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MAGNESIUM SULPHATE IN THE TREATMENT OF PRE-ECLAMPSIA AND ECLAMPSIA

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INTRODUCTION

Pre-eclampsia and eclampsia are hypertensive disorders of pregnancy that cause significant morbidity and mortality in the fetus and mother. The disorders account for about 9% of maternal deaths in Africa and Asia and about one-quarter of maternal deaths in Latin America and the Caribbean [1]. In some parts of northern Nigeria for example, eclampsia alone contributes to almost one third of maternal deaths [2, 3]. The ultimate 'cure' for these disorders is delivery of the baby but there is a relationship between prognosis in eclampsia and the number of fits hence, the choice of anticonvulsant in patient care is very germane.

Modern management of pre-eclampsia and eclampsia could be said to have begun in 1925 with the report by Lazard on the use of magnesium sulphate [4]. While the use of magnesium sulphate went on to become the mainstay of treatment of pre-eclampsia and eclampsia in the United States, drugs such as diazepam, phenytoin and '*lytic cocktail*' became more widely used in the United Kingdom and her commonwealth allies. It was in 1995 that the superiority of magnesium sulphate became established. The Collaborative Eclampsia Trial compared the relative effectiveness of the three most popular treatments, viz., magnesium sulphate, diazepam and phenytoin [5]. Women treated with magnesium sulphate were found to have a 52% and 67% lower recurrence of convulsions than those treated with diazepam and phenytoin, respectively. Seven years later, in another multi-centre, randomized, study involving 33 countries and over 10,000 patients with pre-eclampsia; magnesium sulphate was found to reduce the risk of eclampsia and maternal deaths [6]. Not only have maternal outcomes for pre-eclampsia and eclampsia after magnesium sulphate administration been studied, the perinatal outcomes have been assessed as well. Cochrane review articles reported much better outcomes for the babies, especially when magnesium sulphate was compared to diazepam and phenytoin [7, 8].

Also the long-term safety of magnesium sulphate in both the mother and the baby has been documented in the Magpie follow-up study [9, 10]. Therefore, on the basis of high-quality evidence, the World Health Organisation (WHO) has recommended magnesium sulphate as the most effective, safe and low-cost anticonvulsant drug for pre-eclampsia and eclampsia [11].

Unfortunately despite the evidence, the drug has been listed as one of the 'new but underutilized technologies' especially in the developing countries where it is most needed [12]. There are often systematic gaps between evidence of effectiveness and what is actually practiced. Why has it become so difficult in some countries to translate research findings into clinical practice? With respect to magnesium sulphate, a combination of factors have been identified and some of these factors shall be addressed in this discuss with particular reference to Nigeria.

Ignorance, Apathy and System Failure: In many developing countries like Nigeria, continuing medical education and re-certification of health practitioners are neither mandatory nor obligatory. Hence, health workers practice their trade with whatever knowledge that was acquired at the training schools no matter how obsolete such might be. Few clinicians or policy makers in developing countries are aware of the concept of evidence-based medicine [13]. Secondly, the health care systems in many developing countries are not very efficient and research-led practice seems to be irrelevant when systems are in disarray [14]. On the contrary, uptake of evidence-based, best practices is high in developed countries. For instance, a report in 2004 on the management of eclampsia from Sweden shows the remarkably increased use of magnesium sulphate from 8% during 1980–1989 to 83% during 1990–1999 [15]. Even health workers that might have information on new products and technologies in

some developing countries are not compelled by regulatory bodies to implement best practices. To address the problem of ignorance, organization of seminars and workshops has been proposed but that alone does not work as demonstrated from the report from Mexico and Thailand. The authors concluded that knowledge access is essential but probably not sufficient to lead to changes in health care practices [16]. Therefore, there must be facilitative supervision by the appropriate authorities and regulatory bodies with appropriate sanctions where necessary to overcome the problem of underutilizing new and effective products and technologies.

Dosage: There are two standard protocols for using magnesium sulphate as an anticonvulsant in pre-eclampsia and eclampsia. In both regimens, initiation is by the intravenous route, the difference is in the route of the maintenance doses. With the ***Zuspan regimen***, an initial intravenous bolus dose of 4gm is given slowly over a period of 5-10 minutes and maintenance is with 1-2gm hourly by intravenous infusion for 24 hours using an infusion pump [17]. But in the absence of infusion pumps, which is not uncommon in the developing countries, gravity–fed drip sets can be used with reliance on the duty staff to monitor and control the rate of infusion [18]. In the ***Pritchard regimen*****,** initiation is also with 4gm bolus intravenously over 5-10 minutes and an additional 10gm intramuscularly (5gm each buttock). This is then followed by 5gm intramuscularly at 4 hourly intervals into alternate buttocks for 24 hours [19]. Some consider these regimens excessive and labour intensive, hence the call to research on shorter courses [20]. This has led to an avalanche of shorter and lower dosing protocols [21, 22, 23] with small sample sizes and/or less than rigorous methods. Perhaps, what is needed now is a well coordinated, large, multi-centre, randomized trial to validate these short regimens. Next, is whether or not other routes of administration of magnesium sulphate would be effective especially for use by health workers at the primary health care level?

Fear of Toxicity: The greatest concern with the use of magnesium sulphate has been that of toxicity. But the initial assumption that magnesium sulphate has a narrow therapeutic index has been disproved [24]. There is reasonable margin between the therapeutic levels and levels that would cause toxicity. There are established clinical monitors that can be used to predict the presence or absence of toxicity without the need for serum magnesium estimates. Clinical monitors of deep tendon reflexes, respiratory rate and urinary output have been shown to be adequate in detecting presence or absence of toxicity [25]. However, the concern for clinical monitoring especially with the deep tendon reflexes is the skill to perform the test at district and cottage hospital levels and the fact that in some patients with eclampsia the tendon reflexes are either absent, low or equivocal even before the commencement of any therapy.

Cost of Drug: One advantage of magnesium sulphate that has been constantly advertised is that it is a very cheap drug! This certainly is not the situation on the fields especially in many developing countries. The drug is not locally produced and it is thus scarce or relatively expensive when compared with 'rival' drugs like diazepam. Cost is still a major problem in Nigeria despite efforts by a pharmaceutical company to import and distribute the drug. Unless the drug is subsidized or provided free to patients with pre-eclampsia and eclampsia, the uptake would remain low as most of such patients are impoverished. It has also been argued that because of the limited scope of parenteral magnesium sulphate usage it would need support. Yet there is a group that thinks the drug is too cheap to motivate mass manufacturing, licensing, production and distribution [26]. In Mozambique and Zimbabwe, failure in registration, procurement and distribution mechanisms is said to contribute to its poor availability [27].

Pre-Eclampsia or Eclampsia: The tendency is for patients with pre-eclampsia to decline admission for in-patient care because of the apparent lack of symptoms until the situation deteriorates to full blown eclampsia. Thus we are likely to see more patients with eclampsia on magnesium sulphate than those with pre-eclampsia. Another significant barrier to improving care of women with preeclampsia and eclampsia is the fact that fewer than 60% of women in some countries have access to services where pre-eclampsia could likely be diagnosed, and fewer than 40% have access to professionals who could administer magnesium sulphate. A very significant portion of the maternal deaths from eclampsia reported from many developing countries are among women who had multiple seizures outside the hospital and those

without antenatal care [28, 29]. Improvements in facility-based care including the provision of magnesium sulphate are not likely to affect these women or prevent their deaths.

CONCLUSION

The necessary research to identify the best anti-convulsant drug for the treatment of severe pre-eclampsia and eclampsia has been concluded and the results are clear. Magnesium sulphate is safe, effective and is now available for use. Some countries have achieved success in changing both their policies and practices to incorporate this new knowledge. In Nigeria, most of the obstacles to usage are surmountable. Clinical practices should be audited to ensure best practices. But in the absence of 'auditors', the immediate challenge to us as clinicians and nurse/midwives is to ensure that we use magnesium sulphate in our practice and preach it to those that do not know so that collectively we can give our patients best practices despite the dysfunctional system. Scaling up magnesium sulphate for treatment of eclampsia and severe pre-eclampsia will significantly advance the safe motherhood agenda and contribute to attaining the Millennium Development Goals by 2015 [30]. Yes, we can!

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