CASE REPORT

The application of Mississippi Protocol in superimposed pre-eclampsia patients with class 2 hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome

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Article Info
Received Jul 20, 2024
Revised Oct 23, 2024
Accepted Oct 25, 2024
Published Apr 1, 2025

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Keywords:
Corticosteroids
HELLP syndrome
Mississippi Protocol
Placental abruption
Superimposed pre-eclampsia
Maternal health

ABSTRACT

Objective: To describe the implementation of the Mississippi Protocol (MP) in a case of superimposed pre-eclampsia complicated by class 2 HELLP syndrome.

Case Report: The patient initially received conservative treatment, including anticonvulsant prophylaxis, antihypertensive agents, and high-dose corticosteroids, in accordance with the MP. However, during observation, placental abruption and fetal distress were noted. Consequently, an emergency (green code) Caesarean section was performed. Placental abruption is a known complication associated with pre-eclampsia. The neonatal outcome following pregnancy termination was premature birth, low birth weight, and respiratory distress. Following delivery, laboratory parameters gradually improved. MP therapy was continued for 4 days post-delivery until clinical and laboratory indicators normalized. The administration of high-dose corticosteroids in HELLP syndrome is based on its characteristic excessive inflammatory response, which represents the distinctive feature of this case. Corticosteroid therapy is intended to reduce maternal morbidity and mortality and to enhance neonatal outcomes.

Conclusion: Careful monitoring and comprehensive management are essential when applying the MP in such cases. The definitive treatment for both pre-eclampsia and HELLP syndrome remains the termination of pregnancy. Further research is required to assess the effectiveness of MP in emergency or complicated scenarios.

How to cite: Kusuma AANJ. The application of Mississippi Protocol in superimposed pre-eclampsia patients with class 2 hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):83-88. doi: 10.20473/mog.V33I12025.83-88.

Highlights:

1. The neonatal outcome following pregnancy termination was preterm birth, accompanied by low birth weight and respiratory distress.
2. Following pregnancy termination, laboratory parameters gradually demonstrated improvement over time.
3. Mississippi Protocol therapy was maintained for 4 days after pregnancy termination until both clinical status and laboratory values showed improvement.

INTRODUCTION

Pre-eclampsia is a form of gestational hypertension. This condition is defined by an elevation in systolic blood pressure to 140 mmHg and diastolic blood pressure to 90 mmHg, accompanied by proteinuria of 30 mg/dL or dysfunction of maternal or uteroplacental organs. Maternal organ dysfunction includes renal, hepatic, neurological, and hematological impairment. When this condition develops in a patient with a history of chronic hypertension prior to 20 weeks of gestation, it is classified as superimposed pre-eclampsia.[1]

The global burden of pre-eclampsia affects approximately 39 million pregnancies, with an estimated incidence of 4.6%.[2] Each year, it accounts for around 63,000 maternal deaths.[3] This corresponds to 20 deaths per 100,000 pregnancies and a case fatality rate of approximately 0.8%.[4] The mortality associated with pre-eclampsia is disproportionately higher in low- and middle-income countries. In developing nations, pre-eclampsia and eclampsia are responsible for approximately 30% of all maternal deaths.[3]

HELLP syndrome—characterized by hemolysis, elevated liver enzymes, and low platelet count—represents a more severe variant of pre-eclampsia. Approximately 20–30% of pre-eclampsia cases progress to HELLP syndrome.[5] About 30% of HELLP syndrome cases develop in the postpartum period, typically within 48 hours.[6] Although the syndrome most frequently occurs in the third trimester, a minority of cases may arise between 22 and 24 weeks of gestation, with postpartum occurrence accounting for up to 30%.[5] HELLP syndrome affects approximately 5% of patients with pre-eclampsia and 10–20% of those with severe pre-eclampsia. It carries a maternal mortality rate of 1.1% and is associated with serious complications, including disseminated intravascular coagulation, hepatic hematoma, liver failure, and renal failure. The reported perinatal mortality rate ranges from 6% to 17%.[7]

HELLP syndrome shares a common pathophysiological mechanism with pre-eclampsia, particularly abnormalities in placental development and spiral artery remodeling.[3] These placental anomalies arise due to imbalances in antiangiogenic factors such as soluble FMS-like tyrosine kinase 1 (sFlt-1), placental growth factor (PlGF), and endoglin.[8,9] Accordingly, corticosteroid therapy is incorporated into the Mississippi Protocol.[5] This report aimed to present the application of the Mississippi Protocol (MP) in a case of superimposed pre-eclampsia with class 2 HELLP syndrome.

CASE REPORT

A 43-year-old woman was referred from a community health center at 30 weeks' gestation with gestational hypertension, blood pressure of 200/110 mmHg, and proteinuria (+2). At Prof. Dr. I.G.N.G Ngoerah Hospital, she had no abdominal pain, dyspnea, or visual/epigastric symptoms. Her medical history included uncontrolled hypertension and hepatitis B diagnosed during antenatal care. At the referring center, she received a 4-gram IV bolus of 40% magnesium sulfate (MgSO4), a 6-gram maintenance dose, and 10 mg of oral nifedipine prior to hospital admission.

Physical examination

Upon hospital admission, the patient's blood pressure was 160/110 mmHg, with a Mean Arterial Pressure (MAP) of 126 mmHg, pulse rate of 98 beats per minute, respiratory rate of 20 breaths per minute, and axillary temperature of 36.5°C. General physical examination findings were unremarkable. Obstetric examination revealed a uterine fundal height midway between the xiphoid process and umbilicus, no uterine contractions, a fetal heart rate (FHR) of 158 beats per minute, and cephalic presentation.

Additional examination

Laboratory results are presented in Table 1. Ultrasonographic evaluation revealed a single, viable fetus with a positive FHR and fetal movement, corresponding to a gestational age of 27 weeks and 3 days, with an estimated fetal weight of 1107 grams.

Assessment and management

The patient was diagnosed with G4P2012 at 30 weeks and 1 day, with a single viable fetus, superimposed pre-eclampsia with severe features, class 3 HELLP syndrome, chronic hepatitis B infection, and hypokalemia. Conservative management included administration of 6 grams of 40% MgSO4, dexamethasone 6 mg intramuscularly every 12 hours for 2 days to promote fetal lung maturation, and nifedipine 10 mg intraorally every 8 hours if MAP exceeded 125 mmHg. On the second day of hospitalization, the patient's condition deteriorated, with blood pressure escalating to 200/120 mmHg. Laboratory findings indicated a platelet count of 79.45/µL, elevated lactate dehydrogenase (LDH) of 940 U/L, proteinuria (+3), and evidence of a urinary tract infection. The worsening laboratory parameters prompted reclassification of the HELLP syndrome to class 2.

Table 1. Laboratory examination

Components	Results	References	Unit
WBC	12.3	4.1 – 11.0	10^3/µL
HGB	12.89	13.5 – 17.5	mg/dL
PLT	106.5	150 – 440	10^3/µL
LDH	765	125 - 220	U/L
SGOT	33.2	<34	U/L
SGPT	27	<55	U/L
Albumin	3.1	3.40 – 4.80	g/dL
BUN	8,4	8.4 – 25.7	mg/dL
Creatinine	0.74	0.72 – 1.25	mg/dL
Potassium	2.95	3.6 – 5.2	mmol/L
Proteinuria	(+3)		
HbSAg	reactive		

WBC = white blood cells, HGB = hemoglobin, PLT = platelet, LDH = lactate dehydrogenase, SGOT = Serum Glutamic-Oxaloacetic Transaminase Test, SGPT = Serum Glutamic Pyruvic Transaminase, BUN = blood urea nitrogen, HbsAg = hepatitis B surface antigen

The patient was subsequently managed in accordance with the Mississippi Protocol (MP), receiving intravenous dexamethasone 10 milligrams every 12 hours and intravenous cefoperazone 1 gram every 12 hours to treat the urinary tract infection. During observation, the patient's blood pressure remained persistently elevated; therefore, a continuous infusion of nicardipine at 5 milligrams per hour was initiated. Following dexamethasone administration under the MP, laboratory values improved, with platelet counts rising to 111.7 /µL and 122.7 /µL on the third and fourth days of treatment, respectively. However, on day four, the patient experienced sudden, intermittent abdominal pain with uterine contractions occurring four times in ten minutes, lasting 30–35 seconds each, and a fetal heart rate of 140 beats per minute. Abdominal examination revealed increased uterine tone. Cardiotocography indicated a category 3 pattern (sinusoidal), raising suspicion of placental abruption and fetal distress. An emergency Caesarean section (green code) was therefore performed.

Outcome

The newborn delivered via Caesarean section was diagnosed with very low birth weight (1,000 grams), severe asphyxia, and respiratory distress. Postoperatively, the mother received an oxytocin infusion of 20 IU, 6 grams of 40% $MgSO_4$ for 24 hours, and nifedipine 10 milligrams every 8 hours if MAP exceeded 125 mmHg. Dexamethasone was continued at 10 milligrams every 12 hours on the first postoperative day and tapered to 5 milligrams every 12 hours thereafter. During follow-up, laboratory evaluation revealed normalization of the platelet count by the second day post-termination, while LDH levels remained elevated. By the fourth day, LDH showed a downward trend, suggesting a reduction in systemic inflammation. The patient was discharged on nifedipine and methyldopa. No adverse events related to MP administration were reported by the patient.

DISCUSSION

The diagnosis of pre-eclampsia is established by the presence of hypertension in conjunction with proteinuria, clinical maternal organ dysfunction, or uteroplacental dysfunction.[1] In this case, all diagnostic criteria were fulfilled, complicated by HELLP syndrome, a severe variant of pre-eclampsia. Organ dysfunction in HELLP syndrome involves the hematological system, including thrombocytopenia, hemolysis, and elevated liver enzymes. Numerous risk factors contribute to pre-eclampsia, including chronic renal disease, autoimmune conditions, diabetes mellitus, chronic hypertension, and a history of hypertensive disorders in prior pregnancies. Additional moderate-risk factors include nulliparity, maternal age over 40 years, body mass index (BMI) exceeding 35 kg/m², multiparity, or interpregnancy intervals greater than 10 years.[10] In this case, the patient exhibited risk factors of advanced maternal age (over 35 years) and chronic hypertension, consistent with a diagnosis of superimposed pre-eclampsia. A detailed clinical history is essential for timely identification of such risk profiles.

The primary therapeutic goals of the Mississippi Protocol (MP) are to prevent disease progression from class 2, class 3, or partial HELLP syndrome to class 1, reduce the incidence of major maternal morbidity, prevent maternal mortality, shorten disease duration and treatment time, and minimize perinatal morbidity and mortality.[11] According to the Mississippi criteria, HELLP syndrome is classified into three categories

based on platelet count. When only one or two of the three diagnostic criteria are met, the condition is termed partial HELLP syndrome.[12] In this case, the patient initially presented with an LDH level of 765 IU/L and a platelet count of 106.5 /µL, consistent with class 3 HELLP syndrome. On the second day of MP-based treatment, laboratory findings demonstrated a decline in platelets to 79,450 /µL and a rise in LDH to 940 IU/L, prompting reclassification to class 2 HELLP syndrome. The dynamic changes in laboratory values highlight the importance of close monitoring during the acute management phase.

HELLP syndrome typically develops between 27 and 37 weeks of gestation; likewise, this case manifested at 30 weeks. The syndrome is associated with a more intense inflammatory response than standard pre-eclampsia. Endothelial injury leads to red blood cell fragmentation as they traverse damaged vessels, producing schizocytes and burr cells. This intravascular hemolysis causes anemia and elevated LDH levels. Hemolysis also activates the coagulation cascade, increasing the risk of disseminated intravascular coagulation (DIC). Concentrations of FasL in both trophoblastic villi and maternal circulation are reported to be higher in HELLP syndrome compared to pre-eclampsia without HELLP features.[13]

The heightened inflammatory state in HELLP syndrome is marked by elevated levels of C-reactive protein, interleukin-6, and TNF-alpha, along with increased white blood cell counts.[13] This enhanced inflammatory response provides the rationale for high-dose corticosteroid therapy under the MP. The MP management of HELLP syndrome includes the administration of magnesium sulfate ($MgSO_4$) for seizure prophylaxis and to reduce systemic vascular resistance, the use of oral or intravenous anti-hypertensive agents, and intravenous dexamethasone 10 milligrams every 12 hours for 48–72 hours, continued until platelet counts trend toward normalization (≥100,000/µL).[5]

The definitive treatment for pre-eclampsia is pregnancy termination; however, the timing of intervention—whether immediate or delayed—depends on multiple factors, including gestational age, the severity of maternal illness, and fetal condition. Nonetheless, any decision to terminate must carefully weigh both maternal and fetal status.[14] The likelihood of disease progression can be assessed by measuring plasma levels of proangiogenic and antiangiogenic factors produced by the placenta, which is the primary source of the disorder.[15] Immediate control of maternal hypertension remains the cornerstone of emergency management in severe pre-eclampsia. Magnesium sulfate ($MgSO_4$) acts as the principal prophylactic agent against eclampsia but should not take precedence over achieving effective blood pressure control. Research into emerging adjuvant therapies may enable prolonged gestation, improved perinatal outcomes, and enhanced maternal safety.[16]

The efficacy of corticosteroid therapy has been conclusively validated. One of the most impactful advances in perinatal medicine has been the antenatal administration of corticosteroids to women in the mid to late stages of pregnancy to mitigate complications associated with preterm birth. The broad acceptance of this intervention is supported by substantial evidence demonstrating enhanced neonatal outcomes, particularly through corticosteroid-facilitated maturation of fetal lungs.[17] Supporting this, a study by Chawla (2022) found that administration of a complete course of antenatal corticosteroids at a gestational age of 22 6/7 weeks or less was independently associated with improved survival and survival without major morbidity among neonates delivered between 22 0/7 and 23 6/7 weeks who received intensive care.[18] The Mississippi steroid protocol emphasizes the first 24 hours following steroid initiation and employs high-dose dexamethasone. In patients with HELLP syndrome, prednisolone has been shown to reduce maternal IL-6 levels, though it does not significantly affect IL-1, IL-10, or soluble IL-6 receptor levels. The pathophysiology of pre-eclampsia is also associated with neutrophil activation, which involves neutrophil adhesion and transmigration across the endothelium.[19]

Both maternal and fetal complications are frequently observed in HELLP syndrome. Damaged maternal endothelium has been implicated in the pathogenesis of maternal morbidity associated with severe pre-eclampsia. Moreover, endothelial dysfunction may persist for years after the initial presentation, reflecting long-term vascular compromise.[20] In this case, the neonatal outcome following Caesarean section was very low birth weight (1,000 grams), severe asphyxia, and respiratory distress. Despite 7 days of intensive treatment, the infant's condition deteriorated, and death occurred due to septic shock and complications of prematurity. Prematurity continues to pose a significant challenge in the management of perinatal HELLP syndrome. Therefore, involvement of a dedicated neonatal care team and the availability of comprehensive healthcare infrastructure are critical to reducing neonatal morbidity and mortality.[21] Limitations of this study include the absence of a control group and uncertainty regarding the temporal relationship between exposure and health outcomes. Additionally, specific laboratory indicators of inflammation, such as interleukins, were not evaluated in the patient. However, the observed downward trend

in clinical markers may serve as a surrogate indicator of reduced systemic inflammation.

CONCLUSION

Continuous monitoring and appropriate management are essential when implementing the Mississippi Protocol (MP) in clinical practice. The definitive treatment for both pre-eclampsia and HELLP syndrome remains pregnancy termination. However, premature termination may adversely affect fetal outcomes, whereas delayed intervention increases the risk of maternal organ dysfunction and mortality. Further research is warranted to assess the efficacy of MP implementation in emergency settings or complex clinical scenarios.

DISCLOSURES

Acknowledgment

Prof. Dr. I.G.N.G. Ngoerah Hospital's Maternal Fetal Medicine Division, Obstetrics and Gynecology Department, is acknowledged for their assistance.

Conflict of interest

The author has no conflict of interest.

Patient's consent for publication

The patient had signed the informed consent form and consented to the publication of this case report.

Funding

There is no external funding for this study.

Author contribution

The author has carried out all phases of this research, including preparation, data collection and analysis, drafting of the article.

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