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ASSOCIATION OF INTRAPARTUM INTAKE OF MAGNESIUM SULFATE AND POSTPARTUM HEMORRHAGE: SYSTEMIC REVIEW

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Introduction

Hypertensive disorders of pregnancy such as gestational hypertension, chronic hypertension, and preeclampsia are very challenging because their pharmacological management directly affects the mother and fetus. Preeclampsia is one of the most common complications of pregnancy, which occur during the third trimester and present as new-onset hypertension and proteinuria and further progresses to serious complications such as fatality in both mother and fetus. The cause of preeclampsia is debatable, but intake of Magnesium sulfate during pregnancy is often associated with postpartum hemorrhage.[1]

Magnesium sulfate (MgSO4) is one of the most commonly used medications during labor and in delivery units. The main function of magnesium sulfate is to protect against eclampsia as well as it acts as a neuroprotective agent for fetuses who are at risk of preterm birth.[2]

The mechanism of action of magnesium sulfate is not clearly understood. One of the other side effects of magnesium sulfate is uterine relaxation. This action is mediated by competition with calcium and inhibiting myosin light-chain kinase activity. This theoretical uterine relaxation is not known to stop preterm labor, and therefore it is used as a tocolytic agent and is not recommended usually. Postpartum hemorrhage (PPH) is another major concern that prevents usage of magnesium sulfate and also prevents the uterus contraction appropriately post- delivery.[4]

The previous literature and various studies on the relationship between increased risk of intake of magnesium sulfate and postpartum bleeding are conflicting, with some data suggesting an increased risk of bleeding while other data are providing contradicting data, which reveals nosignificant difference in blood loss at delivery. Postpartum hemorrhage remains a leading cause of maternal morbidity and mortality; therefore, understanding various risk factors for bleeding is essential to prevent any adverse maternal outcomes.[4]

Mechanisms of the Tocolytic action of Mg2+ on the Human Myometrium

The contractile activity of the smooth muscle is regulated by the intracellular level of free calcium ions. The pathway for uterine contraction starts with an increased concentration of intracellular free calcium, which in turn activates myosin light chain kinase and other calcium- dependent kinase

enzymes.[5]

Two decades ago, it was assessed in various in vivo and in vitro studies that magnesium sulfate exerts an inhibitory effect on uterine contraction. Many clinical studies showed the effectiveness of the parenteral administration (intravenous) of magnesium sulfate in the treatment of preterm labor. However, the tocolytic action of Mg2+ on the myometrium in the uterus is not completely understood. Magnesium competes with calcium for certain sites at the neuromuscular junction, which results in the release of the neurotransmitter acetylcholine. Magnesium itself is known to induce relaxation of myometrium at the cellular level and is known to be an important cell function regulator through its indirect effect on the movement of calcium ions.[6,7]

Clinically, the intravenous administration of magnesium sulfate doesn't have an immediate effect, and the tocolytic action for the same takes a minimum of 1 hour. The concentration of extracellular magnesium ions plays an important role here since a high concentration of magnesium ion have an inhibitory effect on intracellular free calcium ions. [8]

In a study, a high extracellular concentration of magnesium ion with a normal intracellular free

magnesium ion concentration had no major effects on the mobilization of calcium ions. However, it was seen that high intracellular free magnesium ion concentration with high extracellular magnesium ion causes suppression of calcium ion influx induced by oxytocin hormone in puerperal myometrial cells. It has been known that an increase in intracellular free magnesium ion concentration inhibits the L-type calcium ion current in cardiac myocytes. Oxytocin itself did not induce a change in the concentration of intracellular free magnesium ions in puerperal myometrial cells. Hence, keeping intracellular free magnesium ion concentration constant is preferred to maintain the functions and activities of cells. Increased intracellular free magnesium ion concentration, caused by submaximal levels of high extracellular magnesium ion, may reduce cell functions and may produce a calcium channel antagonistic effect. The increase in the intracellular level of free magnesium ions may block the calcium channels of the plasma membrane and inhibit calcium ion influx. Therefore, the clinical administration of magnesium sulfate along with calcium blockers is not advisable because the presence of one enhances the other effect excessively. [3,8,9]

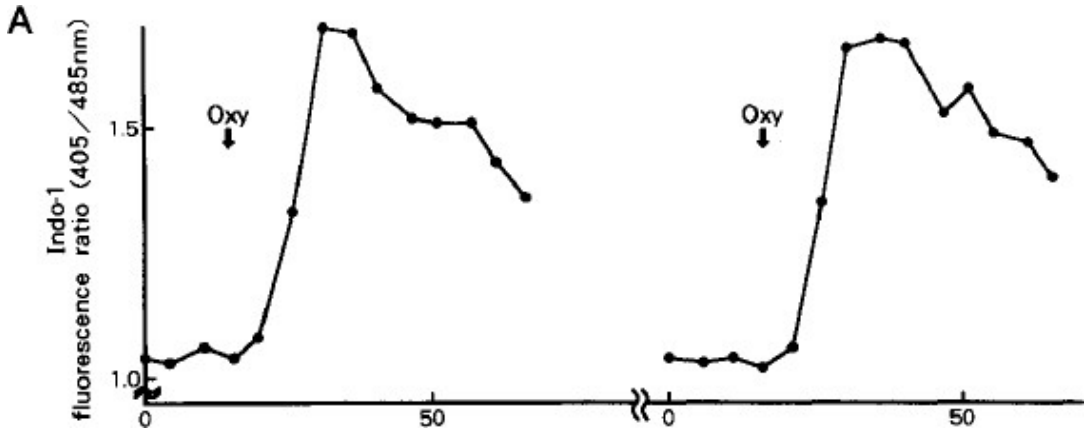

Figure depicting A. Changes in intracellular free calcium ion concentration induced by first and second administrations of oxytocin in normal solution with an interval of 20 minutes.

B. Changes in intracellular free calcium ion concentration induced by oxytocin in normal solution and extracellular magnesium ion solution. Just after the first administration, the normal solution was replaced with extracellular magnesium ion solution; after 20 minutes, oxytocin was added again. **[3]**

Committee Opinion

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal

Medicine have provided a guideline for the usage of magnesium sulfate, according to which short-term use of magnesium sulfate in obstetric care for appropriate durations of treatment is supported. However, the U.S. Food and Drug Administration (FDA) does not favor the use of magnesium sulfate injection for more than a week of preterm labor in pregnant women. This also changes the basis of drug classification for pregnancy from Category A to Category D; the changes also included labeling and new warning information. The change was prompted by concern for fetal and neonatal bone demineralization and fractures associated with long-term in utero exposure to magnesium sulfate. **[10]**

These concerns are based on reports to the FDA's Adverse Event Reporting System and a number of epidemiologic data and studies, although these studies have some important limitations in design. According to the Adverse Event Reporting System database that there are 18 cases reported in fetal and neonatal long bone demineralization and fractures in patients with the average duration of prenatal magnesium sulfate exposure for 9.6 weeks, with a total dose of 3,700 grams. **[10]**

This dose is of a longer duration and much higher dose in comparison to the currently recommended for obstetric use. In many studies, the sample sizes in available population studies were generally small. As a result, this makes the conclusions of these studies subject to confounding and bias. Magnesium sulfate has been used in obstetrics for many years now, and thousands of women have been tested in clinical trials that studied the efficacy of prenatal magnesium sulfate

for a variety of conditions. **[11-13]**

In many studies and recent trials on the use of magnesium for neuroprotection, the complications associated with it, such as fetal and neonatal bone demineralization and fracture, have not been assessed. In obstetric practice, magnesium sulfate includes prevention and treatment of seizures in women with preeclampsia or eclampsia and acts as fetal neuroprotection before any anticipated early preterm (less than 32 weeks of gestation) delivery.
[12,14]

Magnesium sulfate can also be used for the short-term prolongation of pregnancy for up to two days which facilitates the administration of antenatal corticosteroids. Tocolysis is preferred after 34 weeks of gestation. It is mostly contradicted before 24 weeks of gestation. But, the dosage can be managed based on individual circumstances at 23 weeks. Hence, clinicians should not stop using magnesium sulfate for such indications based on the FDA reclassification
system. In the above-mentioned conditions, the prolonged use of magnesium sulfate is never indicated.**[15]**

Conclusion

Magnesium sulfate has been used for many years for the treatment of preeclampsia in obstetrics practice but understanding the potential risk it carries is mandatory. According to the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, continue to support the short-term (less than two days) use of magnesium sulfate in obstetric care for appropriate conditions and for the appropriate duration of treatment such as prevention and treatment of seizures in women with preeclampsia or eclampsia, fetal neuroprotection before anticipated early preterm. Short-term prolongation of pregnancy for up to 2 days to allow for the administration of antenatal corticosteroids in pregnant women who are at risk of preterm delivery within seven days

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