

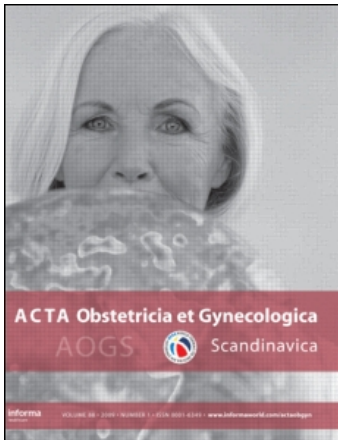
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Rashida Begum<sup>a</sup>; Anowara Begum; Richard Johanson; Mohammad Nawsher Ali; Syeba Akhter

<sup>a</sup> Obstetrics and Gynaecology.

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# A low dose ('Dhaka') magnesium sulphate regime for eclampsia

## Clinical findings and serum magnesium levels

RASHIDA BEGUM<sup>1</sup>, ANOWARA BEGUM<sup>1</sup>, RICHARD JOHANSON<sup>2</sup>, MOHAMMAD NAWSHER ALI<sup>3</sup> AND SYEBA AKHTER<sup>1</sup>

From the Departments of <sup>1</sup>Obstetrics and Gynaecology, and <sup>3</sup>Pathology, Dhaka Medical College and Hospital, Dhaka, Bangladesh and the <sup>2</sup>Department of Obstetrics and Gynaecology, North Staffs Maternity Unit, England

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**Background.** Eclampsia remains a common cause of maternal death in Bangladesh. Early experience of magnesium sulphate use for eclampsia in Bangladesh was based on a lower dose regime, tailored for use in the smaller woman.

**Objectives.** a) To determine the recurrent convulsion rate with the low dose 'Dhaka' magnesium sulphate regime (recognizing the limitations of sample size). b) To identify whether toxicity occurs with this regime. c) To measure serum level of magnesium with this regime.

**Methods.** This prospective study included 65 eclamptic patients receiving lower dose magnesium sulphate therapy at Dhaka Medical College Hospital from 25 March 1998–15 June 1998. The loading dose of magnesium sulphate was 10 gm. Following this 2.5 gm was given intramuscularly 4 hourly, for 24 hours after administration of the first dose. Four blood samples were collected for serum magnesium levels. Patients were monitored hourly by observing their respiratory rate, knee jerks and urinary output. Findings were matched with serum magnesium levels.

**Results.** The range of serum magnesium levels was 1.74 to 6 mg/dl with mean (s.d.) values of 3.87 (0.78). Only five (9%) patients had diminished knee jerks 6, 10, 12, 12 and 15 hours after administration of the loading dose. But at those times the serum magnesium levels were 3.2 mg/dl, 3.8/dl, 3.4 mg/dl and 3.3 mg/dl respectively. Of the 65 patients, only one developed recurrent convulsions. This was 3 hours after the loading dose and was controlled by diazepam treatment and maintenance magnesium sulphate.

**Conclusion.** Half of the standard dose of magnesium sulphate appeared to be sufficient to control convulsions effectively and serum levels of magnesium remained lower than levels which produce toxicity.

**Key words:** eclampsia; magnesium sulphate; magnesium sulphate serum level; toxicity

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Eclampsia remains a serious complication of pregnancy and is one of the important causes of mortality and morbidity during pregnancy, childbirth, and puerperium. Of the estimated 700,000 maternal deaths every year worldwide 10% to 15% are associated with hypertensive disorder of pregnancy (1). In Bangladesh at least 30,000 women die every year due to pregnancy, childbirth and its related causes. Eclampsia itself comprises 16% of all these (2). Lack of health awareness, illiteracy, lack of medical care facilities and poor management are

all contributing factors to the development and high mortality of eclampsia (3).

Until recently, the pharmacological treatment of eclampsia has been determined largely by geography, habit and tradition. Although magnesium sulphate has been the drug of choice in the United States, in Britain and in many parts of the world other agents were preferred. In Bangladesh the standard treatment of eclampsia was with diazepam (4). There is now conclusive evidence that the best available treatment for women who have

had an eclamptic fit is magnesium sulphate. The Collaborative Eclampsia Trial randomized a large number of women to receive diazepam or magnesium sulphate and showed the greater efficacy of magnesium sulphate in terms of seizure control (5). Not only does magnesium sulphate diminish the risk of further convulsions but it also produces less maternal and neonatal morbidity than the commonly used alternative agents (5). A smaller study carried out at Dhaka Medical College at the same time as the Collaborative Eclampsia Trial came to exactly the same conclusions (6). The main difference between these two studies was the dosage regime of magnesium sulphate. The loading dose used in Dhaka was significantly less than that used by The Collaborative Eclampsia Trial (10 g loading dose compared with 14 g). Maintenance treatment, thereafter, was half the dose (2.5 g cf. 5 g). The lower dosage had been chosen principally because of the small size of Bangladeshi women and concerns about toxicity in circumstances in which measuring serum levels of magnesium would be difficult.

The evidence was considered by a working party on Eclampsia in October 1997, and it was agreed that the regime validated for local use would be recommended for national use (3). Guidelines were prepared and disseminated. In Dhaka Medical College Hospital and in the other tertiary level hospitals policies were immediately changed. Since the change took place mortality rates in Dhaka Medical College have fallen dramatically, an effect that one would expect from the observed effects on morbidity shown in the controlled trials (7). However, adoption of this treatment in primary and secondary level hospitals has been delayed by a number of factors, which include a fear of toxicity of the drug. Despite the reassuring findings of the Collaborative Eclampsia Trial there remained significant concerns about using magnesium sulphate in situations where serum levels could not be monitored.

The objective of the current study was therefore to closely record the efficacy of the lower dose 'Dhaka' regime in terms of convulsion control at the same time as noting clinical signs of toxicity and collating these with the simultaneously recorded serum levels of magnesium. By so doing, we hoped to be able to reassure other health professionals about the safety of magnesium.

### **Materials and methods**

This prospective study was undertaken at Dhaka Medical College Hospital between 25 March and 15 June 1998. It had the approval of the Hospital Research Ethics Committee. The agreed guidelines

for management of eclamptic patients were followed (3). Exclusions for treatment with eclampsia included those patients who were moribund. This group included those who were deeply unconscious with cerebrovascular accidents, those with renal failure (severe oliguria or anuria), those with massive pulmonary edema, those with associated massive hemorrhage, and those with disseminated intravascular coagulation and shock (including sepsis). The regime used was that from the Dhaka study (6). This was 4gm magnesium sulphate, given intravenously slowly (over 15 minutes), along with 3 gm given intramuscularly in each buttock, as a loading dose. Maintenance therapy was 2.5 gm, every 4 hours, given intramuscularly in alternate buttocks, until 24 hours after administration of the first dose. Patients were monitored every 30 minutes for the first 6 hours, then hourly, by observing respiratory rate, knee jerks, and urinary output. As indicated by condition, other clinical parameters were also checked.

Blood samples were collected for analysis of serum magnesium levels. According to the protocol four samples would be collected. The first was taken before administration of the drug, the second five minutes after the loading dose, the third, four hours after the loading dose, and the fourth before the last dose. Additional samples were taken when there was suspicion of toxicity, e.g. due to absence knee jerks. Samples were sent to a standard laboratory where serum levels were identified using a photometric colorimetric test with lipid clearing factor (LCF) (Human Geseellschaft for Biochemica and Diagnostica, Taunusstein, Germany). Clinical findings of the patient were correlated with serum magnesium levels.

### **Results**

During the study period 100 patients were admitted to the eclampsia ward with antepartum or postpartum eclampsia. Ninety patients were treated by MgSO<sub>4</sub> and two by intravenous diazepam, with the intention of commencing MgSO<sub>4</sub> later on. However, due to poor general condition, these two patients did not need any further anti-convulsants. Another eight patients were so moribund on admission that they were not given anti-convulsants (seven of these women died). Due to time limitations and availability of the principal investigator, sixty-five of the ninety women receiving magnesium sulphate were included in the study.

The presenting condition of the 65 eclamptic patients who were entered into the study is summarized in Table I. In addition, ten women (15%) were noted to have lung crepitations. Sixty-three women

Table I. Patients profile at admission (n=65)

No. of fits		
1-5	35	(54%)
6-10	20	(31%)
>10	10	(15%)
Diastolic blood pressure		
90-99	7	(11%)
100-110	13	(20%)
>110	46	(69%)
Glasgow coma scale		
15	20	(31%)
12-14	17	(26%)
8-11	28	(43%)
Edema		
nil	1	(1.5%)
+	15	(23%)
++	25	(38%)
+++	24	(37%)
Proteinuria		
nil	2	(3%)
1+	10	(15%)
2+	33	(51%)
3+	20	(31%)

Table II. Serum magnesium level

Samples	Mean (sd)	Range Mg in mg/dl
1st sample (normal level) (n=65)	1.90 (0.20)	1.74-2.4
2nd sample (n=65)	3.72 (0.69)	2.10-4.4
3rd sample (n=65)	3.48 (0.59)	2.08-3.9
4th sample (n=60)	3.34 (0.27)	1.08-6
During absent jerks (n=5)	3.32 (0.78)	3.00-3.8

(97%) were antepartum and only two (3%) were postpartum. Of the 63 with antepartum eclampsia, 53 (84%) were delivered by cesarean section, seven (11%) had spontaneous vaginal deliveries, whilst one was delivered by ventouse and two by forceps.

In 15 (23%) women, treatment started within 5 hours of the first fit, in 40 (62%) it was started between 6 and 12 hours and in the remaining ten (15%), the delay to treatment was more than 12 hours. Forty women were delivered within 12 hours, of the first fit (64%), and the remainder within 24 hours.

All patients maintained normal respiratory rates, between 16-25 breaths/minute. Urinary output was more than 50ml/hour in 20 women and was sufficient to maintain magnesium sulphate treatment in the remainder. Only five (8%) patients had absent knee jerks. These were found 6, 10, 12, 12 and 15 hours after administration of the first dose.

As shown in Table II, the range of serum magnesium levels was 1.74 to 6 mg/dl. The first sample shows normal levels before administration of the

drug. In only 15 patients was the upper limit of serum magnesium more than 4mg/dl. In the patients who had absent knee jerks the magnesium levels were 3.2 mg/dl, 3 mg/dl, 3.8 mg/dl, 3.4 mg/dl and 3.3 mg/dl respectively.

There were no maternal deaths. Only one patient had recurrent convulsions and she was treated with an intravenous injection of 10mg diazepam, following which the convulsions stopped instantly. The magnesium level was not checked. Forty patients (76%) regained consciousness within 6-12 hours of starting treatment and the remainder within the next 8 hours. Three women had respiratory infections, five urinary infections and five wound infections. There was no pulmonary aspiration. Three women developed puerperal psychosis. There were eight still births and three newborn babies died within the first week due to being very low birthweight (<1.25 kg). Twenty-five babies (45%) were low birthweight, ten had birth asphyxia, five jaundice and one a respiratory infection. No babies were thought to be hypotonic.

## Discussion

Prevention of further fits in eclampsia is associated with a reduction in adverse outcomes (8). Magnesium is an ideal drug, with rapid onset of action, a non-sedative effect on mother and baby, a fairly wide safety margin and a readily available antidote in the form of calcium gluconate (5, 9). The Collaborative Trial provided vital evidence that magnesium reduces the risk of recurrent seizures compared to the other standard agents diazepam and phenytoin (5). Furthermore, use of magnesium sulphate does not appear to be associated with detrimental effects on the neonate (10, 11).

The mechanism of action of magnesium sulphate is uncertain, but there is evidence from computed tomography and magnetic resonance angiographic studies implicating cerebral vasospasm and ischemia in the genesis of eclampsia (12-14). Magnesium seems to reverse and ameliorate the effects of cerebral ischemia (15). There may also be a moderate inhibitory effect on cortical discharge (16), with magnesium antagonizing the excitatory glutamate N-methyl-d aspartate receptor (17). Falling serum calcium levels following the administration of intravenous magnesium sulphate inhibit acetylcholine release at the motor end plate. The degree of inhibition is directly related and inversely proportional to the serum calcium level (18, 19). Magnesium also increases production of the endothelial vasodilator prostacyclin (20), inhibits platelet activation (21), and protects endothelial cells from injury mediated by free radicals

(22). There is also evidence that magnesium dilates human uterine arteries (23).

The dose of magnesium sulphate administered has varied according to a variety of empirical regimens. The definition of a desired therapeutic concentration of magnesium has remained controversial and greater attention is commonly directed to avoiding the toxic effects of the drug than to attaining a fixed serum concentration (24). The widespread use of magnesium according to Pritchard regimen includes a combined intramuscular and intravenous regimen (4 gm intravenously and 10 gm intramuscularly given simultaneously, followed by 5 gm intramuscularly 4 hourly thereafter) (25).

In our study we used total of 10 mg MgSO<sub>4</sub> as a loading dose and 2.5 mg, 4 hourly, thereafter, which is just over half of the dose used by Pritchard and in the Collaborative Eclampsia Trial. The response to treatment in our study, in terms of recurrent fits, appears to be satisfactory. However, in view of the selected nature of the case series and small sample size, caution should be exercised in interpreting this result. Although recurrence rates in some other studies, using conventional higher dose regimes, are higher (12.5%, 21% and 13.2%) (6, 26, 27), this may be because they included patients with a more complicated disease picture. We used diazepam to treat the one patient who did have recurrent convulsions, however, an additional MgSO<sub>4</sub> injection is the recommended first line treatment in this situation (5, 28, 29).

No patient developed toxicity with the low dose 'Dhaka' regime. The earliest sign of toxicity would be loss of tendon reflexes, which will usually occur when serum levels of 10mg/dl are reached (28). In the five patients in whom we elicited absent knee jerks, serum measurements taken at the time were at much lower levels. This raises further questions about the increased sensitivity of smaller women to this agent.

Different therapeutic ranges have been proposed. Some authors recommend a value between 4.8–8.4 mg/dl (28), whilst Pritchard described the therapeutic range of serum magnesium concentration as being between 2 and 3.5 mmol/L (25). The range of serum magnesium levels in our patients was 2.1–6mg/dl. This lies within Pritchard's therapeutic range and is lower than levels which have been shown to produce toxicity in other studies.

The regime appeared to be highly effective clinically without any maternal deaths. In our study 76% patients regained consciousness within 6–12 hours, which is the same proportion reported in another setting (26). The cesarean section rate was very high in our study (84%) but as the definitive

treatment of eclampsia is termination of pregnancy, quick delivery by this method may have reduced patients' morbidity in our series. The adverse perinatal outcomes that we have described are well recognized in cases of eclampsia. Seventeen percent of the neonates had birth asphyxia. However, recent evidence has suggested that *in-utero* exposure to magnesium may be associated with higher 1 minute Apgar score and a lower prevalence of cerebral palsy, even in infants born weighing less than 1500 gm (30).

## Conclusion

Magnesium sulphate is the anti convulsant drug of choice for women with eclampsia. The low dose 'Dhaka' regime used for smaller women appears to control and prevent convulsions effectively. Our study of the 'Dhaka' regime showed that serum levels remain well below toxic levels. The present study provides further strong support for the routine use of magnesium sulphate for eclamptic convulsions. As long as there is adequate urinary output clinical monitoring appears to be sufficient. However, in order to increase confidence in these findings a proper randomized comparison of the new lower dose regime should be undertaken with that used in the Collaborative Eclampsia Trial.

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*Address for correspondence:*

Mosammat Rashida Begum  
 Consultant in charge of Eclampsia Unit  
 Obstetrics & Gynaecology  
 Dhaka Medical College and Hospital  
 Dhaka  
 Bangladesh