, male/female                           | 31/26                  |
| Average duration of psychosis, years          | 16.2 (14.0–18.5)       |
| Average dose of lithium carbonate, mg         | 191.2 (133.9–248.4)    |
| Average dose of valproate, mg                 | 361.4 (231.2–491.5)    |
| Average dose of total concomitant             |                        |
| Antipsychotic drugs other than clozapine, mg  | 1740.3 (1622.8–1857.8 mg)* |

Figures in the parentheses are confidence intervals.

* The dose was converted to that of the equivalent chlorpromazine dose.
of sessions 7.68) and the second at two months after the end of ECT. As for patients who did not undergo ECT, the first and second assessment points were at two and four months, respectively, after a randomly chosen time. All analyzes were performed using IBM SPSS, ver. 22. P-values >0.05 were considered to be statistically significant. [NOTE: I deleted the group names (ECT + C, C), as they are not used elsewhere in the manuscript.]

**Results**

1. **Correlations between reduction in WBC count and clinical variables at end of m-ECT.** Among the clinical and demographic variables examined, gender, duration of psychosis, and the presence or absence of ECT, each of which showed a p-value <0.10, were selected as independent variables. Multiple regression analysis revealed that m-ECT (β = 0.346, p = 0.005), gender (males showed greater increase) (β = 0.273, p = 0.023), and disease duration (longer associated with greater increase) (β = 0.258, p = 0.033) were correlated with changed WBC count (ΔR² = 0.277, p < 0.001). No apparent effects associated with the other variables were noted.

2. **Correlations between reduction in WBC count and clinical variables at two months after the end of m-ECT.** The same clinical and demographic variables were used as independent variables for analyzes performed two months after the end of therapy. Multiple regression analysis revealed that m-ECT (β = 0.262, p = 0.039), gender (males showed greater increase) (β = 0.264, p = 0.036), and disease duration (longer associated with greater increase) (β = 0.234, p = 0.068) were correlated with changed WBC count (ΔR² = 0.203, p < 0.007). Again, no apparent effects associated with the other variables were noted.

**Discussion**

Recently, an increasing number of reports have suggested the impact of ECT on the immune system, including natural killer cell activity, interleukin-6 (IL-6), tumor-necrosis-factor-α (TNF-α), and C-reactive protein (CRP).\(^{21-23}\) Notably, the systematic study presented by Yrondi A et al.\(^{24}\) emphasized the roles of IL-6 and TNF-α. Although the results shown in those reports seem to indicate enhanced leukocyte activity after electroconvulsive intervention, their applicability to the present findings is indirect because of different background factors. First, the results presented in those prior reports were derived from patients with drug-resistant depression and it is important to confirm whether the same is true in patients with drug-resistant schizophrenia. Furthermore, any significant impact of ECT on the immune system has only been noted immediately after therapy, while the long-term effects remain to be explored. Additionally, the paper presented by Chaturvedi et al. is the only known to study to note an increase in leukocytes after ECT,\(^{11}\) though the timing of hematologic count differed greatly from that in the present study. Furthermore, they found that the number of leukocytes peaked immediately after ECT and then gradually decreased during the
ensuing hours, while findings showing an increase in leukocytes lasting for more than one month have not been presented.23

It is important to note that the subjects of the present study were unique in several ways, as they were diagnosed with drug-resistant schizophrenia and prescribed clozapine, and then demonstrated alterations of hematologic parameters two months after ECT. To the best of our knowledge, hematologic parameters related to ECT have not been previously investigated under these conditions. In view of the rapid reversal of parameters indicative of an enhanced immune system, including IL-6, TNF-α, and admission C-reactive protein (aCRP) levels, as well as leukocytes within several hours after ECT shown in previous studies, the delayed and lingering effects on leukocytes found two months after therapy in this study require an explanation different from an acute inflammatory response. Delayed leukocytosis is well understood to occur after vigorous strength and endurance exercise.24,25 In contrast to leukocytosis as a result of infectious disease, cytokines such as IL-6 are known to be increased under an inflammatory condition and do not change as a result of endurance exercise. During the late period of leukocytosis following heavy long-lasting exercise, factors responsible for mobilization of leukocytes from marrow to blood are assumed to differ from those related to acute inflammation. Findings in the present study showing delayed leukocytosis in the present study may be similar to those observed after vigorous exercise rather than indicating an inflammatory response.

On the other hand, another explanation is possible. The present results suggest that a delayed increase of leukocytes after ECT corresponds to the duration of illness, thus are potentially suggestive of a direct association of the effect of ECT to increase leukocytes with the schizophrenic process. A meta-analysis of patients with schizophrenia provided evidence for increased total WBC count in those cases,26 thus such an increase may indicate activation of a resilient process in patients with schizophrenia. Furthermore, the increase in leukocytes was more remarkable in males as compared to females in the present study. A previous report noted gender differences related to the effects of ECT on psychiatric symptoms as a function of the baseline IL-6 state.23 Thus, it is possible that changes in laboratory parameters following electroconvulsive intervention could differ based on gender, with a complex interrelationship among the immune system, schizophrenic process, and effects of ECT also suggested.

Recently, increasing attention is being given to the effectiveness of clozapine, which has been shown in several meta-analyses,3,27,28 though findings obtained in the only reported randomized controlled trial support the effects of augmentation with ECT in patients with clozapine-resistant schizophrenia.29 A serious frequent adverse effect of clozapine is agranulocytosis,30 which occurs in 0.8% of treated patients. However, since clozapine is widely recognized as one of the most effective antipsychotic drugs, agranulocytosis presents a significant though separate medical challenge, with blood count monitoring a mandatory procedure. Should leukocytosis be induced and then remain for an extended period, as demonstrated in the present study, then hematologists as well as psychiatrists involved in electroconvulsive intervention for clozapine-treated patients must keep this factor in mind.

The present investigation has several limitations. First, as noted above, no other relevant study conducted under the same conditions has been reported thus far and follow-up
analyzes are mandatory to examine the reliability of our data. Additionally, the implications of these findings for clinical practice remain to be elucidated. Increased leukocytes may provide protection against the myelosuppressive adversary effects of clozapine, though a simple mobilization of leukocytes from bone marrow to peripheral circulation may not enhance the immune system, leading to only a masking of the effects of a potential immuno-insufficient state of the treated patient. We consider that the results obtained in this study require appraisal and confirmation by additional testing.

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