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Original Research

Monotherapy versus polytherapy of enoxaparin and hydroxychloroquine for the treatment of COVID-19: A randomized controlled clinical trial

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Abstract

Objectives: The current study aims to assess the efficacy and safety of Enoxaparin and hydroxychloroquine (HCQ) used as monothrapy or polytherapy versus standard care alone in Coronavirus 2019 (COVID-19) infected patients. **Methods:** The current study included two hundred patients with laboratory confirmed COVID-19 infection. Patients admitted to hospital were randomly allocated into four groups: group I: received standard COVID-19 therapy, group II: received Enoxaparin 40mg/day subcutaneously (SC) plus standard therapy, group III: received 400 mg/day HCQ plus standard therapy & group IV: received a combination of 400 mg/day HCQ and Enoxaparin plus standard COVID-19 therapy. The disease progression was evaluated by duration to a negative polymerase chain reaction (PCR), length of hospital or Intensive Care Unit (ICU) stay, and mortality rate. The safety of treatments was evaluated by measuring adverse effects. **Results:** The length of hospital stay, ICU admission and mortality were significantly decreased in Enoxaparin plus standard COVID-19 therapy group versus other groups. **Conclusion:** These findings suggest that Enoxaparin was safe, effective, and well tolerated and has a role in decreasing the progression of the disease and its complications while HCQ did not discover any evidence of extra therapeutic benefits.

Keywords: COVID-19 infection; enoxaparin; hydroxychloroquine; ICU stay; length of hospital stay; mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (severe acute respiratory syndrome coronavirus 2), continues to raise several serious concerns with its significant morbidity and mortality worldwide. The hasty global spread of COVID-19 has resulted in an enormous health and economic burden. The number of COVID-19 cases are on the rise with many severe cases developing to acute respiratory distress syndrome (ARDS). While many mild COVID-19 patients have been managed through quarantine and self-medication, the management of other hospitalized moderate or severe COVID-19 cases has been quite confusing and challenging.[1] This serious and rapid deterioration of some cases are is due to an over production of cytokines and immune cells that lead to rapid multi-organ system failure in what is known as cytokine storm. Therefore, developing an effective therapeutic approach which suppresses overactive cytokines was an urgent need to contain the increasing complicated epidemic situation. Because of the critical public emergency, some drugs have been rapidly identified as potential low-cost drug candidates such as HCQ and its derivatives. HCQ and its analogues have been long used for prevention and treatment of malaria as well as some rheumatologic conditions such as systemic lupus erythematosus.[2] HCQ was found to be effective against COVID-19 by two potential mechanisms, first by inhibiting the virus entry and replication into human cells,[3] and second by inhibiting the production and activation of several cytokines that are highly elevated in COVID-19 patients.[4] Several randomized controlled trials have observed favorable therapeutic effects of HCQ in COVID-19 patients regarding fever reduction and retarded disease progression and has been officially declared as a medical agent for COVID-19.[4]

In addition to the acute respiratory distress syndrome (ARDS) associated with COVID-19 infections, coagulopathy complications have also been reported. More accumulating evidence indicates that coagulation parameters especially high D-dimers can prognostically indicate patients with

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high thrombotic events and significant mortality.[5] The high incidence of thrombotic complications in 31% of COVID-19 ICU patients,[6] reinforced the recommendation to strictly apply thrombotic prophylaxis to all admitted COVID-19 patients by several organizations, including; the American society of hematology,[7] International Society on Thrombosis and Hemostasis,[8] and CHEST Guideline and Expert Panel.[9] As a results, many anticoagulants such as unfractionated Heparin, Enoxaparin, and Rivaroxaban are now being used as needed in COVID-19 patient management.[1,10] Several observational studies have reported that early Tthrombotic prophylaxis may improve patients' clinical outcomes[11-13] and even reduce mortality risk.[14] The use of low molecular weight heparins (LMWH) has been recommended as the standard therapy in hospitalized COVID-19 patients. LMWHs such as Enoxaparin has been found as attractive therapeutic options due to their specific antithrombotic, anti-inflammatory as well as their antiviral activities against COVID-19.[15] However, the availability of clinical data about Enoxaparin is still limited.[16] Although COVID-19 is nowadays the major global concern and numerous therapeutic agents are under investigation, still there are currently no proven or approved treatments. To date, HCQ and Enoxaparin have had been widely used for COVID-19 patients' management based on very limited data as their efficacy on clinically relevant endpoint as well as their safety concerns are yet to be demonstrated. Therefore, this study aimed to assess the efficacy and safety of Enoxaparin and HCQ used separately or combined added to the standard care versus the standard care alone in COVID-19 infected patients.

MATERIALS AND METHODS

Two hundred hospitalized patients (98 males and 102 female) with ages ranging from 18 to 65 years old were admitted to university hospital, during the period from December 2020 to June 2021. COVID-19 infection was confirmed by positive SARS-COVID-2 PCR test through nasopharyngeal swab. The conventional COVID-19 protocol of the Egyptian Ministry of Health (MOH) was adopted and included the following: paracetamol, oxygen, empiric antibiotic therapy (if needed), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO2 < 60 mmHg, O2 saturation < 90%.

Inclusion criteria

Laboratory confirmed COVID-19 infection by PCR test within 7 days prior to admission to hospital, CT or radiographic findings of pneumonia. All included patients suffered from loss of smell and taste.

Exclusion criteria

Patient who had allergy or contraindication to HCQ, pregnant and lactating females, and patients with immune diseases, cardiac problem, had history of acute kidney injury or who received multiple cycles of anticoagulants were excluded from the study. Written informed consent was obtained from each participant. All study risks and benefits were thoroughly explained to patients' prior participation. The study was conducted in accordance with the guidelines of Good Clinical Practice and was approved by the Research Ethics Committee in accordance with the declaration of Helsinki with serial number: REC-H-PhBSU-21013. The current study is registered in Clinical.Trial.gov. (number: NCT05311813).

Study design

The current study is randomized clinical trial. Study Patients were randomized into four parallel equal groups using a computerized random number generator using simple randomization by a computerized random number generator with an equal allocation ratio. Two hundred and twenty patients were eligible. Twenty patients were excluded due to not meeting the inclusion criteria (n=14) or the decline to be enrolled in the study (n=4). The sample size was calculated by Power version 3.1 for windows (Faul et al., 2009). With a priori calculating the sample size based on the length of stay among the studied groups using one-way ANOVA test (F-test group), at an effect size (0.306), alpha probability (0.05) and power (95%), the calculated sample size was 184 in the 4 groups that increased to 200 (with 6% increase) to overcome the missing of data and dropout or loss of follow up. All included patients were with normal renal function and body weight between 50 and 100kg.

Group I: The control group including 50 patients (n=50) receiving the conventional therapy of COVID-19 adopted by the Egyptian ministry of health for 15 days.

Group II: The Enoxaparin group (n=50) which received 40mg/day SC for 14 days plus the conventional therapy of COVID-19 adopted by the Egyptian ministry of health for 15 days.

Group III: The HCQ group which received 400 mg/day HCQ for five days plus the conventional therapy of COVID-19 adopted by the Egyptian ministry of health for 15 days(n=50).

Group IV: The HCQ plus Enoxaparin combination group including 50 patients receiving combined therapy of 400 mg/day HCQ for five days and 40mg/day Enoxaparin for 14 days plus the conventional therapy of COVID-19 adopted by the Egyptian ministry of health for 15 days.

Eligible patients were subjected to a complete and detailed medical history and full clinical examination. All their demographic and baseline characteristics were recorded (Age, gender, weight, height, BMI). Admission date, discharge date, and respiratory rate were recorded on admission. Liver biochemistries including alanine amino transferase (ALT) and aspartate amino transferase (AST), random blood glucose (RBG) level, systolic and diastolic blood pressure (BP) were measured for all eligible patients at baseline and post therapy. The primary endpoint aimed to evaluate the efficacy of each treatment regimen by determining the duration to negative PCR, the length of hospital stay, or ICU stay and the rate of mortality after 28 days. The progression of the disease was measured by comparing the complications and the symptoms of the studied patients treated by different regimens. The secondary endpoint aimed to evaluate the safety of each regimen by the clinical assessment of liver biochemistries, random blood glucose, systolic and diastolic blood pressure BP and report any problems related to drug used.

Statistical analysis

Statistical analysis was performed using SPSS (version 23). Basic

descriptive statistics including means and standard deviation were calculated. Categorical variables were presented as number and percent. Normality in each group was explored by Kolmogorov Smirnov test. Age and blood pressure BP were compared between groups by one-way ANOVA while Kruskal Wallis was used to compare the four groups regarding the laboratory parameters and length of stay in ICU and hospital. Wilcoxon signed rank was used to compare the laboratory parameters in each group in addition to compare their percent of increase of laboratory parameters as well. Percent of decrease of laboratory parameters were calculated as follows:

[(pre-post)/pre]X100.

Negative signs of means that the labs increased after the intervention. Chi-square test was used for the comparison of qualitative data between groups. P-value ≤ 0.05 was considered statistically significant.

RESULTS

The demographic and baseline characteristics of the treatment groups were presented in Table 1.

As presented in table 1, no significant statistical difference was detected between the four groups at baseline regarding age, sex, BMI, co-morbidities, smoking, and systolic and diastolic BP. There was a significant improvement in symptoms of the group treated with Enoxaparin with no observed side effects indicating that the drug is effective and well tolerated as shown in Figure 1.

As shown in table 2; a significant decrease in the length of hospital stay was observed between the Enoxaparin group compared to all other treatment groups. The length of hospital stay was 7.1±4, 4.6±1.9 ,8.3±3.4 and 7.7±2.3 days for the conventional treatment group, Enoxaparin group, HCQ group and HCQ + Enoxaparin group respectively. In addition, the length of ICU stay was significantly reduced for the Enoxaparin treatment group to be 1.50±0.7 Vs 2.4±1.3, 14.5±11, and 10±7 for the Conventional treatment group, HCQ group and HCQ+

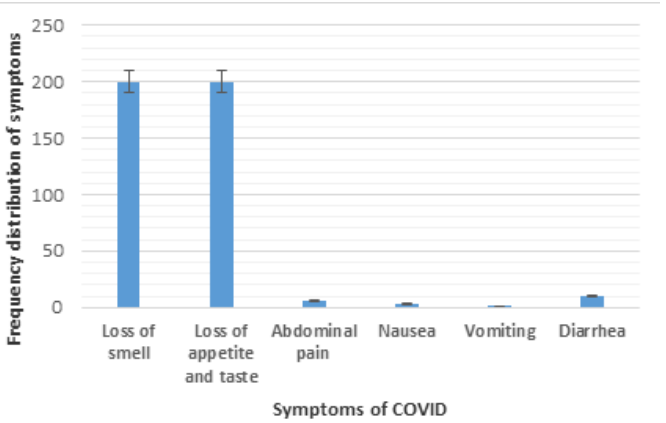

Figure 1. Frequency distribution of symptoms of COVID-19

Enoxaparin groups respectively. In addition, the mortality was significantly reduced in the Enoxaparin group compared to all other groups. However, the duration to negative PCR did not show any significance among all treatment groups (Table 3).

There was no significant difference between baseline and post treatment regarding RBG serum ALT and serum AST for all treatment groups as illustrated in figures 2, 3 and 4. All included patients were hospitalized with healthy diet in order not to elevate the blood glucose level since many theories assured that COVID-19 affects the blood glucose level. Comparison of RBG at baseline and post treatment among all treatment groups showed non-significant difference with P-value of 0.567, 0.205, 0.770 and 0.286 of conventional therapy group, Enoxaparin group, HCQ group and combined group respectively as illustrated in Figure 2.

Comparison of ALT at baseline and post treatment among all treatment groups showed non-significant difference with P-value of 0.688, 0.201, 0.380 and 0.952 of conventional therapy group, Enoxaparin group, HCQ group and combined group respectively as indicated in Figure 3.

Comparison of AST at baseline and post treatment among all treatment groups showed non-significant difference with

Table 1. Demographic and baseline characteristics of the treatment groups (n=200)

Characteristics	Category	Group I (no=50)	Group II (no=50)	Group III (no=50)	Group IV (no=50)	P-value
Age, Yr (mean ± SD)		52.3±19.6	56.9±11.1	48.9±18.6	50±17.3	0.095
Gender, no (%)	Male Female	26 (52.0%) 24(48.0%)	24(48.0%) 26(52.0%)	26(52.0%) 24(48.0%)	22(44.0%) 28(56.0%)	0.830
BMI, no (%)	Normal Overweight Obese	12 (24%) 15 (30%) 23 (46%)	9 (18%) 13 (26%) 28 (56%)	11 (22%) 8 (16%) 31 (62%)	8 (16%) 7 (14%) 35 (70%)	0.571
Smoking, no (%)	Current Ex-Smoker Never	22 (44%) 5 (10%) 23 (46%)	28 (56%) 4 (8%) 18 (36%)	33 (66%) 0 (0%) 17 (34%)	25 (50%) 2 (4%) 23 (46%)	0.381
Co-morbidities		15 (30%)	18 (36%)	13 (26%)	14 (28%)	0.094
Blood Pressure (mmHg)	Pre systole Post systole	118.4±10.7 118.8±10	117.8±9.9 118±9.2	117±6.7 117.6±5.9	116.2±6.7 116.2±6.6	0.615 0.447
	Pre diastole Post diastole	77.3±9.3 78.2±8.2	73.6±11 73.8±10.1	73.2±9.5 74.6±8.4	75±9.1 75.4±7.6	0.154 0.064

Table 2. Clinical disease course in the four treatment groups, (n=200)

Clinical Course in days (mean ± SD)	Group I (no=50)	Group II (no=50)	Group III (no=50)	Group IV (no=50)	P-value
Duration to negative PCR	15.10±2.84	14.94±2.14	15.22±1.97	15.87±2.11	0.12
Length of hospital stay	7.10±4[a]	4.60±1.9[b]	8.30±3.4[a]	7.70±2.3[a]	0.001*
Length of ICU stay	2.40±1.3[a]	1.50±0.7[a]	14.5±11[b]	10.0±7[b]	0.003*
Mortality, no (%)	2 (4.0%)	0 (0.0%)	3 (6.0%)	1 (2.0%)	0.04

*: denotes significant difference between groups.

Table 3. Comparison of the laboratory parameters pre and post each treatment regimens in the four study groups (n=200)

Laboratory parameter Mean ± SD		Group-I (no=50)	Group-II (no=50)	Group-III (no=50)	Group IV (no=50)	P-value
Random Blood Glucose (RBG)	Baseline RBG	140.4±55.7[a]	140.4±43.9	182.1±51.7[b]	178.6±59.5[b]	<0.001*
	Post treatment RBG	135.9±39.8[a]	139.2±52.7[a]	181.2±51.6[b]	178.6±68.2[b]	<0.001*
Paired test P-value (WS)		0.567	0.205	0.770	0.286	
AST	Baseline AST	29.4±9.6[a]	34.4±10.1[b]	36.3±20.9[b]	32.9±14.6[b]	0.002* (KW)
	Post treatment AST	31.8±16[a]	34.2±10.7[b]	36.5±20.6[b]	32.4±11.8[a]	
Paired test P-value (WS)		0.668	0.562	0.459	0.733	
ALT	Baseline ALT	19.8±12.1[a]	24.2±7.9[b]	25.6±14.5[b]	22.4±10.6[a]	<0.001* (KW)
	Post treatment ALT	20±11.8[a]	24.6±8.7[b]	25.9±14.6[b]	22.2±9.2[a]	
Paired test P-value (WS)		0.688	0.201	0.380	0.952	

WS: Wilcoxon signed rank test (for comparison between pre and post)
KW: Kruskal Wallis was used to compare between the 4 groups

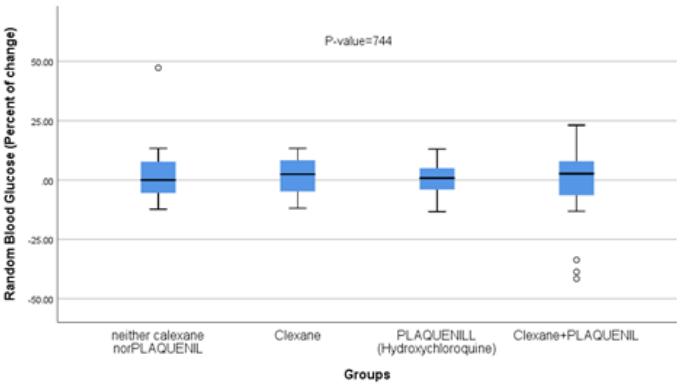

Figure 2. Comparison between the four studies groups regarding the percentage of decrease of RB1

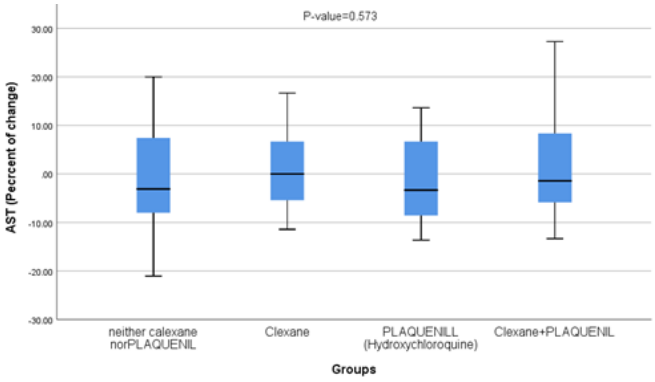

Figure 3. Comparison between the four studies groups regarding the percentage of decrease of AST

P-value of 0.668, 0.562, 0.459 and 0.733 of conventional therapy group, Enoxaparin group, HCQ group and combined group respectively as shown in Figure 4.

DISCUSSION

The dramatic impact of COVID-19 pandemic worldwide has mandated an urgent need to develop effective therapeutic interventions to contain the epidemic. Indeed, the world is still lacking a well-established therapy and fixed treatment protocol. Researchers are now focusing on testing different therapeutic approaches to prevent infections and decrease complications. To date, HCQ and Enoxaparin have been widely used for COVID-19 patients' management based on very limited data. Therefore, this study aimed to assess the efficacy and safety of Enoxaparin and HCQ used separately or combined added to the standard care versus the standard care alone in COVID-19 infected patients. This study has shown that Enoxaparin had a significant decrease in the length of hospital stay, ICU stay compared to other treatment groups, which was consistent with several previous studies. For example, our results were in accordance with Albani et al; another cohort study which reported that Enoxaparin is associated with a decrease in the length of hospital stay, length of ICU stay and lower death rate in patients hospitalized with SARS-COV-2 infection.[17] In addition, another study by Pawlowski et al. has highlighted the superior efficacy of Enoxaparin versus unfractionated heparin use in reducing the 28-day venous thromboembolism and mortality rates in COVID-19 patients.[1]

The more superior clinical effect of Enoxaparin group compared

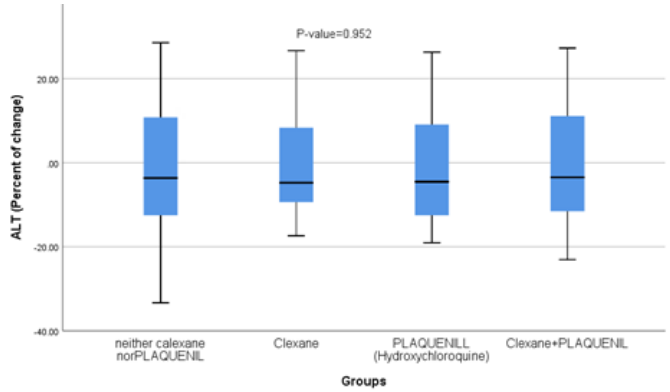

Figure 4. Comparison between the four studies groups regarding the percentage of decrease of ALT

to all other groups may be due to the wide pharmacological action of Enoxaparin which can overcome many aspects of COVID-19 infections. Several previous studies have reported that LMWH such as Enoxaparin can overcome COVID-19 by multiple mechanism including, an antiviral effect that was proven by both in vitro and in vivo studies, anti-inflammatory effect, plus the antithrombotic action.[1,18] A previous study has reported beneficial Enoxaparin effects in reducing all inflammatory markers of COVID-19 patients such as, D-dimer, CRP, lactate dehydrogenase, and interlukeukin-6 (IL-6). This reduction in all inflammatory markers suggests a very good potential in relieving the inflammation in COVID-19 patients which was noted to be more pronounced in patients with severe disease. Another study by Shi et al demonstrated that the use of Enoxaparin led to higher percentage of lymphocytes and lower levels of IL-6 which are of utmost importance in modulating the virus inflammatory response.[19] At the beginning of the pandemic, HCQ was another promising drug to be used in COVID-19 patients where several studies have shown an improved decline in viral load with HCQ use.[20] However later, many conflicting studies results have been published which led to FDA to reconsider the role of HCQ in COVID-19 patients' managements.[21] Our study did not find any extra beneficial effect when using HCQ in COVID-19 patients compared to other treatment groups regarding duration of infections ICU or hospital stay. A previous meta-analysis of several studies that included large number of patients showed that HCQ treatment was associated with less fever, cough and lung lesions. However, no difference was found in viral load or mortality.[22] Furthermore, many other trials did not discover any benefit for HCQ use in COVID-19 and even showed more adverse effects with its use.[23,24] Another clinical trial investigated the effect of HCQ compared with placebo and did not report any improved clinical status at day 14 and even reported longer hospitalizations and mortality rates for the HCQ group.[25] Another study that aimed to assess the efficacy and safety of HCQ in Egyptian COVID-19 patients also showed no significant effect of HCQ on patients-clinical disease progression, need for ventilation and mortality.[21] Furthermore, another clinical trial among hospitalized patients with mild to moderate COVID-19 , the use of HCQ alone or with azithromycin did not add any significant benefits to the patients compared to their standard care during 15 days of treatment.[26] At the beginning, HCQ was a very attractive drug option to be used in COVID-19 management due to its availability, low-cost and safety. However, the results from different studies were not convincing enough to continue its use especially with its potential cardiotoxicity. The results of large multi-center SOLIDARITY trial which will include the use of HCQ across 150 sites is keenly awaited to make more definitive therapeutic decisions on the use of HCQ in COVID-19 patients management. Our study added extra evidence on the lack of benefit of HCQ and the superiority of Enoxaparin in improving the clinical course of COVID-19 patients. However, to draw a firmer conclusion on the role of Enoxaparin and HCQ in COVID-19, needs larger multicenter trials using drugs alone or in combination with other drugs/lines of treatment with different doses ranges. More future studies are needed to enable the development of more efficacious clinical management procedures especially that clinicians are now able to collect data in real world settings as imposed by the COVID-19 critical situation.

CONCLUSIONS

This study concluded that Enoxaparin treatment was both safe and effective and has a role in improving COVID-19 clinical course. However, the use of HCQ alone or in combination with Enoxaparin has no clinical significance and even increased the duration of hospitalization.

Limitation of the study: The limitations of the current study include small sample size, for small duration and the absence of multicenter approach. In addition, in this study, we studied only patients who received one dose of Enoxaparin while different dosages are available for Enoxaparin.

AUTHOR CONTRIBUTIONS

Conceptualization: Amira S.A. Said, Lamiaa N Abdelaty, Alzhraa M. Fahmy, Raghda R.S. Hussein, Ahmed H.A. Hassanein. Data curation: Lamiaa N Abdelaty, Raghda R.S. Hussein., Formal Analysis: Doaa Mahmoud Khalil, Investigation: All authors,Project Administration: All authors, Methodology: Amira S.A. Said, Lamiaa N Abdelaty, Alzhraa M. Fahmy, Raghda R.S. Hussein, Ahmed H.A. Hassanein., Software: Doaa Mahmoud Khalil. Validation: Doaa Mahmoud Khalil., Resources: All Authors. Writing—original draft preparation: All Authors. Writing—review and editing: All Authors. Visualization: All Authors. Project administration: All Authors. Funding acquisition: non, authors have read and agreed to the published version of the manuscript.

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INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and in accordance with the guidelines of Good Clinical Practice and was approved by the Research Ethics Committee with serial number: REC-H-PhBSU-21013. Also, the study was

registered in Clinical.Trial.gov. (number: NCT05311813).

INFORMED CONSENT STATEMENT

Written informed consent has been obtained from patients.

DATA AVAILABILITY STATEMENT

The data will be available from the corresponding author upon request.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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