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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ABSTRACT

Objective: To report the application of Mississippi Protocol (MP) in superimposed pre-eclampsia with class 2 HELLP syndrome.

Case Report: The patient was initially treated conservatively with anticonvulsant prophylaxis, antihypertensives and high-dose corticosteroids, according to the MP. However, during observation, there was placental abruption and fetal distress. Thus a green code Sectio Cesarea (SC) was performed. This placental abruption is one of the complications that can occur in pre-eclampsia. The baby's outcome after pregnancy termination is premature, with low birth weight and respiratory distress. After the termination of the pregnancy, laboratory parameters begin to improve over time. MP therapy was continued 4 days post-termination of pregnancy until clinical and laboratory conditions improved. The rationale for giving high doses of corticosteroids in HELLP syndrome is that the syndrome has an excessive inflammatory response is the uniqueness of this case report. Corticosteroids are expected to prevent maternal morbidity and mortality and improve fetal outcomes.

Conclusion: Monitoring and adequate management are mandatory in applying MP in patients. The definitive management of both pre-eclampsia and HELLP syndrome is the termination of pregnancy. Further study is needed to evaluate the efficacy of MP application in an emergency or complicated cases.

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Highlights:

1. The baby's outcome after pregnancy termination is premature, with low birth weight and respiratory distress.
2. After the termination of the pregnancy, laboratory parameters begin to improve over time
3. Mississippi protocol therapy was continued 4 days post-termination of pregnancy until clinical and laboratory conditions improved.

INTRODUCTION

Pre-eclampsia is a kind of gestational hypertension. This illness is characterized by a rise in systolic blood pressure of 140 mmHg and diastolic blood pressure of 90 mmHg, together with proteinuria of 30 mg/dL or dysfunction of the maternal or uteroplacental organs. Maternal organ dysfunction is renal, hepatic, neurological, and hematological dysfunction. If this situation occurs in a maternal with a history of chronic hypertension before 20 weeks gestation, it is classified as superimposed pre-eclampsia.[1]

The global prevalence of pre-eclampsia is close to 39 million pregnancies, with an incidence of around 4.6%.[2] Approximately 63 thousand deaths occur due to this condition each year.[3] This is equivalent to 20 deaths per 100,000 with a mortality rate of around 0.8%.[4] The pre-eclampsia mortality rate is higher in poor to middle-income nations. Pre-eclampsia and eclampsia contribute to 30% of all maternal deaths in developing countries.[3]

A more severe pre-eclampsia variant is hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Approximately 20-30% of pre-eclampsia develop this HELLP syndrome.[5] In the postpartum period, 30% of cases of HELLP syndrome develop, and they normally occur within 48 hours.[6] This syndrome usually occurs in the third trimester, although a small proportion can occur at 22-24 weeks of gestation, and postpartum can occur at 30%.[5] With a maternal mortality rate of 1.1% and substantial morbidities such as disseminated intravascular coagulopathy, hepatic hematoma, liver failure, and renal failure, HELLP affects approximately 5% of pre-eclampsia patients or 10%–20% of instances of severe pre-eclampsia. The reported range for perinatal mortality is 6%–17%.[7]

HELLP syndrome shares the same pathophysiology as pre-eclampsia, with specific problems in placental growth and development and remodeling of the spiral arteries.[3] Due to an imbalance of antiangiogenic molecules such as soluble FMS-like tyrosine kinase 1 (sFlt-1), placental growth factor (PlGF), and endoglin, this anomaly in placenta production arises.[8,9] Therefore, corticosteroid administration can be considered in the Mississippi protocol.[5] This study aims to report the application of Mississippi Protocol (MP) in superimposed pre-eclampsia with class 2 HELLP syndrome.

CASE REPORT

A woman aged 43 years, a referral from a community health center, came with gestational hypertension at 30 weeks of gestation with a blood pressure of 200/110 mmHg with proteinuria (+2). In the Emergency Midwifery Unit of Prof. Dr. I.G.N.G Ngoerah Hospital, the patient had no complaints of abdominal pain, vaginal discharge, or tightness. The patient's subjective complaints, such as headaches, blurred vision, or heartburn, were also not obtained. The patient did have a history of uncontrolled hypertension since the previous year and had hepatitis B known since the Ante Natal Care at the Health Center. While at the community health center, the patient was given Magnesium Sulfate (MgSO4) 40% bolus 4 grams intravenous followed by a maintenance dose of 6 grams MgSO4 and Nifedipine 10 mg intraoral.

Physical examination

On the physical examination on arrival at the hospital, the blood pressure was 160/110 mmHg, Mean Arterial Pressure (MAP) 126 mmHg, pulse 98 x/minute, respiration rate 20 x/minute, axillary temperature 36.5ºC. The generalist status examination was within normal limits. Obstetric status, uterine fundal height was in the middle of processus xypoideus - umbilicus, no contraction, fetal heart rate (FHR) 158x/minute, head presentation.

Additional examination

Laboratory examination is showed in Table 1. On ultrasound examination, fetal, single, live, FHR (+), and fetal movement (+) with a gestational age of 27 weeks 3 days were obtained, estimated fetal weight was 1107 grams.

Assessment and management

The patient was diagnosed as G4P2012 30 weeks 1 day single/alive, superimposed pre-eclampsia with severe features, class 3 HELLP syndrome, chronic hepatitis B infection, and hypokalemia. The patient was treated conservatively by administering 6 grams of MgSO4 40%, Dexamethasone 6 milligrams every 12 hours intra-muscular for 2 days as lung maturation and Nifedipine 10 milligrams intraoral every 8 hours if MAP >125 mmHg. On the second day of follow-up treatment, the patient's condition worsened with a blood pressure of 200/120 mmHg. Laboratory tests showed a decrease in platelets of 79.45/µL; increased LDH 940 U/L; proteinuria (+3), and an impression of urinary tract infection. The deterioration of laboratory results in patients led to an upgrade 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 then managed according to the MP by administering Dexamethasone 10 milligrams every 12 hours intra-venous and Cefoperazone 1 gram every 12 hours intravenous as a treatment for urinary tract infections. During observation, the blood pressure was persistently high. Thus, Nicardipine drip of 5 milligrams/hour was given. After the administration of dexamethasone, according to the MP, there was an improvement in laboratory results in the form of an increase in platelets to 111.7 /µL and 122.7 /µL on day 3 and day 4 of treatment. However, on the fourth day of treatment, the patient experienced abdominal pain that came and went suddenly. The contraction was 4x/10 minutes, and the duration was 30-35 seconds, FHR: 140 x/minute. Abdominal examination revealed abdominal tension. On the cardiotocography results, category 3 (sinusoidal pattern) was obtained. The patient was suspected of having placental abruption and fetal distress. Thus, doing a green code section Caesarea (SC) was decided.

Outcome

The outcome of the baby after SC was found to be very low birth weight (1,000 grams), severe asphyxia, and respiratory distress. Post SC, the patient was given an Oxytocin drip of 20 IU, 6 grams of MgSO4 40% for up to 24 hours after surgery, Nifedipine 10 milligrams every 8 hours if MAP >125 mmHg and administration of Dexamethasone 10 milligrams every 12 hours on the first day and continued with 5 milligrams every 12 hours. During follow-up, laboratory tests showed that the platelet count returned to normal values ??on the second day after termination of pregnancy, and LDH was persistently high. On the fourth day after termination, there was a tendency to decrease which is a marker of decreased inflammation in patients. The patient was discharged with Nifedipine and Methyldopa therapy. After the administration of MP, there was no adverse event reported by the patients.

DISCUSSION

The presence of hypertension with proteinuria, clinical maternal organ dysfunction, or uteroplacental dysfunction is diagnostic of pre-eclampsia.[1] In this case, these criteria were met, and there was a complication of HELLP syndrome, a variant of severe pre-eclampsia. Organ dysfunction in HELLP syndrome is a dysfunction of the hematological organ systems. There are numerous risk factors for pre-eclampsia. Maternal disorders such as chronic renal disease, autoimmune diseases, diabetes, or chronic hypertension, as well as a history of hypertensive disease during a previous pregnancy, are risk factors for pre-eclampsia. Nullipara, older than 40 years old, body mass index (BMI) of more than 35 kg/m2, who have had several pregnancies or have waited more than 10 years between pregnancies, are at intermediate risk.[10] In this case, risk factors were found in a patient over 35 years and chronic hypertension as risk factors for superimposed pre-eclampsia.

The primary objectives of MP therapy are preventing disease progression from class 2, 3, or partial to class 1, minimizing the development of major maternal morbidity, preventing maternal mortality, reducing disease course time and treatment duration, and minimizing the morbidity of perinatal mortality.[11] According to the Mississippi criteria, HELLP syndrome is divided into three classes based on the platelet count. If one of the three criteria is not met, it is categorized as a partial HELLP syndrome.[12] As in this case, when the patient first arrived at the hospital, there was an increase

in LDH 765 IU/L and a decrease in platelet count of 106.5 /µL. Thus, it was diagnosed as class 3 HELLP syndrome. According to the MP. There was a decrease in platelets to 79,450 /µL and an increase in LDH to 940 IU/L on the second day of treatment. Thus, the class of HELLP syndrome increased to class 2.

HELLP syndrome develops primarily at 27-37 weeks of gestation. Similarly, this case occurred at 30 weeks of gestation. This syndrome has a more severe inflammatory response than pre-eclampsia in general. Endothelial damage causes fragmentation of red blood cells that pass through these blood vessels. These red blood cell fragments are seen as schizocytes and burr cells. This condition causes anemia, known as hemolytic anemia. Hemolysis that occurs will cause an increase in LDH. Intravascular hemolysis products also activate coagulation, thus increasing the risk of Disseminated Intravascular Coagulation (DIC). The concentration of FasL in trophoblast villi and maternal blood is higher in HELLP syndrome compared to pre-eclampsia without HELLP syndrome.[13]

Heavier inflammation in HELLP syndrome is characterized by higher concentrations of c-reactive protein, interleukin 6 and TNF alpha compared to pre-eclampsia. The white blood cell count was also found to be higher.13 This severe inflammation underlies the administration of high doses of corticosteroids, according to the MP. The principle of management of HELLP syndrome with the MP is the administration of MgSO4 as an anticonvulsant prophylaxis and reducing systemic blood vessel resistance, intraoral or intra venous antihypertensive therapy, and Dexamethasone 10 milligrams intra venous every 12 hours within 48-72 hours, until a tendency to normalize platelet values 100,000/µL.[5]

The definitive treatment for pre-eclampsia is termination, but whether it should happen right away or wait depends on several factors, including gestational age, the severity of the mother's illness, and the welfare of the fetus. However, the termination still has to consider the maternal and fetal conditions.[14] The plasma concentrations of proangiogenic and antiangiogenic substances generated by the placenta, which is the primary source of disease, can indicate the likelihood that the condition will advance.[15] The cornerstone of emergency care for women with severe pre-eclampsia will continue to be the prompt control of maternal hypertension. MgSO4 functions as a major preventative measure for eclampsia, depending on the situation, and should not take priority over properly lowering blood pressure. The research of novel adjuvant drugs may allow us to prolong pregnancy longer, enhance perinatal outcomes, and safeguard the mother.[16]

The effectiveness of aggressively administering corticosteroids has been conclusively demonstrated. One of the most significant developments in perinatal medicine is the prenatal administration of corticosteroids to pregnant mothers in the middle to late stages of pregnancy to prevent preterm birth. The widespread acceptance of this medication is owed to a substantial body of research demonstrating improved infant outcomes following antenatal corticosteroid exposure, particularly due to corticosteroid-driven maturation of fetal pulmonary function.[17] It supported by Chawla's (2022) study that found exposure to a full course of prenatal steroids at GA 22 6/7 weeks or less was independently linked with higher odds of survival and survival without substantial morbidity among children delivered between GA 22 0/7 and 23 6/7 weeks who received intensive care.[18] The Mississippi steroid protocol concentrated on the first 24 hours following steroid therapy and used large dosages of dexamethasone. Prednisolone reduces maternal IL-6 levels in humans with HELLP syndrome but not IL-1, IL-10, or soluble IL-6R. The pathophysiology of pre-eclampsia has been linked to neutrophil activation, which necessitates neutrophil binding and movement through the endothelium.[19]

Both maternal and fetal complications can occur in HELLP syndrome. It has also been proposed that damaged maternal endothelium has a role in maternal morbidity linked to severe pre-eclampsia. It has been demonstrated that damaged endothelium functions improperly years after the first diagnostic symptoms disappear.[20] In this case, the outcome of the baby after SC was a very low birth weight (1,000 grams), severe asphyxia, and respiratory distress. During the 7 days of treatment, the infant worsened and died from septic shock and prematurity. The prematurity factor has still become a problem in dealing with perinatal cases of HELLP syndrome. Thus, a pediatric team is needed, and good health support facilities are available to reduce the risk of neonatal morbidity and mortality.[21] The study's limitations are the absence of a control group and the hazy timing of the exposure-health outcome association. In addition, laboratory markers of inflammation such as Interleukin were not tested in patients. However, a decrease in the tendency in patients may be used as a marker of decreased inflammation.

CONCLUSION

Monitoring and adequate management are mandatory in applying MP in patients. The definitive management of both pre-eclampsia and HELLP syndrome is the termination of pregnancy. However, early termination of pregnancy will harm the fetus. Conversely, it will

risk causing organ dysfunction and maternal mortality if it is late. Further study is needed to evaluate the efficacy of MP application in an emergency or complicated cases.

DISCLOSURES

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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.

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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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