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Article

Anticonvulsant for preeclampsia: Magnesium sulfate or Diazepam ?

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A B S T R A C T

Preeclampsia is a multisystem disorder which is still the leading cause of maternal death today. The occurrence of seizures in preeclampsia (eclampsia) increases the risk of maternal and perinatal morbidity and mortality. Therefore, seizure in preeclampsia should be prevented and should be managed accurateely.

The standard therapy for managing severe preeclampsia/eclampsia is the use of an anticonvulsant that is aimed to prevent/stop seizures, prevent the recurrence of attacks, to minimize and to manage their complications, and optimize the time for the birth of the baby. On the other hand, the selection of anticonvulsants needed is still controversial, so debates and studies on the effectiveness between each anticonvulsant are necessary.

Comparative research between magnesium sulfate and diazepam is widely carried out, both retrospective and prospective. Magnesium sulfate is more effective than diazepam, especially in terms of overcoming seizures, and suppressing maternal mortality and perinatal morbidity, so the choice of magnesium sulfate over diazepam is more realistic.

I. INTRODUCTION

Preeclampsia is a multisystem disorder that is usually associated with an increase in blood pressure and proteinuria. Preeclampsia is the leading cause of maternal death, alongside bleeding and infection. Eclampsia, a seizure that occurs in connection with proclamation syndrome, increases the risk of maternal and perinatal morbidity and mortality. Eclampsia is responsible for 10% of direct maternal deaths (Ikramullah et al., 2009). Therefore, it is essential to provide a valuable and successful service for eclampsia.

Preeclampsia is a worldwide disease with incidence varying between 2 % - 8 % (Jeyabalan et al., 2014), with an average of 4.6 % (Abalos et al., 2013); while in developing countries, it varies between 1.8 % - 16.7 % (Osungbade and Ige, 2011). The incidence reported in Indonesia is still dominated by hospital-based reports, especially from teaching hospitals. At Dr. Cipto Mangunkusumo Hospital Jakarta in 2011, an incidence of 16.6% was obtained (Library of the Faculty of Medicine UI, 2012); at Sanglah Denpasar Hospital and Wahidin Sudirohusodo Makasar Hospital in 2010, the incidents were 9.32% and 14.10% respectively (Lidapraja et al, 2011), while at Dr M. Djamil Padang Hospital was 7.1% (Joserizal, 2012).

The incidence of eclampsia in Europe and developing countries is about 1 in 2000 childbirth, while in developing countries, it varies between 1 in 100 to 1 in 1700 deliveries (Ikramullah et al., 2009). Eclampsia is more common in low-moderate "income" countries, with 16-69 cases per 10,000 births. It is estimated that from 1,500,000-8,000,000 cases of preeclampsia worldwide, 1,500 developed into eclampsia (Duley et al.,, 2010). According to WHO, of the approximately 60,000 female deaths per year from preeclampsia, less than half are related to eclampsia (Ikramullah et al., 2009).

Broadly speaking, prevention of preeclampsia can be classified into antenatal surveillance, lifestyle modification, nutritional supplements and pharmacological therapy. The definitive therapy of preeclampsia/eclampsia is simply the termination of pregnancy. Currently, the standard for treating severe preeclampsia/eclampsia is the use of anticonvulsant that aimed to prevent/stop seizures, to prevent recurrence of seizures, to minimize and to manage complications, and to optimize the time for the birth of the baby (Kassie et al., 2014a).

Although the standard of handling is the use of anticonvulsants, the selection of anticonvulsants needed is still controversial, so the debate about the appropriate one becomes "vociferous", otherwise it will be called "vitriolic". Among the disputed anticonvulsant options were magnesium sulfate (MgSO4) and diazepam, each with various advantages and disadvantages/side effects reported (The Eclampsia Trial Collaborative Group, 1995).

This paper will be briefly reviewed on magnesium sulfate and diazepam, as well as some comparative research on magnesium sulfate and diazepam in preeclampsia/eclampsia management. So it is hoped that later there can be an inspiration whether this controversy needs to be continued or another paradigm arises.

II. METHODS

Comparative research between magnesium sulfate and diazepam is widely carried out, both retrospective and prospective. Magnesium sulfate is more effective than diazepam, especially in

terms of overcoming seizures, and suppressing maternal mortality and perinatal morbidity, so the choice of magnesium sulfate over diazepam is more realistic.

III. RESULT

1. "Which anticonvulsant for women with eclampsia?. Evidence from the Collaborative Eclampsia Trial" by The Eclampsia Trial Collaborative Group in 1993, and published in 1995.

   This multicentre randomised trial compared the efficacy of standard anticonvulsant magnesium sulfate and diazepam, involving 905 pregnant women with eclampsia as respondents (453 got a magnesium sulfate regimen and 452 got a diazepam regimen). The main outcomes assessed were recurrent seizures and maternal mortality. The secondary outcomes assessed were other life-threatening conditions such as pulmonary udem, cardiac arrest, respiratory depreesi, pneumonia, DIC, cerebro-vasculer accident and hepar failure. The results showed that recurrence of seizures was significantly lower in the magnesium sulfate regimen than in the diazepam regimen (13.2% vs. 27.9%; $p<0.05$); But there were no significant differences in maternal mortality and other indicators of maternal morbidity and perinatal mortality and morbidity. From this study, it was concluded that the seizure in eclampsia was more easily overcome with magnesium sulfate

2. "Eclampsia: A randomized double blind trial of magnesium sulphate and diazepam in Lgos, Nigeria" by Ola et al., published in 2004.

   In the center of the study, the anticonvulsant of choice was diazepam. This randomized comparative and blind clinical trial aims to evaluate the efficacy of magnesium sulfate and diazepam to overcome and prevent recurrent seizures in pregnant women with eclampsia.Sixty pregnant women (30 each for each group) were involved as respondents to the study. The main outcomes assessed were recurrent seizures and maternal mortality. The secondary outcomes assessed were other life-threatening conditions such as pulmonary oedema, cardiac arrest, respiratory depression, aspiration pneumonitis, kidney failure, DIC, cerebrovascuer accident, hepar failure, post-partum hemorrhage and Glassgow Coma Scale Score (GCSS). Other indicators are the mode of delivery, the Apgar Score, treatment in the NICU and perinatal death. The results showed that the incidence of serious morbidity (such as recurrent seizures, complications of the respiration system, kidney complications and loss of consciousness was less in the magneium sulfate group.Likewise, pervaginam deliveries are more numerous and operative deliveries are fewer in this group. In contrast, the incidence of a low Apgar Score is twice as frequent in the diazepam group. Early neonatal death occurred 4 cases of the diazepam group and was absent in the magnesium sulfate group. From the results of this study, it is concluded that there is a reliable advantage for mothers and babies with the use of magnesium sulfate in the management of pregnant women with eclampsia.

3. "Magnesium Sulfate Versus Diazepam Infusion in Eclampsia" by Ikramullah et al., 2007, published in 2009.

   In this study, there were 45 cases of antepartum eclampsia (25 managed using magnesium sulfate and 20 with diazepam) studied. Dosage is monitored clinically. The outputs assessed were maternal and perinatal morbidity and mortality.The results showed that magnesium sulfate was better than diazepam in terms of total morbidity ($p<0.05$), prevented recurrent

seizures (16% vs 30%), maternal mortality (0 vs 5%), fetal morbidity (28% vs 90%), low AS at 1 minute (4% vs 15%), low AS 5 in minutes (0 vs 10%), intubation (8% vs 25%) and special care unit (4% vs 15%).

4. Magnesium sulphate versus diazepam for eclampsia" by Duley et al., (Cochrain) in 2010.

   This randomised trial study aims to assess the effect of magesium sulfate over diazepam in arranging women with eclampsia. In this research there were 7 trials involving 1396 eclampsia women. The results showed that magnesium sulfate had a better effect meaningfully in preventing recurrent seizures and lowering maternal mortality. There is no difference in perinatal and neonatal mortality.

5. "Maternal outcomes of magnesium sulphate and diazepam use in women with severe pre-eclampsia and eclampsia in Ethiopia" by Kassie et al., 2012 and published in 2014.

   This retrospective study aims to compare the maternal outcomes of severe preeclampsia or eclampsia patients administered with magnesium sulfate or with diazepam. 357 patients (217 getting magnesium sulfate and 140 getting diazepam) were involved in the study. Tendon reflexes, breath frequency and urine/hour production are monitored clinically to ensure the safety of magnesium sulfate use. The results of this study showed that the duration of treatment was shorter and the recurrence of seizures was significantly less in the magnesium sulfate group than in the diazepam group. It was concluded that magnesium sulfate is more effective than diazepam in managing severe preeclampsia and eclampsia patients to prevent recurrence of seizures, duration of treatment (less than 4 days) and reduction of maternal morbidity.

6. "Perinatal Outcomes of Magnesium sulphate and Diazepam use in Severe Pre-eclamptic and Eclamptic Mothers" by Kassie et al., 2012 and published in 2014.

   This retrospective study aims to compare the perinatal outcomes of severe preeclampsia or eclampsia patients administered with magnesiu sulfate or with diazepam. 357 births (217 getting magnesium sulft and 140 getting diazepam) were involved in the study. The results showed that stillbirth occurred in 24.5% of the magnesium sulfate group and 35.1% in the diazepam group. Apgar Score <7 at 1 and 5 minutes less in the magnesium sulfate group. Infants requiring neonatal care were 18.1% in the magnesium sulfate group and 31.8% in the diazepam group.It was concluded that magnesium sulfate is more effective than diazepam in managing pregnant women with severe preeclampsia or eclampsia regarding the improvement of the Apar Score, reducing stillbirth and treatment in neonatal units.

7. Ofutet, EO, Mfem CC, Okpo-ene IA and Agu CE. "Comparative Effect of Two Anticonvulsants (Magnesium Sulphate and Diazepam) on 4-Aminopyridine - Induced Seizures in CD1 Mice" by Ofulet et al., 2016.

   This experimental study was conducted on mice induced with 4-aminopyridine/4-AP (a potassium channel blocker) to cause seizures. 4-AP improves calcium conductance by blocking potassium channels on the cytoplasmic side of cell membranes, causing depolarization and opening of voltage-gated calcium channels. This study aims to see which is more effective between magnesium sulfate and diazepam to prevent these induced seizures. The variables assessed were onset of trembling, wild running, jerking, tonic clonic seizures

and time of death. The results showed that both anti-seizures slowed the onset of seizures but could not prevent seizures. In other words this study does not support that the mechanism of action of these two drugs prevents seizures through the opening of potassium channels or blocking of calcium channel. From these studies, it can be seen that magnesium sulfate is more effective at preventing seizures and reducing mortality and neonatal morbidity.

IV. DISCUSSION

1. MAGNESIUM SULFATE

Magnesium sulfate (MgSO4) has been used in women with eclampsia since the 1920s, inspired by its ability to control tetanus-induced seizures. Magnesium sulfate has become the standard therapy for treating eclampsia seizures in some countries. Originally this drug was given at a low dose, but now it has been administered in relatively high doses. Generally, the intial loading dose is given 4 grams intravenously, followed by inravena or intramuscular administration (Duley e al., 2010).

Magnesium sulfate is a natural mineral that is very important in various body systems, especially muscles and nerves. It is an important co-factor for enzymatic reactions and plays an important role in terms of neurochemic transmission and muscular excitability. Magnesium sulfate prevents and controls seizures by blocking neuromuscular transmission and lowering the amount of acetylcholine release by nerve impulses in the end plate (Ofutet et al., 2016).

Another mechanism of action that is put forward in controlling and preventing the rise of recurrent seizures is (Duley e al., 2010)

- Allegedly mediated through its role as an N-methyl-D-aspartate (NMDA) antagonist. Stimulation of NMDA receptors by neurotransmitters such as glutamate can cause seizures, especially when overactivation occurs.
- Magnesium sulfate causes cerebral vasodilation that will reduce cerebral ischemia, which further blocks neuronal damage due to hypoxia. This mechanism is also suspected through NMDA inhibition.
- Magnesium as a calcium antagonist, and as a smooth muscle relaxant. Reduced intracellular calcium can limit the transpotation of intravascular matter such as ions and proteins, which can trigger cerebral udema and seizure rise.
- The antagonistic effect of calcium can also result in a decrease in systemic blood pressure, but this is not supported by the presence of "evidence of randomized trials".

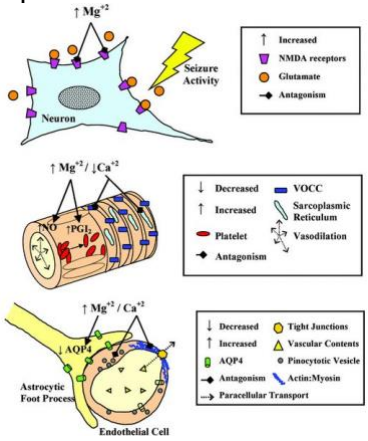

Fig 1. **The mechanism of action of magnesium sulfate**

The side effects of magnesium sulfate are mainly associated with its role as a muscle relaxant. The very serious side effects are respiratory depression, respiratory arrest or cardiac arrest, but the occurrence is a "dose response". Tendons reflex are lost at serum magnesium levels of 10 mEq/L, respiratory depression is appeared at 15mEq/L, and cardiac arrest is appeared at levels greater than 15 mEq/L. The presence of this "dose response relationship" suggests that with a strict monitor, the toxicity and side effects can be avoided (Duley e al., 2010).

Magnesium is excreted mainly through urine, so women with impaired renal function will immediately experience an increase in magnesium levels and are exposure to experiencing side effects should the dose is not reduced. Therefore, urine production needs to be monitored. In case of toxicity, calcium gluconas as an antidotum has to be administered immediately (Duley e al., 2010).

Another problem in the use of magnesium sulfate as an anticonvulsant is regarding the technique of administration, especially in countries of low resource settings where electric infusion pumps are not owned for intravenous administration, while repeated intramuscular administration that causes pain causes its use to be not optimal (Kassie et al., 2014a).

2. DIAZEPAM

Diazepam, a kind of benzodiazepines, was first used in the treatment of eclampsia in the 1960s. Other widespread uses of it are anxiety, insomnia, spasms and muscle spasm. Diazepam administration begins with a loading dose of 40 mg of intravenous injection, then continues with an infusion of a solution of 20 mg / 500 ml, with sedation titration but can still be awakened (Duley e al., 2010).

The mechanism of action of diazepam is thought to be through binding to specific sites of γ-aminobutyric acidA receptors (GABAA), which are inhibitory of the main neurotransmitter of the central nervous system. GABAA receptors are inhibitory channels, which when activated it will reduce neuronal activity (Duley e al., 2010). Diazepam is a positive allosteric modulator against GABAA receptors. These receptors are ligand-gated selective chloride ion channels that activate GABA. The binding of diazepam to this receptor complex further improves the binding of these receptors to GABA, thereby increasing the flow of chloride ions passing through the membrane of nerve cells (Ofutet et al., 2016). The onset of action of diazepam is an intermediate one. It rapidly cross the blood brain barrier, with a duration of action of 20-30 minutes, and a half-life of 20-50 minutes. The main elimination is by the enzyme hepar (Duley e al., 2010).

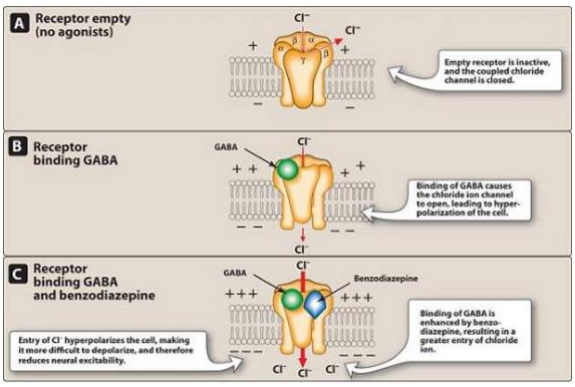

Fig 2. **The mechanism of action of diazepam**

V. CONCLUSION

1. The mechanism of action of diazepam in suppressing the rise of seizures is central while magnesium is peripheral and central.
2. Magnesium sulfate is more effective at stopping and preventing the rise of seizures.
3. The choice of magnesium sulfate is more realist, but its efficacy needs to be considered.

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BIOGRAPHY

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