

Magnesium Sulphate and Nifedipine in Management of Preterm Premature Rupture of Membranes

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ABSTRACT

Premature rupture of membranes (PROM) is defined as rupture before delivery that can occur at any gestational age. If it occurs before 37 weeks of gestation, it's called Preterm Premature Rupture of Membrane (PPROM). PROM is a condition that still occurs in both developed and developing countries and cause a serious threat to the fetal and maternal well-being if not managed properly. Conservative management is chosen in PPROM until the fetus is viable, consist of hospitalization, assessment of sign of infection, well-being of the fetal and maternal. Specific treatment includes the administration of corticosteroid, antibiotics, and tocolytics. Tocolytic agents that are widely used as first-line agents are magnesium sulphate (MgSO₄) and nifedipine, one of the Calcium Channel Blocker (CCB) groups. MgSO₄ and nifedipine both have an effect in reducing myometrial contractility. MgSO₄ also has a neuroprotective effect in PPROM less than 31 weeks if there is a threat of delivery within 24 hours. Meta-analysis related to the use of these two agents in PPROM is still subject to differing result. Some studies have shown nifedipine is considered to have milder side effect than MgSO₄, more easily tolerated by oral administration, and more affordable. However, some studies have shown that the two agents have the same efficacy. Other studies have shown no significant benefit in administering nifedipine to neonates or prolong pregnancy in women with PPROM without contractions.

Keywords: Magnesium sulphate, nifedipine, premature ruptures of membrane, preterm, tocolytic.

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I. INTRODUCTION

Premature rupture of membranes (PROM) can be defined as a rupture of the membranes before delivery that can occur at any gestational age. PROM can occur at gestational age before 37 weeks which is called Preterm Premature Rupture of Membrane (PPROM) or after 37 weeks which is called Premature Rupture of Membrane (PROM) [1]. PROM is still a problem in the field of obstetrics. The incidence of PROM ranges from 8-10% of all pregnancies. In term pregnancy the incidence varies between 6-19% while in preterm pregnancy the incidence is 2% of all pregnancies. The incidence of PROM recorded at Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar in July 2015-June 2016 was 166 people with 85.5% being PROM in term pregnancy and 14.5% are PROM in preterm pregnancy [2]. PROM is a condition that still occurs in both developed and developing countries and poses a serious threat to the welfare of the mother and fetus if not managed properly [3].

There is no single factor that causes PROM, there are several risk factors that are closely related to the incidence of PROM such as low socioeconomic status, smoking, genital tract infections, previous history of PROM, history of preterm delivery, gestational gemelli, polyhydramnios, and vitamin C deficiency. Extrinsic factor which also has an effect is high activity during pregnancy. Physical work during pregnancy that is too heavy can result in fatigue. Fatigue at work causes

the amniotic chorion to weaken, resulting in PROM [5].

Some causes of PROM include ascending infection from the vagina, antepartum bleeding, trauma to the abdomen, cervical insufficiency, and invasive procedures such as amniocentesis. The rupture of the amniotic membrane is related to changes in the biochemical processes that occur in the extracellular matrix collagen. Changes in the structure, number of cells, and collagen catabolism cause changes in collagen activity. The fetal and decidual membranes react to stimuli such as infection and stretching of the membranes by producing mediators such as prostaglandins, cytokinins, and protein hormones that stimulate matrix degrading enzyme activity. Collagen degradation is mediated by matrix metalloproteinases (MMPs). Collagen degradation then causes weakening of the amniotic membrane [6].

PROM is associated with complications of preterm birth and the occurrence of infectious chorioamnionitis so that it can become sepsis which increases perinatal morbidity and mortality. PROM in preterm pregnancy has the most significant risk of complications of prematurity, the most reported of which is respiratory distress. Preterm PROM with intrauterine inflammation has also been associated with an increased risk of neurodevelopmental disorders. Maternal chorioamnionitis after preterm PROM is associated with a higher risk for neonatal sepsis followed by prolonged oligo/anhydramnios which can lead to bronchopulmonary dysplasia (BPD) with perinatal mortality of up to 80%. Given

the high infant mortality rate in preterm PROM, more aggressive management is needed, which requires an approach to balance the benefits of maintaining pregnancy against the risk of intra-amniotic infection and the consequences for the mother and fetus [7].

Until now the management used is the administration of antibiotics to maintain pregnancy, reduce maternal and infant infections, and reduce maternal and infant morbidity. In addition, corticosteroid administration is also beneficial in lung maturation and reduces neonatal mortality, respiratory distress syndrome, and intraventricular hemorrhage [8]. Tocolytic administration in preterm PROM is also considered beneficial. Tocolytics are used to inhibit uterine contractions and delay labour. The most used tocolytic agents are magnesium sulphate (MgSO₄) and nifedipine. The choice of first-line tocolytic therapy in preterm PROM varies among countries. Decisions about which agent to use, route of administration, dose, and length of time are all factors that influence tolerance and effectiveness of tocolytics. It is also necessary to consider the risk-benefit ratio, especially regarding the known side effects of each tocolytic agent before deciding. Based on this description, this time we will discuss the role of magnesium sulphate and nifedipine in the management of cases of preterm PROM [9].

II. DISCUSSION

A. PROM in Preterm Pregnancy

PROM in preterm pregnancy or known as PPRM is a rupture of the amniotic membranes that occurs in pregnancy before 37 weeks. Premature birth is a risk factor for cerebral palsy, which is a condition characterized by abnormal movement control and posture resulting in limitation of activity [10]. More than 90% of cases are confirmed based on patient complaints and inspections by direct monitoring of the amniotic fluid that comes out of the External Uterine Orifice. (EUO) to the vaginal canal. The diagnosis becomes more relevant with the help of a nitrazine test and ultrasound showing oligo/anhydramnios. Internal examination is not recommended unless active management in the form of termination of pregnancy is imminent [11]. After rupture of the membranes there is a threat of labor in the next few days. If the pregnancy is still preterm, conservative management is chosen until the fetus is viable with hospitalization, periodic assessment of signs of infection, maternal and fetal well-being. Specific treatment includes administration of corticosteroids, antibiotics, and tocolytics.

B. Magnesium Sulphate (MgSO₄)

Magnesium Sulphate (MgSO₄) in obstetrics can be used as a tocolytic, anticonvulsant in the treatment of preeclampsia, and is thought to act as neuroprotection against the fetal brain [12]. As a tocolytic agent, MgSO₄ can inhibit uterine contractions. Administration of MgSO₄ can inhibit the activity of myosin light-chain kinase by competing with intracellular calcium or reducing the entry of calcium into cells through the cell membrane during the depolarization process which causes a decrease in myometrial contractility.

The American Congress of Obstetricians and Gynecologists (ACOG) recommends MgSO₄ as a neuroprotectant in fetuses at less than 32 weeks gestation.

The Indonesian Obstetrics and Gynecology Association recommends the use of MgSO₄ for neuroprotection in preterm PROM less than 31 weeks if delivery is expected within 24 hours. MgSO₄ is given as an intravenous bolus of 6 grams over 40 minutes followed by 2 grams hourly for maintenance doses until delivery or up to 12 hours of therapy [13].

Research conducted at Stanford University Medical Center and Santa Clara Valley Medical Center in 2007 showed that MgSO₄ had more side effects than nifedipine as a tocolytic agent, namely shortness of breath and pulmonary edema [14].

C. Nifedipine

Nifedipine is a calcium antagonist or calcium channel blocker (CCB). Nifedipine works by inhibiting the entry of calcium into smooth muscle cell membranes, preventing the release of calcium from the sarcoplasmic reticulum and reducing the effect of intracellular calcium enzymes on actin-myosin interactions so that it can inhibit myometrial contractions [15]. Nifedipine is easily soluble in fat so that it is easily absorbed in the gastrointestinal tract when given orally or sublingually, therefore nifedipine is considered to be more easily tolerated. Based on several studies, nifedipine can be used as a first-line tocolytic in preterm labor by reducing the risk of labor within 7 days after initiation of treatment and delivery before 34 weeks with improvement in neonates [16].

The initial dose of nifedipine for tocolytics is 10 mg sublingually every 15 minutes for the first 1 hour. The goal of low doses is to achieve a reduction in uterine contractions while minimizing the side effects of nifedipine such as headache (most commonly) and hypotension as a result of vasodilation. The maintenance dose is 20 mg every 6-8 hours given orally [17].

III. THE ROLE OF MGSO₄ AND NIFEDIPINE AS MANAGEMENT OF PROM IN PRETERM PREGNANCY

Efforts to prevent and manage PROM in preterm pregnancy are carried out to increase the probability of newborn life by minimizing complications that can occur. One way to inhibit signs of preterm labor is to inhibit uterine contractions pharmacologically with tocolytics which aims to prolong pregnancy and delay labor. Currently, the most widely used tocolytic is the CCB group, which is nifedipine. It is said that this drug is quite effective in inhibiting the process of preterm labor, with minimal side effects [18]. Previous studies have shown the success of nifedipine in preventing preterm labor and relieving contractions in contractile uterine patients reaching 86.4% and reducing pain scale to 74.28% [19]. Other studies have shown that the success rate of nifedipine therapy as a tocolytic in patients with postpartum prematurus imminens at the Prof. Dr. I.G.N.G. Ngoerah Central General Hospital Denpasar in 2014-2016 is 47.05% [20].

Giving MgSO₄ to pregnant women before the birth of a premature baby is reported to be useful as a neuroprotector agent so that it can prevent the occurrence of cerebral palsy in the subsequent development of the baby. MgSO₄ functions as an N-methyl-D-aspartate (NMDA) antagonist to prevent fetal brain nerve damage.12 Other mechanisms of action

include cerebral vasodilation and increase levels of neuroprotective markers, Brain Derived Neurotrophic Factor (BDNF) which is produced by the brain after administration. This can prevent the possibility of nervous system lesions that can cause permanent defects in the neurological system in preterm labor [21].

Compared with MgSO₄, nifedipine resulted in decreased maternal side effects and decreased duration of neonatal intensive care. A study showed that nifedipine was more effective than MgSO₄ in delaying labor for more than 48 hours. Use of nifedipine tocolytics in preterm PROM still controversial. A study also showed no significant benefit to the administration of nifedipine in neonates or prolongation of pregnancy in women with preterm PROM without contractions [22].

IV. CONCLUSION

The use of MgSO₄ and nifedipine as a treatment for PROM in term pregnancy is still controversial with different research results. MgSO₄ is useful in the management of PROM in pregnancies of less than 32 weeks if there is a threat of delivery within 24 hours because it has a neuroprotective effect on the fetus. Nifedipine has a tocolytic effect on PROM in preterm pregnancy as a delay in labor and prolongation of gestational age. MgSO₄ can cause more side effects on the mother and fetus compared to nifedipine which has less side effects, is more tolerable, and is more affordable.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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