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Research Article

Effect of Magnesium Sulphate in Mothers suffering from Toxemia of Pregnancy and their Neonates

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Background: Severe pre-eclampsia is one of the major causes of high maternal mortality rate in both developed and developing countries. The goals of management are to prevent progression to eclampsia thus preventing convulsions, to control the blood pressure and to prevent untoward effects in the foetus. The first-line option for the treatment and prevention of eclamptic seizures is magnesium sulphate.

Objective: To determine the serum magnesium, urea and electrolyte levels in neonates of mothers treated with magnesium sulphate and compare the findings with the levels in non-exposed neonates.

Methodology: A quasi experimental design was adopted where test subjects were neonates of mothers suffering from preeclampsia and severe eclampsia and were being treated with magnesium sulphate just before delivery at Pumwani Maternity hospital. The control group comprised neonates of hypertensive mothers without preeclampsia being treated using other drugs. Blood samples were obtained from the mother at onset of labor and from the neonates at birth and analyzed in the clinical chemistry laboratory of the University of Nairobi.

Results: A total of 54 mothers and their neonates were enrolled with 27 in each arm of the study. The mean maternal serum magnesium in the test group was significantly higher than in the control group ($p = 0.008$). The mean neonatal serum magnesium in the test group was also significantly higher compared to the control group ($p = 0.008$). There were statistically significant differences in serum sodium ($p = 0.015$), urea ($p = 0.043$) and creatinine ($p = 0.008$) levels between the maternal test and control groups. There were significant differences in serum urea ($p = 0.007$) and chloride ($p = 0.017$) between the neonatal test and control groups. The calcium and potassium levels were elevated in the test group but not to significant levels. There was a positive correlation between maternal and neonatal serum magnesium levels in both groups stronger in the test group ($r = 0.56$, $p = 0.003$) as compared to the control group ($r = 0.35$, $p = 0.087$).

Conclusion: Maternally administered magnesium sulphate raises urea and creatinine levels to significant levels in mothers. Calcium levels are also raised while in mothers not receiving magnesium sulphate they were slightly lower. In neonates the urea and chloride levels are elevated to significant levels while the calcium and potassium levels are not significantly elevated. We suggest monitoring of both in the immediate post-partum period.

Keywords: Preeclampsia, eclampsia, magnesium sulphate, neonate, serum urea and electrolytes.

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1. Introduction

Pre-eclampsia (PET) also referred to as toxemia of pregnancy, is defined as the development of

hypertension accompanied by proteinuria and edema during the third trimester of pregnancy. In a patient with pre-existing essential hypertension, it is diagnosed if the systolic blood pressure (BP) increases by

30mmHg or the diastolic increases by 15mmHg. In severe cases, convulsions may appear and the condition is thus termed eclampsia.

Severe PET is one of the major causes of high maternal mortality rate in both developed and developing countries. The goals of management are to prevent progression to eclampsia thus preventing convulsions, to control the BP by stabilizing the diastolic pressure to between 90-100 mmHg and to prevent untoward effects in the foetus.

The first-line option for the treatment and prevention of eclamptic seizures is magnesium sulfate (Sibai, 2004). It has been found that women with PET had a lower risk of progression to eclampsia and a lower mortality rate when treated with magnesium sulphate. For prophylaxis, MgSO₄ has been shown to be superior to diazepam, phenytoin, nimodipine and placebo (Altman et al, 2002).

MgSO₄ is given as a 4g intravenous loading dose, immediately followed by 10g intramuscularly and then by 5g every 4 hours in alternating buttocks or a loading dose of 4g followed by a maintenance infusion of 1 to 2 g/h by controlled infusion pump. The clinical effect and the toxicity of MgSO₄ depends on its serum levels. For treatment of eclamptic seizures, a concentration of 1.8 – 3.0 mmol/L should be achieved. Magnesium is excreted mainly by the kidney with the half-life being 4.66 hours (Idama and Lindow, 1998).

The free magnesium diffuses into the extravascular-extra cellular space, bone and across the placenta and foetal membranes into the amniotic fluid and the foetus (Hallak and Cotton, 1993).

Neonates born to mothers treated with MgSO₄ for severe PET and eclampsia may be born with significant high levels of magnesium concentration ranging from 3 – 11 mmol/L (Lipsitz and English, 1967).

The APGAR (Activity Pulse Grimace Appearance Respiration) score was invented in 1952 as a means of quickly assessing the health of newborns. It is calculated at 1 minute and 5 minutes after birth by scoring the heart rate, respiratory rate, muscle tone, skin colour and reflex response with each receiving a score of 0-2 d. A score of 10 means the infant is healthy while a low score is predictive of high morbidity and mortality rates.

Studies done at Pumwani Maternity hospital the research area (Bansal, 1985), have shown neonates born to mothers with severe PET and eclampsia were underweight at birth and had low APGAR scores. This could be attributed to in utero magnesium sulphate exposure used for the management of PET and eclampsia in their mothers. Hypermagnesemia in the neonate has been shown to be associated with asphyxia and decreased serum calcium levels on long term use. Neonatal neurological depression may occur with respiratory depression, loss of reflexes and muscle weakness. This may result in low APGAR scores. Thus the study aimed at finding out whether there was a link between the low birth weights and low APGAR scores in neonates of mothers with preeclampsia/eclampsia and

the in utero magnesium sulphate exposure when mothers were treated with magnesium sulphate.

2. Methodology

2.1 Study design and study area

The research design was a quasi-experimental study. The study was conducted at Pumwani Maternity hospital, the biggest government maternity hospital in East and Central Africa catering for both low and middle income earners. It has one labor ward, two ante-natal wards and 5 post-natal wards. Pumwani maternity hospital has an average of 70 deliveries per day, 30,000 per year.

2.2 Target population

The test population was made up of neonates of mothers who had been treated with magnesium sulphate for severe preeclampsia. These were compared to the controls who were neonates of mothers who had preeclampsia but were treated with other drugs other than MgSO₄ such as nifedipine, hydralazine and methyldopa.

2.3 Sampling

Sample size was calculated using the Karl Fischer's method. With an incidence of 1.8% (Osungbade and Ige, 2011), the desired sample size was 27 mothers and their neonates for the tests and 27 mothers and their neonates for the controls. Sampling was by convenient sampling method due to the limited number of patients presenting with severe PET and eclampsia.

2.4 Inclusion/exclusion criteria

The patients included in the study for the test arm had to be patients diagnosed with severe PET and eclampsia (Sibai, 2005) and on MgSO₄ therapy. For the control arm, the patients had to be diagnosed with preeclampsia but not on treatment with MgSO₄. All patients had to have given birth to live babies who were also included in the study.

Patients receiving magnesium for treatment of any other ailments or suffering from conditions which might present with symptoms similar to hypermagnesemia i.e. adrenal insufficiency, renal failure, hypocalcaemia, hypokalemia, hypoparathyroidism, hypothyroidism and rhabdomyolysis which may precipitate hypermagnesemia were excluded from the study

Patients from whom samples could not be obtained for both mother and baby or who refused to give consent were excluded from the study.

2.5 Data collection

Data was collected after a successful pilot study had been carried out. Patient's particulars were filled in a data collection form by the investigators. The signs and symptoms used to diagnose the patient were also noted from the patient file and confirmed with the patient. The patients were observed for any signs indicating toxicity like increase or decrease of seizures, urine output, presence or absence of deep tendon reflexes.

With assistance from the nurses in the labour ward, blood samples were drawn from the mothers some 2-3 hours after a loading dose of MgSO₄ had been given to allow for the apparent volume of distribution to be reached (Lu et al, 2000). Blood samples were also collected from the neonate at birth. For the control group samples were obtained from the mother an hour after the oral drugs had been given and from the neonates at birth. The samples were then centrifuged and the serum obtained analyzed.

2.6 Data analysis

The serum urea and electrolyte levels were measured and reference made to the normal ranges. The mean magnesium levels were determined and the deviation from reference ranges determined. The serum magnesium levels in the exposed neonates were measured and compared to serum magnesium in neonates not exposed to MgSO₄ and these were also correlated with the maternal serum magnesium levels. The APGAR scores and birth weight for the neonates exposed were compared to those of the non-exposed group.

2.7 Ethical considerations

Approval to carry out the study was given by the Kenyatta National Hospital/University of Nairobi Ethics Committee and the Pumwani Maternity Hospital administration as per the letter referenced **KNH-ERC/A/165**. Confidentiality of the respondents as well as of all records evaluated was observed. No patient names were used. All patients were adequately treated and any their neonates managed for any untoward symptoms before discharge.

3. Results

Study participants characteristics

The mean age of mothers in the test group was 25.3 years (SD 4.6) compared to a mean age of 25.7 years (SD 4.7) years among controls. The modal age group in the test group was 21- 25 years (n=11) and in the control group 26-30 years (n=10). There was no significant difference in the mean age of mothers in the two groups ($t = 0.29$; $p = 0.76$).

The median gestation age in the test group was 38 weeks and the range was 34 to 40 weeks while that of the control group was 39 weeks and 36 to 41 weeks respectively. Mothers receiving magnesium sulphate treatment were mostly delivered during week 37-38 (48.2%) while most (48.2%) mothers in the control group delivered at 39-41 weeks.

Maternal hypertension

The mean diastolic BP among mothers in the test group was 115.4 mmHg (SD 12.1) compared to a mean BP of 98.3 mmHg (SD 5.7) in the control group. The difference was statistically significant ($p < 0.001$). 17 mothers in test group had severe hypertension, while there was a bimodal distribution of BP measurement in the control group; with patients equally likely to have mild

hypertension ($n = 11$) or normal blood pressure ($n = 11$).

Maternal and neonatal serum magnesium

The mean maternal serum magnesium in the test group (mean = 2.9 mmol/L, SD = 0.9) was significantly higher than the control group (mean = 2.3 mmol/L, SD = 0.6, $p = 0.008$).

The mean neonatal serum magnesium in the test group (mean = 3.0 mmol/L, SD = 1.0) was significantly higher than the control group (mean = 2.3 mmol/L, SD = 0.6, $p = 0.008$).

Maternal urea and electrolytes levels

There were statistically significant differences in serum sodium, urea and creatinine levels in the test and control groups (**Table 1**). Serum sodium was higher in control group while creatinine and urea were higher in the test group. Maternal serum levels of potassium, chloride and calcium did not show significant differences between the test and control groups.

Neonatal urea and electrolytes levels

There were significant differences between tests and controls in levels of serum urea ($p = 0.007$) and chloride ($p = 0.017$). Urea levels were significantly higher in the test group compared to the control group (mean = 4.0 mmol/L versus 2.9 mmol/L), while mean chloride levels were 99.4 mmol/L for the test group vs. 97.2 mmol/L for the control group (**Table 1**).

Neonatal APGAR scores

There was no significant difference between the APGAR scores of the neonatal test and control groups. 89 % of the neonates in the test had a score of 7-8 at 1 minute and at 5 minutes 59% had a score of 9-10. In the control group, 59% had a score of 7-8 at 1 minute while at 5 minutes, 59 % had a score similar to that of the test group (**Figure 1**).

Neonatal birth weight

74% of the neonates in the test group were underweight with only 19% being of normal birth weight. In the control group, only 41% were underweight with 52% being of normal birth weight. 7% of neonates in both groups were overweight. The median birth weight in the test group was 2.2 kg (IQR 1.8 to 3.0) compared to a median of 3 kg (IQR 2.3 to 3.6) in the control group. There was a statistically significant difference in birth weight of neonates in the test and intervention groups, Mann Whitney test p value = 0.003.

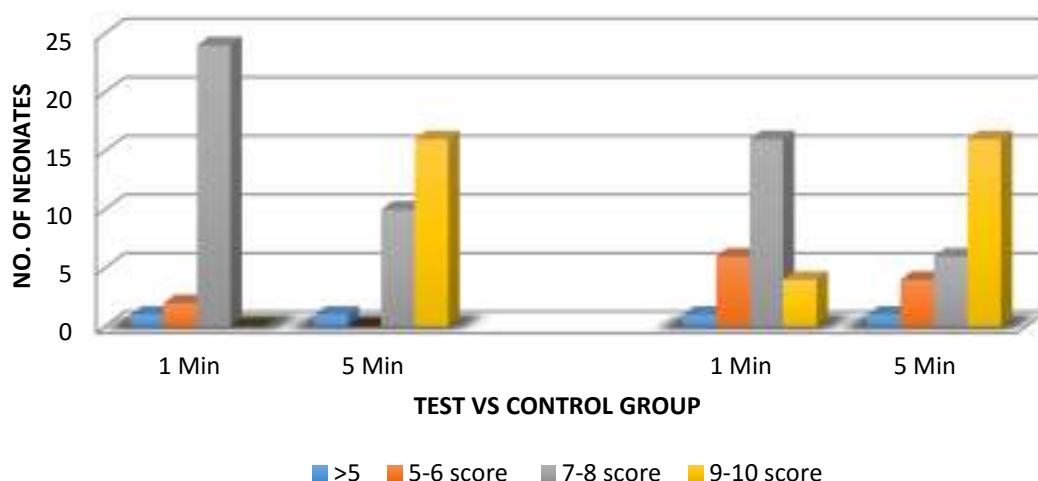
Infant birth weight was not significantly associated with neonatal serum magnesium sulphate levels after adjusting for the test group. The mean serum magnesium level was 0.66 mmol/L higher in neonates in the test compared to control group ($p = 0.008$). The neonatal magnesium serum levels increased by 0.07 mmol/L for each additional kilogram of birth weight but this increase was not significant ($p = 0.605$).

Table 1: Maternal and Neonatal urea and electrolytes in test and control groups

	Maternal					Neonatal				
	Tests		Controls		P value	Tests		Controls		P value
	Mean (mmol/L)	SD	Mean (mmol/L)	SD		Mean (mmol/L)	SD	Mean (mmol/L)	SD	
Sodium	135.9	3.8	138.4	3.6	0.015	138.6	6.0	138.4	4.4	0.883
Potassium	4.5	1.6	4.3	0.8	0.495	5.1	1.6	4.9	0.7	0.689
Chloride	99.6	3.8	98.8	2.3	0.371	99.4	3.2	97.2	3.2	0.017
Urea	3.3	1.7	2.6	0.8	0.043	4.0	1.8	2.9	1.0	0.007
Creatinine	89.8*	24.7	71.5*	23.0	0.008	99.0*	27.6	82.1*	37.0	0.067
Calcium	2.0	0.4	1.9	0.3	0.629	2.4	0.4	2.3	0.3	0.241

*: $\mu\text{mol/L}$

Test vs control group APGAR scores

**Figure 1:** Neonatal APGAR scores

Correlation between maternal and neonatal serum magnesium levels

There was a positive correlation between maternal and neonatal serum magnesium levels in both the test and control groups. The correlation was stronger in the test group ($r = 0.56$, $p = 0.003$) compared to the control group ($r = 0.35$, $p = 0.087$).

None of the patients developed any signs which would have signified toxicity (seizures, urine output, presence or absence of deep tendon reflexes) indicating that the magnesium sulphate levels in the serum were well within the therapeutic range of 1.8 -3 mmol/L.

4. Discussion

MgSO₄ is the recommended first-line option for the treatment and prevention of eclamptic seizures (Altman et al, 2002). Accordingly, in our study, patients presenting with severe PET (headache, oedema, blurred vision, confusion and a diastolic BP above 110 (Sibai, 2003; Cooray et al, 2004) were first given a loading dose of 4g of MgSO₄ then an infusion of 1g /hour as a

maintenance dose. 70% of the mothers in the test group presented and delivered at a gestation age below 38 weeks as compared to 11% in the control group. This is in line with studies that recommend delivery as the definitive treatment for severe preeclampsia after 34 weeks (Wagner, 2004; Sibai, 2005).

The serum magnesium levels were found to be significantly high in the test group as compared to the control group. For treatment of eclamptic seizures, a concentration of 1.8 – 3.0 mmol/L should be achieved (Idama and Lindow, 1998). In this study the serum level of magnesium were well within the recommended levels for treatment and not elevated to toxic levels.

Maternal serum urea and creatinine were found to be elevated in the mothers in the test group. Serum creatinine levels are used as a marker for kidney injury. This is significant because MgSO₄ is excreted through the renal route and in view of the damage caused to the kidney by the disease, magnesium toxicity could occur. There is an increased risk for development of kidney injury after preeclampsia and eclampsia (McDonald et al, 2010). In eclampsia, abnormalities in blood urea

nitrogen and serum creatinine among other findings are statistically significant and thus serum creatinine levels in eclamptic patients should be monitored (Sibai et al, 1982; Ries et al, 2000).

Serum calcium levels in the controls were lower than in the test group. Low calcium levels in pre-eclamptic women not on treatment with MgSO₄ have been found previously. After magnesium therapy the levels are raised indicating that ionized calcium levels appeared to be tightly regulated in the presence of elevated serum magnesium levels (Mason et al, 1996).

The neonatal serum magnesium levels in our study correlated with the maternal serum magnesium levels. The levels in the neonatal test group were higher than in the control group. There is transfer of magnesium from maternal circulation into the foetal blood (Hallak and Cotton, 1993). An increase in magnesium serum levels in both mother and foetus after administration occurs (Chelsey and Tepper, 1957). Such newborns of mothers exposed to MgSO₄ have elevated serum magnesium levels ranging from 3-11 mmol/L (Widdowson and Mccance, 1965).

The serum levels of all electrolytes were elevated in the neonatal test group as compared to the levels in the control group. The urea levels were significantly elevated. The high electrolyte levels could be explained by the fact that at birth, renal blood flow is low and the immature kidney has limited adaptability in case of excess administration of drugs and thus a higher risk of toxicity. In preterm neonates born at 26- 34 weeks gestation age, the increase in the glomerular filtration rate is limited because of incomplete nephrogenesis. Thus clearance of drugs from the circulation is limited resulting in elevated serum levels (CPMP/PEG/35132/03, 2004).

In our study the serum creatinine was found to be elevated in the test group. Creatinine levels are used as a marker for kidney function. Serum creatinine has been shown to be elevated in the first days of life reflecting maternal creatinine and a low intrinsic glomerular filtration rate. The lower the gestation age at birth, the more elevated is the serum creatinine. Because the neonates in the test group were born before term, this could explain the elevated serum creatinine levels.

The neonatal serum calcium levels in both groups of our study were higher than the maternal serum calcium levels. Studies have shown active transfer of calcium from the mother to the neonate during the last trimester of pregnancy whereby the cord calcium levels are higher than the maternal serum calcium levels (Schauberger and Pitkin, 1979). In our study, neonatal serum calcium levels in the test group were slightly higher than in the control group but not significantly different. Similar results to our study have been reported (Donovan E.F. et al, 1980). A rise in serum magnesium levels inhibits secretion of parathyroid hormone which results in increased urinary excretion of calcium (MacIntyre et al, 1963). In a study of five newborn infants whose mothers had been treated with IV magnesium sulfate for periods ranging from 5 to 14 weeks, radiographic bony abnormalities in two of the infants were noted (Lamm et al, 1988). Foetal hypermagnesemia due to long term treatment with

magnesium was found to depress parathyroid hormone release resulting in foetal hypocalcaemia (Savory and Monif, 1971). No neonatal symptoms have been associated with either calcium levels (Donovan et al, 1980).

The neonatal serum potassium levels in both groups were found to be higher than the maternal serum potassium levels while the serum sodium levels were found to be lower in the neonates. There is physiological hyponatremia and hyperkalemia in healthy newborns which is highly suggestive of functional hypoaldosteronism (Martinerie et al, 2009). This may be due to the adaptive process from intrauterine aquatic environment where renal sodium reabsorption is dispensable, to life outside the uterus where strict sodium control by the kidney is essential. In our study the serum potassium levels in the test group were slightly higher than in the control group. Higher aldosterone and potassium levels in preterm newborns as compared to term healthy newborns have been demonstrated (Nader and Procianoy, 1996; Semama et al, 2007; Mildenberger and Versmold, 2002).

There was a statistically significant difference in birth weight of neonates in the two groups. Low birth weight has been found in a neonate with severe hypermagnesemia (Hyun et al, 2011). But there was no correlation between the birthweight and the serum magnesium levels which implies that the low birth weight was more of a function of the disease than the effect of administered magnesium sulphate.

5. Conclusion

Maternally administered magnesium sulphate raises urea and creatinine levels to significant levels in mothers. Calcium levels are also raised while in mothers not receiving magnesium sulphate they were slightly lower. In neonates the urea and chloride levels are elevated to significant levels while the calcium and potassium levels are not significantly elevated. We suggest monitoring of both in the immediate post-partum period.

Conflict of Interest Declaration

The authors declare no conflict of interest.

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