Research Article

Effect of Hydroxychloroquine Therapy on Hematology and Ocular Manifestations of Systemic Lupus Erythematosus Patients

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that mainly affects women and has various clinical manifestations involving multiple organs. The use of hydroxychloroquine (HCQ) provides some advantages. This study aimed to analyze hematological and ocular effects following short-term HCQ administration in SLE patients. A cross-sectional study was conducted from April to July 2022 at Zainoel Abidin Hospital, Banda Aceh, Indonesia, involving 23 female SLE patients. Blood laboratory parameters were assessed, and an ophthalmologist performed ocular examinations. The study showed an average hemoglobin of 11.6 g/dL. Other blood laboratory results were within normal limits. The mean duration of SLE diagnosis and HCQ use was 21.0 months and 9.7 months, respectively. There was no correlation between HCQ use duration and hematological parameters (hemoglobin, leukocytes, and thrombocyte*s; p values 0.38, 0.14, and 0.62, respectively). This study showed that only one SLE patient taking HCQ for less than five years had ocular problems. The prevalence of ocular and hematological effects in SLE patients treated with HCQ for less than five years is minimal.*
Keywords: *systemic lupus erythematosus, hydroxychloroquine, hematology, ocular effect.*

Efek Pemberian Hidroksiklorokuin pada Aspek Hematologi dan Okular Pasien Lupus Eritematosus Sistemik

Abstrak

Lupus eritematosus sistemik (SLE) adalah penyakit autoimun kronis yang terutama menyerang wanita dan memiliki berbagai manifestasi klinis yang melibatkan banyak organ. Penggunaan hidroksiklorokuin (HCQ) memberikan beberapa keuntungan. Penelitian ini bertujuan untuk menganalisis efek hematologi dan okular setelah pemberian HCQ jangka pendek pada pasien SLE. Penelitian potong lintang yang dilakukan April hingga Juli 2022 ini menganalisis 23 pasien SLE wanita dewasa di Rumah Sakit Zainoel Abidin, Banda Aceh, Indonesia. Parameter laboratorium darah dianalisis, dan pemeriksaan okular dilakukan oleh dokter spesialis mata. Penelitian ini menunjukkan hemoglobin rata-rata 11,6 g/dL. Hasil laboratorium darah lainnya dalam batas normal. Durasi rata-rata diagnosis SLE dan penggunaan HCQ masing-masing adalah 21,0 bulan dan 9,7 bulan. Tidak ada korelasi antara durasi penggunaan HCQ dengan parameter hematologi (hemoglobin, leukosit dan trombosit) dengan nilai p masing-masing 0,38, 0,14 dan 0,62. Penelitian ini menunjukkan bahwa hanya satu pasien SLE yang mengonsumsi HCQ kurang dari 5 tahun mengalami masalah okular. Prevalensi efek okular dan hematologi pada pasien SLE yang diobati dengan HCQ di bawah 5 tahun sangat minimal.
Kata kunci: *lupus eritematosus sistemik, hidroksiklorokuin, hematologi, efek okular.*

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that mainly affects women of childbearing age and certain racial groups. This disease has various clinical manifestations and undergoes a disease process such as relapse and remission. Many organs and tissues are involved in SLE, such as the kidneys, heart, nerves, skin, joints, pleura, and pericardium. The prognosis of SLE was not so good earlier, especially in patients with organ involvement and frequent recurrences. Currently, the life expectancy of SLE patients is increasing, even in lupus nephritis, one of the most severe forms of SLE. A better understanding of the disease, earlier diagnosis, and better treatment compared to the past are said to lead to better outcomes in SLE patients.[1,2]

Despite having a better prognosis today, SLE is still a challenge for clinicians because most lupus patients require continuous treatment with glucocorticoids and/or immunosuppressive agents, which have significant side effects. This iatrogenic morbidity can impair the quality of life and long-term prognosis of SLE patients. The use of biologic agents can reduce the dose of synthetic drugs. However, the long-term safety and efficacy of available monoclonal antibodies, along with their high costs, limit the use of extensive biologic therapy in SLE patients. The use of hydroxychloroquine (HCQ) may offer several advantages, including controlling constitutional symptoms, avoiding the need for glucocorticoids, reducing the risk of flares and organ damage, and increasing the life expectancy of SLE patients. HCQ may reduce the risk of complications of antiphospholipid syndrome and can be used safely in pregnant women. In addition, HCQ is low-cost and has few side effects, encouraging greater use not only in patients with mild SLE but also in those with organ involvement.[3–5]

HCQ is increasingly being used in the treatment of SLE. However, HCQ has been associated with irreversible vision loss due to retinal toxicity. Retinal toxicity of HCQ is much more common than previously thought, with an overall prevalence of approximately 7.5% identified in patients taking HCQ for more than five years and increasing to nearly 20% after 20 years of treatment. SLE disease itself can manifest clinically in many parts of the eye, including the eyelids, ocular adnexa, sclera, cornea, uvea, retina, and optic nerve,[6,7] as well as hematologic disorders such as anemia, leukopenia, and thrombocytopenia.[8] Ocular manifestations of SLE are common and can lead to permanent blindness. Additionally, HCQ can also lead to agranulocytosis, aplastic anemia, and hemolysis.[9] This blindness and hematologic disorder can be the result of an underlying disease or a side effect of HCQ.[2,8] Therefore, this study aimed to examine hematological and ocular side effects such as visual acuity, corneal opacity, and retinal disorder (retinopathy) in SLE patients who used HCQ for less than five years.

Methods

This cross-sectional study was conducted at the Rheumatology and Ophthalmology Polyclinic of Zainoel Abidin Hospital (ZAH) from April to July 2022 with the approval of the Research Ethics Commission of the Faculty of Medicine Universitas Syiah Kuala/Zainoel Abidin Hospital No. 053/EA/FK-RSUDZA/2022. A consecutive sampling method was used in this study, and a total of 23 respondents were calculated using the Lameshow formula for a cross-sectional study.[10]

The respondents in the study were adult outpatients diagnosed with SLE using the 2019 revised diagnostic criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), who met the inclusion and exclusion criteria.[11,12] Patients are willing to participate in this study in writing by signing an informed consent after receiving an explanation about the study. Subjects were selected based on the following inclusion criteria: patients aged >18 years who had used HCQ for at least 1 month and were treated at the outpatient center of ZAH.

Exclusion criteria were patients with diabetes mellitus (DM) and hypertension, pregnant, and with previous ocular disorders. Subjects were

evaluated for ocular function, including visual acuity (checked with a Snellen chart), corneal opacity (assessed with a slit lamp), and retinal disorders/retinopathy (assessed with fundoscopy) by an ophthalmologist. Furthermore, the patient underwent laboratory blood tests, including hematology parameters, kidney function, electrolytes, and homeostatic function. The data were analyzed using tables and graphs, with the student t-test and Pearson correlation. The value of $p<0.05$ was considered significant.

Result

This study analyzed 23 patients who met the inclusion and exclusion criteria, with sample selection as shown in Figure 1.

Figure 1 showed that the initial respondents were 25 patients, but two patients were excluded because they had a history of diabetes mellitus, and another patient had suffered from ocular disorders. Table 1 showed that all patients in this study were female, with an average age of 29.4 years. The mean duration of SLE diagnosis was 21.0 months, and the median duration of HCQ therapy was 9.7 months.

Patients were also in mild to moderate disease activity, with a SLEDAI score of 6 at the time of examination. Regarding immunosuppressant therapy, most patients (n=19) used mycophenolate mofetil, and all patients used low-dose methylprednisolone.

Table 2 showed that the average SLE patient taking HCQ is mildly anemic with normal leukocyte and platelet counts. In addition, the patient did not experience impaired kidney function, with normal urea, creatinine, and proteinuria, and normal electrolyte values.

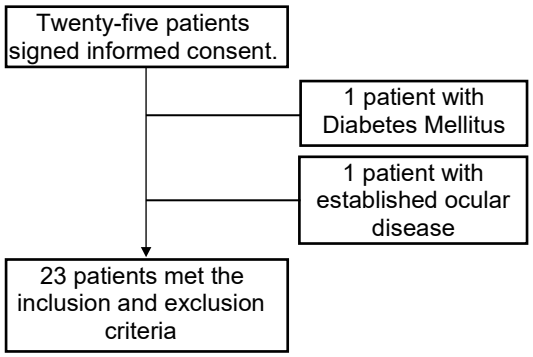

Figure 1. Selection Process of Respondents

Table 1. Baseline Characteristics of Respondents

Characteristic	Frequency
Sex - Female (n)	23
Age (years old) (mean ± SD)	29.4 ± 8.4
Duration of SLE Diagnosis (months) (mean ± SD)	21.0 ± 17.7
Duration of HCQ Therapy (months) (mean ± SD)	9.7 ± 6.2
SLEDAI score (median, min-max)	6 (4−6)
Immunosuppressant Therapy (n)	
Mycophenolate mofetil	19
Methotrexate	3
Cyclosporin	1
Methylprednisolone	23
Prednisone	1

Patients' hemostatic function was also normal with regular PT (INR) and aPTT ratio.

The relationship between HCQ treatment duration and laboratory parameters was examined to evaluate potential effects in patients with SLE (Figure 2). Pearson's correlation analysis, presented in, demonstrated no significant association between the length of HCQ therapy and haematological parameters, as indicated by p values greater than 0.05 and low correlation coefficients (r). In addition to laboratory assessments, ocular disorders were evaluated among SLE patients who had been receiving HCQ for less than five years. The analysis revealed that only one patient experienced visual impairment, characterized by reduced visual acuity, while no cases of corneal opacity or retinal abnormalities, including retinopathy, were observed. Collectively, these findings suggest that within the studied treatment duration, HCQ use was not associated with notable hematological alterations or significant ocular complications, aside from a single instance of diminished visual acuity.

Table 2. Laboratory Parameters of SLE Patients using Hydroxychloroquine

Laboratory Parameters	Mean ± SD
Hemoglobin (g/dl)	11.6 ± 1.0
Leukocyte (x10^{3}cells/mm^3)	9.6 ± 3.1
Thrombocyte (x10^{3}cells/mm^3)	332 ± 71.5
Urea (mg/dL) (median, min-max)	26 (12−64)
Creatinine (mg/dL)	0.77 ± 0.2
Proteinuria (semi-quantitative) (median, min-max)	0 (0−2)
Natrium (mmol/L)	141 ± 2.5
Kalium (mmol/L)	4.1 ± 0.3
Chloride (mmol/L)	109 ± 2.0
PT (INR)	1.05 ± 0.1
aPTT ratio	1.0 ± 0.1

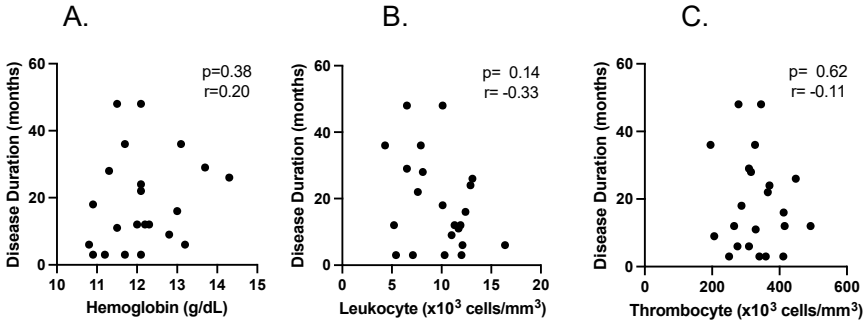

Figure 2. **Correlation Between Hematology Parameters (Hemoglobin, A, Leukocyte, B and Thrombocyte, C) with Duration of HCQ Therapy With 95% Confidence Interval of -0.32 To 0.49, -0.40 to 0.42 and -0.41 to 0.41 Respectively.**

Discussion

This study analyzed the ocular effects of HCQ therapy in 23 SLE patients who met the inclusion and exclusion criteria and had used the drug for less than 5 years. The baseline characteristics of the study sample showed that all SLE patients were female. It has been stated in all literature related to SLE that the prevalence of

female SLE patients is around 90%.[2,8,13] SLE is a prototypical systemic autoimmune disease that involves almost all parts of the immune system, but humoral autoimmunity, with characteristic autoantibody production and serum cytokine dysregulation, is a hallmark of this disease. SLE is characterized by a 9:1 disease incidence ratio between women and men, with a higher female predominance during the peak reproductive years. Despite recent advances in the understanding of SLE, the striking 9:1 disease incidence ratio in women and men remains largely unexplained.[8]

Many theories explain why SLE is predominantly a disease of women. One of the main differences between men and women is the ability to reproduce the placenta. Elevated interferon-alpha (IFN-α) is thought to play a pathogenic role in SLE, and the placenta expresses this cytokine. Many experts suggest that IFN-α contributes to successful placental reproduction, and the potential for upregulation of this cytokine system in women can increase reproductive capacity and simultaneously increase susceptibility to SLE.[14,15]

In terms of age, the average SLE patient is a young woman with an average age of 35 years. This has been widely reported in the literature, which states that the peak incidence of disease in women occurs in the reproductive age (20−30 years), while men tend to reach their peak in middle age (45−60 years). Genetic factors play an important role in the pathophysiology of SLE at a young age, as more than 7% of patients develop the disease due to a single-gene mutation, with the remainder carrying a genetic variant required for disease progression that requires additional factors. The increased genetic impact likely contributes to earlier disease onset and more severe phenotype.[2,8,13,14,16]

The relatively short duration since SLE diagnosis among patients may be attributed to the recent development of diagnostic support facilities at ZAH, following the establishment of the Rheumatology Polyclinic in 2018. Although the prognosis of SLE patients worldwide tends to be better, data on survival in Aceh or Indonesia are not yet available. Furthermore, the duration of HCQ use is relatively short in SLE patients in the hospital. This is due to HCQ being available in ZAH only after the COVID-19 pandemic began in 2020. Initially, the HCQ drug was provided by ZAH as a COVID-19 therapy when HCQ was still one of the additional therapies for COVID-19.[17] HCQ tends to be prescribed in private practice in the Province of Aceh previously, and most patients cannot afford to buy the drug because it is still rarely found in pharmacies and the price is relatively high.

We also assessed SLE disease activity in patients attending the Rheumatology Polyclinic of ZAH using the SLEDAI-2000 score. The primary advantage of SLEDAI-2000 is its ease of assessment, which enables its use in clinical practice. Another advantage of this SLEDAI score is that it can be used for retrospective studies.[18] It appears that patients who seek treatment at the Rheumatology Polyclinic of ZAH have an average SLEDAI score of 6 with a range of 4−6 and are included in the category of mild (1−5) and moderate disease activity (6−12).[19] Flares in SLE range in severity from mild or moderate, which can be managed in the clinic, to life-threatening flares that require hospitalization. These disease flares increase the risk of permanent organ damage, are linked to substantial morbidity, and contribute to elevated healthcare costs. Limiting the frequency and severity of flares has been an ongoing goal in the management of SLE, so it is important to assess a patient's disease activity at least once a month.[20]

We also assessed immunosuppressant therapy used by patients with SLE. All patients took methylprednisolone as a maintenance immunosuppressant. In addition, most patients (n=19) used Mofetil Mycophenolate as the primary immunosuppressant therapy. Only a few patients were treated with methotrexate and cyclosporine. This is in line with the management guidelines published by the Indonesian Rheumatology Association, which divides non-renal SLE therapy based on the degree of SLE disease: mild, moderate, and severe. Whereas for mild degrees, it is recommended to give steroid therapy plus HCQ or methotrexate, and administration of Mofetil Mycophenolate or cyclosporine for

patients with moderate degrees. Alternative therapies such as azathioprine are not available at ZAH, so they are rarely prescribed at the Rheumatology Polyclinic.[12,21]

To assess the effect of HCQ on hematologic and metabolic parameters, we analyzed laboratory results at the time patients arrived at the Polyclinic. The results indicated that hematological, renal, electrolyte, and hemostasis parameters remained within normal limits among SLE patients receiving HCQ therapy. This is also in line with disease severity, which showed that most patients were in a mild stage without involvement of multiple organs.

Anemia is a common hematological disorder in SLE, defined as hemoglobin <12g/dL in women and <13.5 g/dL in men.[22] The type of anemia in this study patient is not known because most of the existing laboratories do not include hematological profile examinations, such as serum iron, TIBC, ferritin, and reticulocytes. Future studies should further examine the causes of anemia in SLE patients attending polyclinics, enabling better treatment. Furthermore, this study did not find leukopenia or thrombocytopenia in all patients studied. Decreased white blood cell count (leukopenia) usually correlates with disease activity in SLE patients. Thrombocytopenia in SLE can also be caused by more complex mechanisms, such as the interaction of antiphospholipid antibodies and antibodies to platelet antigens[20,21]

Of the various organ systems, renal involvement is a primary concern in SLE disease and affects many patients, causing significant morbidity and mortality. Urea and serum creatinine are the most common laboratory markers of renal dysfunction, regardless of the cause. It is well recognized that the renal manifestations of lupus (including proteinuria, hematuria, and urinary casts) are an important feature of SLEDAI and are closely related to SLEDAI.[25,26] Serum electrolytes are also an important parameter of SLE disease progression, with hyponatremia as the most common electrolyte disorder occurring in SLE patients.[27] This study did not find a decrease in serum electrolyte levels in the patients.

The study showed that the mean INR and aPTT ratio were expected in the SLE-studied patients. INR and aPTT are markers of thrombosis that are often monitored, as SLE patients tend to have an increased risk of thrombosis. The age at onset of thrombosis in SLE patients is lower than in the general population, and the incidence of thrombosis increases in the first year. The increased incidence of early thrombosis may be due to higher levels of disease activity, circulating immune complexes, cytotoxic antibodies, or a more inflammatory state.[28,29]

This study also assessed the relationship between HCQ therapy duration and hematological parameters in SLE patients receiving HCQ, and found no correlation between the two variables. This is probably due to the duration of HCQ therapy, which was still new. A study by Zahr et al.[30] on the pharmacokinetics and pharmacodynamics of HCQ in 55 SLE patients found that HCQ clearance from the blood depends on platelet count, with higher platelet counts associated with lower HCQ clearance.[30] This decrease in elimination may be due to the binding of HCQ to platelets, which leads to maintaining HCQ in the bloodstream and reducing HCQ elimination.[30] Another explanation for the lack of association between HCQ duration and hematologic parameters may be that the SLE patients included in this study were consistently using HCQ, thereby preventing disease flares that could otherwise affect hematologic values. A study by Aohab et al[31,] which assessed the effect of discontinuing HCQ therapy in more than 500 SLE patients, showed that patients who discontinued HCQ after less than 1 year of treatment were at greater risk of relapse than those who took HCQ for more than 1 year.[31] Similarly, a randomized, prospective, controlled trial conducted by the Canadian HCQ Study Group in 1999 evaluated the effects of discontinuing hydroxychloroquine therapy over six months in 47 patients with SLE. The study found that patients who discontinued HCQ were more likely to experience disease flares and had a shorter time to flare onset compared to those who continued therapy.[32]

This study found that only one patient developed an ocular disorder (reduced visual acuity) after using HCQ for less than 5 years. This ocular disorder was probably not related to the duration of HCQ use since 22 other patients did not show reduced visual acuity. Most studies showed that the therapeutic effect of HCQ generally occurs after five years of treatment; therefore, ophthalmological screening for HCQ effects is performed before administration, after five years of administration, and every year thereafter.[7,9,21,22,33,34] Ocular disturbances are a dreaded complication of HCQ use. As previously mentioned, the effect of HCQ on disease activity and clinical manifestations of SLE, including ocular toxicity, is highly dependent on its blood levels. A study by Zahr et al. [35] stated that the concentration of HCQ in blood is a predictor of SLE disease activity, including ocular toxicity.[30] Research by Petri et al (2020) also reported that blood levels of HCQ predict retinal toxicity and should be used in clinical practice to guide future HCQ dosing.[35] Retinopathy is more common at higher blood levels of HCQ and usually occurs in patients treated for more than five years. The study concluded that HCQ levels should guide dose reduction to minimize toxicity.[35] However, another recent study by Lenfant et al[36] found no similarly significant association between HCQ levels and the risk of ocular toxicity. The study included 23 patients taking HCQ with retinal toxicity and 547 healthy controls taking HCQ for more than six months.[36] This study identified an association between the cumulative dose of HCQ and longer duration of drug use and risk of retinopathy.[36] The low finding of ocular disorder in SLE patients who used HCQ for less than five years in this study is consistent with the existing studies that showed the effect of using HCQ in SLE patients is a long-term effect after five years of therapy. However, further study with more respondents should be done to exclude HCQ as a cause of ocular disorder in SLE patients below five years of treatment.

This study has weaknesses because it analyzed only a limited number of respondents. However, this is due to the limited number of SLE patients who visited the Rheumatology Polyclinic of ZAH, a provincial referral hospital. Additionally, the examination of blood laboratory parameters was incomplete, and no examination of HCQ levels was performed due to the hospital's limited resources. In addition, this study involved direct ocular examination by an ophthalmologist, thereby reducing biases in the interpretation of results.

Conclusion

No abnormalities were observed in laboratory parameters of female SLE patients using HCQ for less than 5 years. Additionally, the study also did not find a correlation between hematological parameters and the duration of HCQ therapy. Although one patient exhibited impaired visual acuity, this ocular disturbance did not appear to be associated with the duration of HCQ therapy.

Ethics Statement

The study had been approved by the Research Ethics Commission of the Faculty of Medicine Universitas Syiah Kuala/Zainoel Abidin Hospital No. 053/EA/FK-RSUDZA/2022.

Consent for Publication

No personal data or images are included.

Competing Interests

The authors declare no conflict of interest.

Authors' Contributions

All authors were involved in the study design. MM, MS, VA and EN were involved in data collection and data analysis. All authors were involved in manuscript writing, critically revising, and approving the final version.

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Availability of Data and Materials

The data used in the study are not publicly available.

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