

# BMJ Open Efficacy of combining aspirin with hydroxychloroquine in pregnancies at high risk for pre-eclampsia: a prospective, multicentre, open-label, single-arm clinical trial, investigator-initiated study (HUGS study)

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## ABSTRACT

**Introduction** The use of hydroxychloroquine (HCQ) during pregnancies complicated by systemic lupus erythematosus or refractory antiphospholipid antibody syndrome has demonstrated a significant ability to prevent pre-eclampsia (PE). As such, the potential for the administration of HCQ to prevent PE in other high-risk pregnancies is an important clinical research agenda among maternal and fetal medicine specialists. Mechanistically, the anti-inflammatory and immunomodulatory effects of HCQ can offer vascular protection and inhibit the placental dysfunction-associated thrombotic changes underlying the pathophysiology of PE, fetal growth restriction (FGR) and fetal death in utero (FDIU). Placenta-mediated complications exhibit a distinctive overlapping syndrome between pregnancies, and low-dose aspirin is the only prevention method currently in use. This study investigated the effects of improvements in outcomes with HCQ administration in high-risk pregnancies complicated by a previous experience of PE, FGR or FDIU.

**Methods and analysis** This multicentre, open-label, single-arm trial commenced on 31 May 2022, in three tertiary hospitals in Korea. Pregnant women with a prior history of PE, FGR or FDIU are eligible to participate. This single-arm study set the previous study with the most similar inclusion criteria, aspirin dose and drug administration period as the comparison group. The required sample size was determined to be 58, with an expected dropout rate of 10%.

**Ethics and dissemination** This study protocol was approved by the following institutions and committees: Institutional Review Boards of Chung-Ang University Gwangmyeong Hospital (2304-082-056), Samsung Medical Center (2021-11-087-003) and Kyungpook National University Chilgok Hospital (2021-06-005-006) and the Ministry of Food and Drug Safety. The results will be disseminated to the general public, grant funder, maternal-fetal medicine specialists and other researchers.

**Trial registration number** NCT05287321.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a clinical trial to evaluate the effects of hydroxychloroquine in the prevention of recurrent adverse pregnancy outcomes due to placental insufficiency, including pre-eclampsia, fetal growth restriction or fetal death in utero.
- ⇒ To address the statistical limitations of single-arm studies, our study includes a comparator group to confirm the efficacy and feasibility of hydroxychloroquine treatment during pregnancy through comprehensive clinical evaluation.
- ⇒ One limitation of our protocol is that single-arm, open-label clinical trials may be statistically underpowered compared with randomised controlled trials.
- ⇒ Since the study population includes three indications of previous adverse outcomes—pre-eclampsia, fetal growth restriction or fetal death in utero—the effects of hydroxychloroquine may vary depending on the specific indication.

## INTRODUCTION

Pre-eclampsia (PE) is a serious obstetric disease, affecting 5%–10% of all pregnancies and leading to pregnancy complications. In Korea, PE was the third-leading cause (5.5%) of maternal mortality from 2009 to 2014.<sup>1 2</sup> Global health data from 1990 to 2013 indicate that hypertensive disorders of pregnancy are responsible for 10%–20% of maternal deaths, being the second most common cause of direct maternal death.<sup>3</sup> PE is highly implicated in preterm delivery, fetal growth restriction (FGR) and fetal death in utero (FDIU). It often shares underlying mechanisms with other morbidities, particularly those related to placental insufficiency

and defective placentation, contributing to a high recurrence rate.<sup>4</sup> The high recurrence rate of PE in subsequent pregnancies underscores the importance of preventive treatment.<sup>5</sup> Although aspirin is the most commonly recognised preventive agent for PE, its reduction rate was only 10%–50% compared with that observed with no treatment.<sup>6–9</sup> Furthermore, despite the high recurrence rates of FGR and FDIU, no preventive measure has been established beyond close fetal surveillance; therefore, clinical studies on preventive medications are needed.

PE, FGR and FDIU are strongly inter-related with uteroplacental ischaemia and exhibit a high recurrence rate in subsequent pregnancies. Brosens *et al* suggested that different degrees of restricted remodelling and obstructive lesions of the myometrial spiral arteries could be associated with PE, FGR, preterm labour, preterm premature rupture of membranes, spontaneous abortion, abruptio placentae and placental infarcts with FDIU.<sup>4</sup> Importantly, those conditions show a significant clinical correlation, with a history increasing the risk of recurrence in subsequent pregnancies.

During the past two decades, the efficacy of aspirin as a prophylactic agent for PE has been proven. Numerous studies have established the preventive efficacy of low-dose aspirin use during pregnancy, for PE as well as for other placenta-related pregnancy complications such as FGR, FDIU, preterm delivery and recurrent pregnancy loss.<sup>10–15</sup> The reduction of PE varies between 10% and 50%, depending on the study. Most obstetrics guidelines recommend low-dose aspirin for patients with risk factors for PE.<sup>16–21</sup>

Recently, practice advisory from the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2021) endorsed the US Preventive Services Task Force (2021) recommendation for the use of aspirin in the presence of one or more high-risk factors or two or more moderate risk factors.<sup>20 22</sup> The US Preventive Services Task Force additionally included in vitro fertilisation as a moderate risk factor and further divided sociodemographic characteristics into black and low income. This decision was made based on the relationship between socioeconomic status and healthcare, rather than solely on biological racial characteristics.<sup>20</sup> Prophylactic aspirin use resulted in a 50% prevention rate of PE in the high-risk group and a 25% prevention rate in the moderate-risk group, suggesting a need for improvement in PE risk factor assessment to close the quality gap.<sup>23</sup>

Moderate risk factor includes the obstetric history such as previous adverse pregnancy outcomes or prior FGR. While the American College of Obstetricians and Gynecologists guideline (2018) does not recommend the use of aspirin based solely on personal history factors, previous adverse pregnancy is often accompanied by other moderate risks, making them mostly indications for aspirin use. Additionally, prior studies supported that use of aspirin in pregnancy with risk of PE showed reducing FGR rate.<sup>8 9 24 25</sup> However, the effectiveness of aspirin in

preventing FGR recurrence is insufficient. The lack of well-designed randomised controlled trials in low-risk groups for PE is the main reason for the limited evidence on the prevention of FGR, and previous studies have mainly focused on high-risk groups for PE.

Hydroxychloroquine (HCQ), a pregnancy-compatible medication, is commonly used to treat systemic lupus erythematosus (SLE), to maintain remission and to treat disease symptoms, during pregnancy.<sup>26</sup> Notably, the 2020 American College of Rheumatology Guideline strongly recommends the use of HCQ for pregnant patients with SLE or anti-Ro/La positivity.<sup>27</sup> Various mechanisms of HCQ have been suggested to explain its therapeutic effect on autoimmune disease during pregnancy. First, inhibition of lysosomal activity and Toll-like receptor signalling result in immunomodulatory or anti-inflammatory effects.<sup>28</sup> Second, HCQ is assumed to have antithrombotic effects on autoimmune disease with a secondary coagulopathy caused by endothelial inflammation.<sup>29–31</sup> Prior meta-analysis suggested the use of HCQ showed a reduction of obstetric complications, including PE, IUGR and preterm delivery, in pregnancies with SLE or antiphospholipid antibody syndrome.<sup>32–34</sup>

The positive effect of HCQ on pregnancy outcomes in patients with a poor pregnancy history has been widely investigated in recent years. The recent randomised controlled BBQ trial (NCT0316513) and ILIFE trial (NCT03671174) were initiated to demonstrate the effectiveness of HCQ in preventing miscarriage in patients with a recurrent history of pregnancy loss.<sup>35 36</sup> The French BBQ trial evaluated the use of HCQ (HCQ 400 mg or placebo), initiated before conception and stopped at 10 weeks' gestation, to prevent miscarriage in patients with recurrent pregnancy loss.<sup>35</sup> The Chinese ILIFE trial investigated the efficacy of HCQ (in maximal tolerance dose ranges from 100 to 400 mg daily orally) and low-dose prednisone (10 mg once daily orally) in preventing pregnancy loss in patients with undifferentiated connective tissue disease.<sup>36</sup> These interventions were started before conception (3–6 months) and stopped at 6 weeks' gestation.

With this knowledge, we hypothesised that HCQ would have the potential to prevent placenta-insufficient diseases, specifically PE, FGR and FDIU. The aim of this multicentre, open-label, single-arm clinical trial, investigator-initiated study is to demonstrate a new preventive treatment for placenta-related disease, based on the anti-inflammatory and immunosuppressive effects of HCQ combined with aspirin.

## METHODS AND ANALYSIS

### Study design

We are conducting a multicentre, open-label, single-arm trial in three tertiary institutions in South Korea: Samsung Medical Center, Chung-Ang University Gwangmyung Hospital and Kyungpook National University Chilgok Hospital. When this trial was initiated in 2022, the study

was designed as a multicentre, open-label, randomised controlled trial. For 1 year, the severity of the candidates' pregnancy history unintentionally influenced randomisation and resulted in a low rate of enrolment. Thus, the existing study plan was revised to a single-arm trial to reduce bias and increase recruitment. As the comparison group, we used a similar previous study, which investigated the effects of low-dose aspirin alone on pregnancy outcomes in women with a history of PE risk factors<sup>37</sup>. In detail, these authors conducted a prospective, randomised, double-blind, placebo-controlled, chronotherapy trial with 350 high-risk pregnant participants. The inclusion criteria for high-risk pregnancies with PE include those with a familial or personal history of gestational hypertension or PE, chronic hypertension, cardiovascular, endocrine, bleeding or metabolic disease, personal history of spontaneous abortion, multiple pregnancy, obesity and adolescent or middle-aged nulliparous pregnancy (<18 or >35 years). They compared the composite morbidity of PE, preterm birth and FGR in three groups (times 1, 2 and 3) categorised by the timing of aspirin intake (on waking, 8 hours after waking and at bedtime). The number of study subjects was determined by calculating the composite morbidity expected from aspirin and HCQ combination therapy based on the composite morbidity observed in each of the time 1, time 2, time 3 and total categories of previous studies. Among the four categories, the smallest number of study subjects was calculated when composite morbidity at time 1 was set as the comparison group (online supplemental table 1). Given the limited number of eligible patients with the disease, the results from time 1, which had the smallest number of study subjects, were selected as the comparison group to facilitate the recruitment of subjects. As a result, we calculated our number of study subjects under the assumption that combined administration of aspirin+HCQ would have a lower composite morbidity rate than the 0.293 reported for the aspirin-treated group in that study. A comprehensive account of the methodology employed in determining the number of study subjects is provided in the sample size section.

### Study population

Women aged 19–50 years with a singleton pregnancy and a history of PE, FGR or FDIU in a prior pregnancy, who agree to enrol in the study and give their informed consent, are eligible for this trial. The definition of PE is a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher after 20 weeks of pregnancy and any of the following conditions: (1) proteinuria: 300 mg or more per 24-hour urine collection or protein/creatinine ratio of  $\geq 0.3$  mg/dL or dipstick reading of 2+; (2) (thrombocytopenia below  $100\,000\,10^9/L$ ; (3) renal insufficiency (serum Cr >1.1 mg/dL or a doubling of the serum Cr); (4) liver insufficiency (Aspartate aminotransferase or Alanine aminotransferase increase to more than twice the normal upper limit of the test institution); (5) severe symptoms including

headache, visual disturbance, convulsion and (6) pulmonary oedema. FGR is a condition where a baby is born with a birth weight below the 10th percentile for their gestational age, without any congenital infection, chromosomal abnormality or fetal abnormality. Alternatively, it can be defined as a birth weight of less than 2.5 kg when delivered at 37 weeks or later. FDIU is the diagnosis of fetal death during pregnancy, between 14 and 42 weeks, except when caused by infection, chromosomal abnormality or fetal abnormality.

The exclusion criteria are as follows:

1. Severe disorders of the cardiovascular, immune, respiratory, gastrointestinal/liver and biliary, kidney and urinary, nervous and musculoskeletal systems; psychiatric illness; infectious disease or malignancy.
2. Previous inclusion in another intervention study within 3 months of screening (except non-interventional observational studies).
3. Major malformation of the fetus is diagnosed at 11–13 weeks of gestation.
4. Elevated blood concentration ( $>1.1$  g/dL) of creatinine.
5. Elevated blood concentrations (more than two times the normal values) of liver transaminases (Aspartate aminotransferase or Alanine aminotransferase).
6. Conditions related to aspirin treatment.
  - Non-steroidal anti-inflammatory drugs exposure within 28 days of screening.
  - Bleeding disorder (von Willebrand's disease, peptic ulceration).
  - Hypersensitivity to aspirin.
7. Conditions related to HCQ treatment
  - Previous exposure within 28 days of screening.
  - Hypersensitivity to HCQ or 4-aminoquinoline compounds.
  - Maculopathy.
  - Medications with the potential for visual disturbance.
  - Conditions in which 4-aminoquinoline compounds can cause changes in the retina or visual impairment.
  - Galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
  - Prolonged QT interval (congenital or acquired) on electrocardiogram or risk factors for QT prolongation (heart failure, arrhythmia and myocardial ischaemia).
  - Low blood level of potassium—low blood level of magnesium.
8. Not suited for participation based on medical evidence acquired by the investigator

Patients undergo a screening test to determine if they have the underlying disease and if they meet the inclusion criteria (online supplemental table 2). Two additional screening assessments are performed on patients who satisfy the initial inclusion criteria. A thrombophilic test, including assays for lupus anticoagulant, anti- $\beta_2$  glycoprotein 1 antibodies (IgG and IgM) and anti-cardiolipin

antibodies (IgG and IgM), will be conducted to exclude thrombotic disorders such as antiphospholipid antibody syndrome. Though the direct correlation between thrombophilia and PE remains controversial, placental insufficiency associated with PE or FGR should be differentiated from pregnancy complications caused by thrombophilia.<sup>38</sup> Additionally, individuals with retinal disease or arrhythmia undergo specific assessments to evaluate whether HCQ could aggravate their condition.<sup>39–41</sup> These assessments include fundoscopy without the use of mydriatics, optical coherence tomography and electrocardiography.

### Intervention

All registered patients will receive a combination of aspirin (100 mg) and HCQ (200 mg) without random assignment, following the single-arm design of the study with the approval of the Ministry of Food and Drug Safety. Both drugs will be taken orally once daily, starting from 12 weeks of gestation (up to 22+6 weeks) and continuing until 36+6 weeks. The study supervisor provides guidance and monitors the medication compliance of the patients to ensure that it remains at 80% or higher. Medication compliance (%) will be calculated using the following formula:

Medication compliance (%) = (actual dose/total amount of drug to be administered) × 100.

Drug administration will be stopped and the patient will be withdrawn from the study in the following cases: (1) if the subject withdraws consent during the drug administration period, (2) in the event that a pregnancy is terminated at the patient's request, rather than due to medical indications or spontaneous abortion and (3) if the subject experiences an acute reaction (such as an allergy or hypersensitivity reaction) to the test drug, or if a 'serious adverse reaction' occurs and continuous administration is not possible. If the investigator determines that the subject is unsuitable, or if the subject is judged to not meet the selection criteria during the study, drug treatment or other treatment that may affect the clinical trial results is administered without instructions from the doctor in charge. In case of an adverse reaction caused by the drug, the patient will be directed to seek treatment from a specialist in the relevant department. The medical expenses will be covered by the research fund.

### The dose of 200 mg of HCQ daily

The therapeutic dose of HCQ recommended in SLE is below 5 mg/kg of real body weight.<sup>42</sup> Indeed, the prophylactic use of HCQ during pregnancy has not been extensively studied, and as a result, the optimal prophylactic dose has not been established. The primary focus of this process remains minimising side effects and maximising therapeutic effectiveness. Previous studies have reported that HCQ use improves pregnancy prognosis and have demonstrated the safety of HCQ use during pregnancy. Two prior meta-analyses suggested that HCQ use was not associated with any significant increases in the rates

of major congenital malformations<sup>32 43</sup>; however, these studies did not report the correlation between dose and the risk of malformation. One population-based cohort study tested the correlation between major congenital malformations and exposure to HCQ during the first trimester of pregnancy. According to those findings, a daily dose ≥400 mg of HCQ increased the risk of malformations compared with a dose <400 mg.<sup>44</sup> These results suggest that the risk of malformations could be dose-dependent and period-dependent, with higher doses associated with increased risk. Therefore, this study uses a dose of 200 mg of HCQ beginning at 12 weeks of gestation to balance the potential benefits of the medication against the need to minimise the risk of adverse effects, including malformations.

### Study plan and procedures

Two weeks after each patient begins taking the medication, adverse drug reactions are evaluated; a blood test is conducted for aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine and alkaline phosphatase, and the medication diary is monitored. If no abnormalities are detected during this evaluation period, the patient is asked to visit the hospital every 4 weeks for follow-up. During those visits, the examinations and ultrasound imaging are repeated to monitor the patient's condition and to ensure the safety and efficacy of the treatment.

During each ultrasound examination, the uterine artery Pulsatility index, umbilical artery Pulsatility index and systolic/diastolic ratio, and middle cerebral artery Pulsatility index are monitored, to assess placental blood flow and detect other abnormalities that could indicate placental insufficiency. Between 20 and 34 weeks of gestation (visits 4, 5 and 6), the Sft-1/PIGF test is performed to predict PE.

Unless the patient drops out of the study or has an adverse drug reaction or premature delivery, the drugs will continue to be taken until 36+6 weeks. The termination visit is defined as 5 weeks post partum, corresponding to the puerperium. The following clinical data are collected at the time of delivery: gestational age at delivery, method of delivery, maternal complications (infection, postpartum haemorrhage, blood transfusion, pulmonary embolism and admission to intensive care unit), sex of the newborn, neonatal weight, Apgar score and neonatal complications (infection, respiratory distress syndrome, jaundice, brain damage, neonatal necrotising enterocolitis, retinopathy of prematurity, anaemia of prematurity and admission to neonatal intensive care unit). If the patient does not deliver at the implementing institution, information from the delivery is obtained by a telephone interview.

### Primary outcomes

The primary outcome is the composite morbidity including PE, FGR, FDIU and preterm delivery. The period of diagnosis of composite morbidity is defined

until delivery regardless of gestational age. The definition of PE is the same as in the above study population section. FGR is defined as a birth weight lower than the 10th percentile for gestational age or lower than 2.5 kg at delivery after 37 weeks. FDIU does not include cases associated with infection, malformation or chromosomal abnormality and is defined as fetal death diagnosed after 14 weeks of gestation.

### Secondary outcomes

The secondary outcomes focus on assessing the severity of the primary outcomes and involve further categorisation:

1. Severe PE: the occurrence of PE with uncontrolled blood pressure (systolic blood pressure >160 mm Hg or diastolic blood pressure >110 mm Hg on two occasions at least 4 hours apart), persistent epigastric pain, new-onset headaches, pulmonary oedema, thrombocytopenia (platelet count  $<10 \times 10^9/L$ ), elevated liver enzymes (twice the upper limit) and impaired renal sufficiency (serum creatinine >1.1 mg/dL)
2. Occurrence of fetal growth below the fifth percentile for gestational age.
3. Incidence of early preterm birth (between 23+0 weeks and 33+6 weeks).
4. Incidence of late preterm birth (between 34+0 and 36+6 weeks).

### Sample size

This study is conducting a one-sample proportion test using the Z-test with the comparison group set to time 1 composite morbidity (29.3%) from Ayala's previous study. The hypothesis is stated as follows:  $H_0: p \geq p_0$  vs  $H_1: p < p_0$  (where  $p$  represents the incidence rate and  $p_0$  is the minimum incidence rate of the composite morbidity for aspirin+HCQ). The significance level is set at  $\alpha=0.025$ , and the power is assumed to be  $1-\beta=0.8$ . The expected incidence rate of the composite morbidity for aspirin+HCQ is assumed to be 0.13. The minimum incidence rate ( $p_0$ ) of the composite morbidity for aspirin+HCQ is set at 0.293. Based on these calculations, the required number of study subjects is set at 52. Considering a dropout rate of 10%, 58 subjects are required (online supplemental table 1). PASS V.22 software (V.22.0.2, NCSS) is used to calculate the sample size for this study.

### Recruitment

To recruit participants, study notices will be displayed in areas frequently visited by pregnant women within the institution. Additionally, the researcher will approach eligible outpatients and inpatients to provide detailed information about the study and encourage participation. It is essential that participation is voluntary, with no undue pressure or coercion.

### Data collection methods

Data management is recorded on paper Case report form by both the Clinical Research Associate and Principal Investigator. Prior to the start of the study, all three institutions and CRO attended and received training on

research methods and data management and record keeping. Researchers who participated in the study were required to obtain a research ethics certificate from an accredited institution recognised by the IRB. Continuous monitoring and patient education will be implemented to ensure treatment compliance remains above 80%. For participants whose compliance is less than 80% or who discontinue the protocol, we plan to conduct additional intention-to-treat analysis without treating them as dropouts.

### Statistical analysis

Statistical tests are typically conducted at a significance level of 5% using two-tailed tests, and statistical software (IBM SPSS statistics V.26) is used to carry out the tests. To analyse the primary endpoint, descriptive statistics (frequency and proportion) for the occurrence of composite morbidity will be presented when using aspirin+HCQ treatment, and a 95% CI for the composite morbidity rate will be provided. A Z-test (one-sample proportion test) will be used to determine whether the composite morbidity rate is lower than the rate observed in the historical control group (0.293). In analysing the secondary endpoints, the frequency and proportion of severe PE, early preterm delivery, late preterm delivery and severe FGR will be represented in the aspirin+HCQ treatment group, and a 95% CI compared with aspirin treatment will be provided, using a  $\chi^2$  test. If the total number of cells with an expected frequency <5 exceeds 20% of all cells, we will perform Fisher's exact test.

### Monitoring

To ensure the safety and effectiveness of the research, each institution's monitoring committee conducts biannual monitoring, and the CRO conducts additional monitoring. Although the Ministry of Food and Drug Safety has not specified a monitoring period, it will be carried out during the study period due to the vulnerability of our research subjects, including pregnant women and fetuses.

An interim analysis will be conducted when half of the target number is reached. To ensure the safety of the subjects during clinical trials, we will fully comprehend the drugs, check the health status of each participant and carefully review their suitability. If an adverse reaction occurs during the test, appropriate medical measures will be taken until the subject recovers.

### Patient and public involvement

Patients and the public were not involved in the design of this trial protocol or in the drafting of the manuscript.

### DISCUSSION

Placenta-related complications such as PE, FGR and FDIU have a high overlapping recurrence rate. Despite this, the establishment of prophylactic therapy for these conditions is a complex and ongoing area of research. HCQ

has shown promise in improving pregnancy outcomes, including reducing the risk of PE and FGR, in pregnant patients with autoimmune diseases. Although it is not yet widely used for secondary purposes in pregnancy, its potential benefits for pregnancies in patients without autoimmune conditions have been recognised clinically.

Our trial is the first to evaluate the effectiveness of HCQ for preventing placenta-related morbidity, and not an autoimmune disease, in pregnancy, and has been registered at ClinicalTrials.gov (<https://classic.clinicaltrials.gov/ct2/show/NCT05287321>). In March 2022, our study was designed as a multicentre, open-label, two-arm, randomised trial; however, due to a lack of patient recruitment, it was changed to a single-group study in February 2023.

As a limitation, this single-arm study has lower statistical power than a randomised controlled trial. If the combination therapy of aspirin and HCQ proves to be more effective than the current standard treatment in reducing pregnancy comorbidities, it will significantly advance our knowledge regarding the benefits of the use of HCQ during pregnancy.

### Ethics and dissemination

Ethics approval was obtained from the Ministry of Food and Drug Safety (Cheongju, South Korea). They evaluated the study's background, feasibility, necessity, rationale for HCQ dose setting and safety over 6 months. Additional approval was obtained from the Institutional Review Board of each of the three participating institutions (Chung-Ang University Gwangmyeong Hospital 2304-082-056, Samsung Medical Center 2021-11-087-003 and Kyungpook National University Chilgok Hospital KNUCH 2021-06-005-006) in the study, following approval from the Ministry of Food and Drug Safety.

This study protocol was approved by the institutional review board of each participating institution. All enrolled patients are planned to provide written informed consent for the collection of clinical data and the result of this trial. To ensure patient confidentiality, a unique patient study number is assigned and used to identify the patient by name. Access to the final trial dataset was restricted to the PI, Co-PI and CRA to ensure the protection of patient information. If a clinical trial participant experiences an adverse reaction, they are compensated through the Victim Compensation Protocol and Trial Insurance.

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**Contributors** The guarantor of the study is S-YO. S-YO accepts full responsibility for the completed work and the conduct of the study. Y-MK had access to the data and was involved in the decision to publish. Y-MK, H-HC, J-HS and S-YO designed and prepared a proposal for research funding. Y-MK and S-YO drafted and revised the manuscript. Y-MK, JS, JHK, GN, GJK, WJS, H-HC, S-JC, C-RR and J-HS participated in the study design and protocol and performed the study at their respective hospitals. All authors read and approved the final version of the manuscript.

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