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Review Article

The use of magnesium sulphate for the treatment of severe pre-eclampsia and eclampsia

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Abstract

Background: Pre-eclampsia and eclampsia are important causes of maternal and perinatal morbidity and mortality in the developing countries. There is need to provide the most effective management to pre-eclamptic and eclamptic patients. There is now evidence that magnesium sulphate is the most effective anticonvulsant.
Method: In this article**,** a literature review was made on the contribution of pre-eclampsia and eclampsia to maternal mortality and how it can be curtailed by the use of magnesium sulphate.
Results: The drug is administered by the Pritchard or Zuspan regimen, although modifications in the two protocols have been reported.
Conclusion: A Nigerian national protocol has been developed on its use. There is need for further training of health workers on how to use this important drug.

Keywords: Eclampsia; maternal mortality; magnesium sulphate; training

Résumé

Contexte: Pre-eclampsia et éclampsie sont importantes causes de morbidité maternelle et périnatale et mortalité dans les pays en développement. Il est nécessaire de fournir le plus une gestion efficace de patients pre-eclamptic et eclamptic. Il y a maintenant preuve que le sulfate de magnésium est le plus efficace Antiépileptique.
Method: en Cet article une revue documentaire a été effectuée sur la contribution de traiter les prééclampsies et éclampsie à la mortalité maternelle et comment il peut être ralenti par l'utilisation de sulfate de magnésium.
Résultats: le médicament est administré par le schéma thérapeutique Pritchard ou Zuspan bien que les modifications apportées à les deux protocoles ont été signalés.
Conclusion: Un protocole national nigérian a été développé sur son utilisation. Il y a besoin de davantage de formation des travailleurs de santé sur l'utilisation de cette drogue importante.

Mots cles: Éclampsie; la mortalité maternelle, sulfate de magnésium; formation

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Introduction

Eclampsia is a common cause of maternal mortality worldwide but particularly in the developing countries. It is estimated that every year eclampsia is associated with about 50,000 maternal deaths worldwide, most of which occur in developing countries.[1] Nigeria has one of the highest rates of maternal mortality in the world. Eclampsia has been noted to be among the most common causes of maternal mortality in Nigeria. The review of maternal deaths in Kano state for example showed that eclampsia was the most common cause of the deaths and contributed 46.3% of all the deaths in one study[2] and 31.3% in another.[3] In Birnin Kudu, eclampsia contributed 43.1% of all maternal deaths,[4]

while in Yenagoa and Ilorin, the contribution was 40%[5] and 27.5%,[6] respectively. It could indeed be argued that these are merely hospital statistics which do not reflect what is really happening in the community. However in an environment where registration of birth and death are not compulsory, these figures are often all that is available to give an indication of the real picture. What is quite clear is that eclampsia is a major killer of pregnant women in our environment and all efforts aimed at reducing its menace are welcome.

In the developing countries, there is low utilization of both antenatal and intrapartum care and the patients may present to the hospital only as a last resort. The opportunity to detect women at the pre-eclamptic phase is therefore usually lost. In addition, the World Health Organization (WHO) estimates that only 40% of births in developing countries take place in health facilities.[7] When delivery care is sought, it is done late, after a lot of delays and this contributes to maternal mortality. Yet, prenatal care and supervision of delivery by trained birth attendants are said to be the best and cost-effective means of reducing maternal and perinatal mortality and morbidity.[8,9]

The Magpie Trial

Magnesium sulphate ($MgSO_4$) was first introduced to control convulsions in 1925, but it was the Collaborative Eclampsia Trial in 1995 that confirmed the efficacy of $MgSO_4$ in the treatment of severe preeclampsia and eclampsia. The trial (also called Magpie trial) was a randomized, placebo-controlled study that enrolled over 10,000 women in 33 countries and across a wide variety of clinical settings. Four centers in Nigeria---Ibadan, Sagamu, Port Harcourt and Sokoto---participated in the study.[10] Women treated with $MgSO_4$ had a 52% and 67% lower recurrence of convulsions than those treated with diazepam and phenytoin, respectively.[11] Use of $MgSO_4$ in patients with severe pre-eclampsia reduced the risk of progression to eclampsia by more than half and reduced maternal mortality.[12] The effect of $MgSO_4$ on perinatal outcomes was also studied, demonstrating significantly improved outcomes for newborns compared to phenytoin.[13] Recently, the 2-year outcome following the use of $MgSO_4$ in the Magpie trial was published. The reduction in the risk of eclampsia following prophylaxis with $MgSO_4$ was not associated with an excess of death or disability for the women after 2 years in the group that had $MgSO_4$ compared to placebo.[14] The children whose mothers were treated with $MgSO_4$ were also studied at the age of 18 months. The use of the $MgSO_4$ was not associated with a difference in the risk of death or disability for the children at 18 months of age compared to those whose mothers were treated with placebo.[15]

Mechanism of Action

The mechanism of action of $MgSO_4$ is not completely understood. It is thought to cause dilatation of cerebral blood vessels thus reducing cerebral ischemia. It is also thought that the magnesium blocks calcium receptors by inhibiting *N*-methyl-D-aspartate receptors in the brain.[16] Magnesium also produces a peripheral (predominantly arteriolar) vasodilatation[17] thus reducing the blood pressure. It also acts competitively in blocking the entry of calcium into synaptic endings thus altering neuromuscular transmission. This transmission is affected by a preponderant presynaptic as well as a post-synaptic effect. The presynaptic release of acetylcholine is also reduced thus altering neuromuscular transmission.[18] The precise mechanism of action for the tocolytic effects of $MgSO_4$ is not clearly defined but may be related to the action of magnesium as a calcium blocker thus inhibiting muscle contractions.[19]

Availability of $MgSO_4$

On the basis of the available evidence, The World Health Organization (WHO) has recommended $MgSO_4$ as the most effective, safe, and low-cost drug for the treatment of severe pre-eclampsia and eclampsia.[20] There are indeed several reports of its successful introduction in several countries including Nigeria and its effectiveness and safety for mother and baby.[21-24]

However, the drug has remained largely unavailable in several developing countries where it is incidentally needed the most. Leading advocates, researchers, non-governmental organizations, representatives of the WHO and national health ministries from all over the world recently met and identified the main barriers to the use and availability of $MgSO_4$. These included the lack of guidelines on its use, non-inclusion in many national essential drug lists, the wrong perception that the drug is meant for use only at the highest level of facilities (such as those with intensive care facilities), lack of training of health workers on its use, little incentive for pharmaceutical companies to commercialize the drug, and ready availability of prepackaged forms of less effective drugs.[25]

In Nigeria, $MgSO_4$ had remained a drug one read about but hardly saw. It was initially been produced by the drug-manufacturing unit of the University

College Hospital, Ibadan, but this was not enough for the country. However, in the last 1 year, a pharmaceutical company has started importing the drug at an affordable rate. The drug is currently available in a number of centers and will hopefully replace the commonly available diazepam in this country in the near future. With the availability of the drug comes the need for training and retraining on the use of this important drug.

$MgSO_4$ Regimens

There are principally two main regimens available for the administration of $MgSO_4$. In the Pritchard Regimen, the loading bolus dose of 4 g of $MgSO_4$ is given slowly intravenously over 5-10 min and this is followed by 10 g given intramuscularly (5 g in each buttock). Subsequently, 5 g is given intramuscularly into alternate buttocks every 4 h.[26] In the Zuspan regimen, the loading dose consists of an initial intravenous dose of 4 g slowly over 5-10 min followed by a maintenance dose of 1-2 g every hour given by an infusion pump.[27] A gravity fed infusion set can be used in the absence of the pump especially in the developing countries. It should be noted that for the 50% $MgSO_4$, 1 ml of the solution contains 0.5 g of $MgSO_4$, while for the 20% solution, 1 ml contains 0.2 g of $MgSO_4$. Monitoring is important to ensure that the right doses are administered and this is not an easy task. Whatever regimen chosen, the drug should be administered till 24 h after delivery or after the last fit (whichever comes last).

The choice of which regimen to use depends on a number of factors such as availability of staff to monitor the drug as well as the expertise of the staff. In resource-constrained settings, the Pritchard regimen may be easier to administer since it is given intramuscularly (could thus be administered by lower cadre of health workers). It, however, has the disadvantage of being very painful, a situation which is not desired for a patient on whom efforts are been made to lower the blood pressure. To counteract this, the intramuscular dose could be administered with about 2 ml of 1% xylocaine in the same syringe.

Some workers have reported modifications in the above-mentioned regimens. $MgSO_4$ has been used with the dose reduced to a loading dose of 4.5 g intravenously and maintained on intramuscular 1.5 g every 4 h until 12 h after delivery or the last fit.[28] In another study, the loading dose was 10 g intramuscularly followed by a maintenance dose of 2.5 g intramuscularly every 4 h for 24 h.[29] The drug has been used as in Pritchard regime, but the duration of its administration reduced to 12 h after the initial loading dose.[30] The fetomaternal outcome was similar to the two more famous regimens (Pritchard and Zuspan).

Clinical Detection of Toxicity

The main fear of toxicity was also laid to rest with the Magpie trial. Toxicity of the drug was monitored using clinical parameters. The parameters that need to be monitored are the knee jerk (should be present), respiratory rate (should be more than 16/minute), and urine output (should be more than 25 ml/min). These clinical parameters have been compared with serum levels of $MgSO_4$. The first warning sign of toxicity is loss of the knee jerk which occurs at serum magnesium level of 3.5–5 mmol/l. Respiratory paralysis occurs at 5-6.5 mmol/, cardiac conduction is altered at more than 7.5 mmol/ while cardiac arrest occurs when serum magnesium exceeds 12.5 mmol/l[10, 31] However, with the above-mentioned protocols, the expected serum range of magnesium is 2-3.5 mmol/l[10]. Using the Pritchard regimen, a mean serum magnesium level of 2.1 mmol/l was found.[32] Should toxicity be detected, however, the antidote is 1 g of 10% calcium gluconate given intravenously slowly over 10 minutes.

Training on $MgSO_4$

The need has now emerged for refresher trainings for health workers in the use of $MgSO_4$. Clinical protocols are particularly useful in guiding such workers. The Federal Ministry of Health has developed a national clinical service protocol for obstetric care. The protocol outlines the management of eclampsia and how $MgSO_4$ can be used and monitored.[33] There is need to distribute this protocol and train health workers all over the country on its use. It is also recommended that the protocol should be utilized nationally as a guideline thus ensuring universal dosage regimen that will also help in uniform studies and research.

Some workers have also reported the utilization of the protocol to suite the working environment in respect of the available facilities, staff, investigations, and even the regimen of $MgSO_4$ used. In Kano state, for example, the protocol was institutionalized under the guidance of the state safe motherhood committee to incorporate the role played by non-physicians in the care of patients with eclampsia including referral where necessary [Figure 1].

Conclusion

If all stakeholders are brought on board to ensure the availability and utilization of $MgSO_4$ for the treatment of severe pre-eclampsia and eclampsia,

Clinical Features

SYMPTOMS	SIGNS
Headache	Fitting
Visual disturbance	Unconsciousness
Upper abdominal pain	Elevated BP (diastolic > 90mmHg)
Vomiting	
Fitting	Check:
	Foetal heart rate
	Pelvic examination (condition of cervix)

INVESTIGATIONS

Full Blood cell Count, Urine analysis, Random Blood Sugar

MANAGEMENT

- Shout for help;
- Check airway and breathing: free airway, put oropharyngeal tube;
- If not breathing: assisted ventilation with ambu bag + suction of secretions;

Control fitting

- MgSO4 4gm IV bolus over 5-10 minutes (loading dose)
- Additional MgSO4 of 10g (5g in each buttock IM) +2ml of 1% Xylocaine IM
- If convulsions recur after 15 minutes, give 2 g of 50% MgSO4 IV over five minutes
- Maintain with 5g IM 4hrly in alternate buttocks for 24hrs after delivery or for 24 hours after the last fit (whichever comes last)
- Put patient in left lateral position;

Monitor for MgSO4 toxicity

- Patella deep tendon reflex should be present (first to go if there is toxicity)
- Respiratory rate should be > 16/min
- Urine output should be >30ml/hour

MgSO4 toxicity

- Administer 1g of 10% Calcium gluconate IV (slowly over 5-10 minutes)

Control BP:

If diastolic BP > 110: 10 mg hydrallazine slowly iv (in 5 minutes);
then 5 mg iv every 30 minutes until diastolic BP <100mmHg

Supportive management:

- Catheterise bladder;
- Monitor fluids input and output;
- Maintain airway, regular suction;
- Monitor vital signs: pulse, BP, temperature, respiration;
- Turning of patient regularly (2 hourly)

- Call for doctor or refer;

Deliver the baby within 12 hours:

- If not in labour: Caesarean section
- If in labour: consider augmentation of labour and shorten 2nd stage with forceps or vacuum extraction;

- Avoid ergometrine after delivery; rather use syntocinon infusion (10 IU bolus IV followed by 40 IU per litre of 5% Dextrose to run over 6hrs)

Figure 1: Kano State Eclampsia Protocol

their contribution to maternal mortality is likely to be reduced. These stakeholders include policy makers, trainers, health workers and even the patients and their relations.

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