

**SERUM MAGNESIUM LEVELS IN NEONATES BORN TO
MOTHERS WHO RECEIVED MAGNESIUM SULPHATE DURING
LABOUR
AT
KENYATTA NATIONAL HOSPITAL**

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A dissertation submitted in part fulfillment of the requirement for the award of the degree of Masters of Medicine in Paediatrics and Child Health of the University of Nairobi.

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DECLARATION

I declare that this dissertation in part fulfillment of my M.Med degree in Paediatrics and Child Health is my original work and has not been presented for a degree award in any other university.

Signed Wivie Date 18-11-2009

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LIST OF ABBREVIATIONS

1. Ca ²⁺	Calcium
2. C/S	Caesarean Section
2. G.B.D	Gestation By dates
3. Gms	Grammes
4. Hrs	Hours
5. IV	Intravenous
7. K.N.H	Kenyatta National Hospital
8. Mg ²⁺	Magnesium
9. MgSo ₄	Magnesium sulphate
10. Mmol/L	Millimoles Per Litre
11 .Na ⁺	Sodium
12. NBU	New born Unit
13. N.N.R	Neonatal reflexes
14. R.P.M	Revolutions per minute
15. S.H.O	Senior House Officers
16. S.V.D	Spontaneous Vertex Delivery
17. W.H.O	World Health Organizations
18. MIN	Minute

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DEDICATION

To my husband Evans, for his support and patience, and our lovely sons Ian and Mike.

To the children of this country who are so dear to me.

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OPERATIONAL DEFINITIONS

1. NEONATE - A baby in the first 28 days of postnatal life
2. PRETERM - A neonate delivered before 37 completed weeks of gestation.
3. LOW BIRTH WEIGHT - Neonates weighing less than 2500g at birth
4. HYPOMAGNESEMIA - Serum magnesium levels $<0.75\text{mmol/l}$
5. HYPERMAGNESEMIA - Serum magnesium levels $>1.04\text{ mmol/l}$
6. HYPOCALCEMIA - Serum calcium levels $<2\text{mmol/l}$
7. HYPERCALCEMIA - Serum calcium levels $>2.75\text{ mmol/l}$

ABSTRACT

Background: Magnesium sulphate administered to the mother parenterally is transported actively through the placenta to achieve equilibrium in fetal serum. It takes about 2 hrs for the maternal and fetal plasma levels to reach equilibrium. Neonatal serum magnesium concentration remains elevated for the first 72 hrs of life. Neonates whose mothers receive magnesium sulphate during labour have been found to have high serum magnesium levels, a lower Apgar score and respiratory depression.

Objectives: To determine the serum magnesium levels in neonates born of mothers who received Magnesium sulphate at K.N.H during labour, to document the clinical effects, if any, in the neonates and to relate the levels of serum magnesium to the observed clinical signs in the neonates.

Methodology: This was a quasi-experimental study, conducted at Kenyatta National Hospital New Born Unit and Post natal wards.

The study subjects were 49 neonates, matched for gestational age with 49 controls.

Neonates born of mothers with severe pre-eclampsia/Eclampsia who received magnesium sulphate during labour were recruited as exposed study subjects. The controls were neonates of mothers who had mild pre-eclampsia and so did not receive magnesium sulphate. Sampling of consecutive neonates was done until the required sample size was attained. Serum magnesium and calcium were measured on a semi-automated analyzer (Humalyzer) using commercial reagents.

Data Analysis: A standard data collection form was used to collect all the data which was analyzed using the SPSS version 12. Independent sample t-test was used to determine whether the mean serum magnesium differed significantly in the magnesium exposed and non-exposed neonates. P values below 0.05 were considered significant.

Results

There were 49 neonates in each arm of the study. The two groups were comparable in terms of birth weight and gestational age. Neonates whose mothers received magnesium sulphate were found to have higher serum magnesium levels than those whose mothers did not, with mean serum magnesium levels of 2.22mmol/l and 1.22mmol/l respectively, $p < 0.001$. All the 49 (100%) study subjects had magnesium levels > 1.04 mmol/l compared to 22 (44.9%) controls. The study subjects were also more likely to have depressed neonatal reflexes than the controls but the difference was not statistically significant, $P = 0.297$.

The study subjects were found to have a lower Apgar score at both one and five minutes when compared with the controls. The mean score at 1 minute was 6.8 and 7.5 for study subjects and controls respectively ($p = 0.019$) while at 5 minutes it was 8.1 and 8.9, respectively. $p = 0.010$.

Conclusions

Neonates whose mothers received magnesium sulphate had higher than normal serum magnesium levels and were also found to have lower Apgar scores than the controls.

Recommendations

Close monitoring of neonates whose mothers receive magnesium sulphate during labour is recommended. Further research that will follow up the neonates for a longer period to establish the pattern of morbidity and mortality and determine whether it is associated with the serum magnesium levels in the neonates is recommended.

INTRODUCTION AND LITERATURE REVIEW

Pre-eclampsia is a multisystem disorder of pregnancy usually associated with raised blood pressure, proteinuria and reduced organ perfusion secondary to vasospasm and endothelial activation. It complicates 2–8% of pregnancies^{1, 2}. Although the outcome is often good, pre-eclampsia is a major cause of morbidity and mortality for mothers and their babies^{3, 4}. It accounts for 10% of maternal deaths, and is also associated with increased perinatal mortality^{5, 6}. Eclampsia is the occurrence of seizures superimposed on pre-eclampsia that cannot be attributed to other causes. The seizures are grand mal and may appear before, during, or after labour⁷. It affects 1 in 100 to 1 in 2000 deliveries and is associated with a considerable increase in morbidity and mortality⁸.

The rate of pre-eclampsia is higher in developing countries, with the highest rate reported from Zimbabwe at 7.1% of all the deliveries⁹. Similarly the rate of eclampsia is higher in developing countries with the highest rate reported from Colombia at 8.1 / 1000 deliveries and the lowest in United Kingdom at 4.9 / 10000 deliveries¹⁰. In Kenya the rate of pre-eclampsia has been reported to be 5.3% of all the deliveries and eclampsia at 6 / 1000 deliveries¹¹.

In a cross-sectional study done by Sanchez -Carrillo C. et al in Mexico, to determine the association between preeclampsia/eclampsia and adverse perinatal outcomes, the neonates were found to have a low birth weight, intrauterine growth retardation and a higher risk of perinatal death than matched controls. Lower Apgar scores were also more noticeable in the study subjects. He, therefore, concluded that pre-eclampsia, even without administration of magnesium sulphate, is associated with adverse perinatal outcomes¹².

In a case control study done by Suka et al in Japan to elucidate maternal characteristics and pregnancy complications associated with low APGAR score, a case-control study of low APGAR score was conducted matching both gestational age and route of delivery, in

full-term deliveries at a Japanese hospital with 102 cases and 204 controls. Occurrence of preeclampsia was more frequently observed in the low Apgar score cases¹³.

In a study by Harbans Lal, to estimate plasma and erythrocyte magnesium levels in preeclampsia and eclampsia, the mean plasma as well as erythrocyte magnesium concentrations were found to be significantly lowered than the controls¹⁴. A similar study assessing magnesium and calcium in the plasma and cerebrospinal fluid of Nigerian women with pre-eclampsia /eclampsia, eleven patients and twenty three controls were recruited. The extra cellular calcium and magnesium were reduced in patients with pre-eclampsia and eclampsia when compared with controls¹⁵.

At K.N.H in 1982, perinatal mortality rate of babies born to pre-eclamptic mothers was found to be 245/1000 and even higher rate in eclamptics at 379/1000 which was two and half times the general K.N.H perinatal mortality-97/1000¹⁶.

Magnesium sulphate is currently the drug of choice for both the prevention and treatment of eclampsia¹⁷. The Magpie trial (The Magnesium sulphate for trial prevention of eclampsia), which was a multicentre trial, carried out in 175 hospitals in 33 countries compared magnesium sulphate with placebo for women with pre-eclampsia.

A total of 10,141 women were recruited, 8804 before delivery. Overall, 9024 children were included in the analysis of outcome at discharge from hospital. Women given magnesium sulphate had 58% lower risk of eclampsia and also had lower maternal mortality (RR 0.55, 0.26-1.14) than those given placebo. There did not appear to be substantive harmful effects for the mother or baby, in the short term. There was no clinically important effect on the risk of the baby dying before discharge or being in a special care nursery for more than 7 days (RR 1.02, 95% CI 0.95 to 1.09). 576 babies (12.7%) died in the study group compared to 558 (12.4%) in the placebo.¹⁸

The effect on baby death was consistent regardless of severity of pre-eclampsia or gestational age at trial entry. The only exception was the small subgroup of women who had received an anticonvulsant before trial entry, where there appeared to be an increase

in the risk of the baby death (relative risk 1.49 ,95 % CI 1.11-2.00).Baby mortality was particularly high for women with eclampsia (six of 40, 15 % vs 12 of 96, 12%).¹⁸

The recommended dose of magnesium sulphate for severe pre-eclampsia and eclampsia is 4-6 g I.V loading dose over 15-20 min, then 2g/hour as a continuous infusion that is discontinued 24 hours after delivery .Electrolyte concentrations do not differ appreciably in women with pre-eclampsia compared with those of normal pregnancy unless there has been vigorous diuretic therapy, sodium restriction, or administration of water with sufficient oxytocin to produce antidiuresis¹⁹ .

Magnesium sulphate administered to the mother parenterally is transported actively through the placenta to achieve equilibrium in fetal serum ¹⁹. Serum calcium concentration has been found to be higher and parathyroid hormone lower in hypermagnesemic study infants when compared to control infants. It has been speculated that elevated serum magnesium levels in these infants result in a shift of calcium from bone to plasma, and that elevated serum magnesium and calcium concentrations further suppress neonatal parathyroid²⁰. Unlike neonatal hypomagnesaemia, hypermagnesemia is a less well known entity, affecting mainly infants born of mothers treated with i.v magnesium sulphate for pre-eclampsia.^{21,22}

Maternal magnesium sulphate treatment causes an early neonatal hypermagnesemia that is associated with a prolonged blunted production of parathyroid hormone among the exposed infants .Thus careful monitoring of the electrolyte status in the magnesium sulphate exposed infant is warranted ²³.

In neonates, the commonest cause of hypermagnesemia is intravenous magnesium sulphate administered to mothers ²⁴. The longer the period of magnesium administration before delivery, the more the manifestations of excess magnesium will appear in the neonate ^{24, 25}. Neonates born of mothers treated for eclampsia with magnesium sulphate have been reported to have serum magnesium concentrations between 1.5-5.5 mmol/l ²⁶. The normal reported value of serum magnesium in neonates on day one of life is 0.75-

1.04 mmol/l²⁷. The prevalence of hypermagnesemia in studies done on samples selected randomly from those submitted to the clinical chemistry laboratory in hospitalized patients ranges between 5.7-9.3%^{28, 29}.

If continuous intravenous infusion of magnesium sulphate is used and especially if given for more than 24 hours, one can anticipate a newborn manifesting all the signs of hypermagnesemia. It takes about 2 hours for the maternal and fetal plasma levels of magnesium sulphate to equalize³⁰. In contrast to the adult, the newborn does not excrete a magnesium load satisfactorily and plasma concentration remains elevated for the first 72 hours of life as the renal elimination is slower in immature kidneys.³⁰

Neonates born of mothers who received magnesium sulphate during labour may present with respiratory depression, generalized hypotonia, gastrointestinal hypomotility mimicking intestinal obstruction, long bone demineralization and congenital rickets^{31, 32}. Magnesium toxicity has been shown to relate to the serum magnesium levels. Reportedly, symptoms of hypermagnesemia manifest at serum magnesium levels above 2mmol/l. At high magnesium levels, the central nervous system is depressed and the infants have profound respiratory depression which requires mechanical ventilation³³. Serious symptoms rarely occur at levels below 2.1mmol/l. Hypermagnesemia is associated with higher mortality and increased length of stay in ICU.^{34, 35}

Gul A, et al³⁶ compared perinatal outcomes in pregnancies complicated by severe pre-eclampsia and eclampsia, with and without complications. Clinical and laboratory findings and neonatal outcomes of all pregnancies with severe pre-eclampsia and eclampsia with and without complications were prospectively recorded. Analysis was performed according to gestational age before and after 32nd gestational week. The difference of perinatal mortality between the two groups was not significant ($p = 0.644$ and $p = 0.250$), suggesting borderline difference³⁶.

A study done to compare total magnesium levels in extremely preterm infants(32weeks of gestation) with neonates >35 weeks of gestation reported that extremely preterm infants even without additional exposure to magnesium are at risk for elevation of ionized magnesium which should be considered during management of these infants. Total magnesium was also found to be significantly higher.^{37.}

Magnesium is the second most abundant intracellular cation and the fourth most abundant cation in the body. Almost all enzymatic processes using adenosine triphosphate (ATP) as an energy source require magnesium for activation.^{38.} Magnesium is a cofactor for more than 325 cellular enzymes involved in cellular energy production and storage, protein synthesis, Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) synthesis, cell growth and reproduction, adenylate cyclase synthesis, maintenance of cellular electrolyte composition and stabilization of mitochondrial membranes^{38.}

Because magnesium is bound to adenosine triphosphate inside the cell, shifts in intracellular magnesium concentration may help to regulate cellular bioenergetics. As a consequence of these biochemical activities, magnesium plays a pivotal role in control of neuronal activity, cardiac excitability, neuromuscular transmission, muscular contraction, and vasomotor tone^{39.} High magnesium concentration competitively inhibits several calcium-dependent reactions, resulting in muscle paralysis and dilatation of resistance vessels. Approximately 70% to 80% of plasma magnesium is ionized and diffusible, while the remainder is bound to protein^{40.}

Magnesium homeostasis differs in the neonate compared with the adult. Magnesium reabsorption occurs predominantly in the proximal tubule rather than the loop of Henle in neonates, possibly due to immaturity of the paracellular pathways^{41, 42.}

Pathophysiologically, excess magnesium causes blockade of neuromuscular transmission and depresses the conduction systems of the heart and sympathetic ganglia. Excess magnesium also prevents the release of presynaptic acetylcholine from both sympathetic and neuromuscular junction^{42.}

In a study done to determine the effect of magnesium sulphate therapy on ionized magnesium in cord blood of pregnancies complicated by pre-eclampsia, total magnesium and ionized magnesium were significantly elevated in cord samples of the treated group and the conclusion was that fetal ionized magnesium levels parallel maternal levels during magnesium sulfate therapy for pre-eclampsia⁴³.

Matsuda et al, did a study in 1997 which looked at the effects of magnesium sulphate administered to the mother on neonatal bone abnormalities, Chest x-ray films were obtained within 48hrs after birth .The total number of neonates with bone abnormalities among the off springs of women receiving magnesium sulphate totaled 13 (11.4%). In the control group, bone abnormalities were not observed. Cases showing low Apgar scores and high magnesium levels were more noticeable in the study group. The gestational ages and the total doses of magnesium sulphate in pregnant women were the main factors related to the onset of neonatal bone abnormalities. The cases with onset of bone abnormalities seemed to be associated with symptoms attributable to hypermagnesemia which affects parathyroid hormone and calcium levels leading to hypocalcaemia⁴⁴.

In another study done by Robert Mittendorf et al to determine whether higher magnesium levels in umbilical cord blood at delivery are associated with increased total pediatric (fetal + neonatal + post neonatal) mortality, there were findings of a dose relationship between serum ionized magnesium and deaths in children.

Ionized magnesium levels were available for 82 children. Seven deaths occurred (one immediately before delivery, three as neonates, and three in the post neonatal period).

The median level of ionized magnesium among the seven dead children was 0.76 mmol/L and among the 75 survivors, the median level of ionized magnesium was 0.55 mmol/L⁴⁵.

Mittendorf et al, in a study conducted at the University of Chicago in 1997, found an increased *number of neonatal deaths among babies of women who took magnesium sulphate* in comparison with those who took an alternative drug. The neonatal death rate was higher *among babies of women who received magnesium sulphate. (8 deaths out of*

75 pregnancies) than the control group (1 death out of 75 pregnancies). The dose was 4g loading and 2-3gms/hr. The difference was statistically significant ⁴⁶.

A study looking at lipoprotein metabolism alterations in magnesium-exposed 7 singleton term neonates of women with pre-eclampsia treated with magnesium sulphate was done. Controls were 26 term neonates of uncomplicated pregnancies. The lipoprotein profile was more atherogenic in magnesium-exposed neonates and this may be a potential risk factor of cardiovascular heart disease ⁴⁷.

Magnet (Magnesium and Neurological Endpoints Trial) was a randomized trial to see whether antenatal magnesium decreased the frequency of cerebral palsy among preterm infants. Enrollment was suspended when interim safety data showed that nine pediatric deaths were linked to magnesium exposure. Intraventricular hemorrhage was significantly associated with increased maternal magnesium serum levels among 90 mother-baby pairs. The mothers of 12 neonates who developed intraventricular hemorrhage had a mean serum level of magnesium of 0.75 mmol/ L, compared with 0.56 mmol/L in the mothers of unaffected infants ⁴⁸.

A study done by Riaz M et al, to evaluate the effects of maternal magnesium sulphate treatment on newborn outcome concluded that the 26 infants born of mothers treated with magnesium sulphate were more likely to be hypotonic and have lower Apgar than the 26 control infants ⁴⁹.

In a study done by Rasch et al, looking at the effects on the newborn infant of maternal magnesium sulphate therapy for treatment of pre-eclampsia, impairment of neuromuscular transmission, as well as neurobehavioral differences when compared to controls, were found in neonates whose mothers had received magnesium sulphate ⁵⁰.

STUDY JUSTIFICATION

Previously conducted studies have shown that magnesium sulphate crosses the placenta to achieve equilibrium in the fetus and the mother. Neonates have been reported to develop hypermagnesemia following maternal administration of magnesium sulphate. Symptoms of hypermagnesemia manifest at serum magnesium levels above 2 mmol/l. The neonates present with respiratory depression, generalized hypotonia and low Apgar scores. High levels of magnesium in the neonates are associated with increasing morbidity and mortality.

Magnesium sulphate is routinely administered to mothers with severe pre-eclampsia and eclampsia at K.N.H to control /prevent convulsions.

No studies have been conducted at K.N.H to determine the levels of serum magnesium in the neonates. There is need to investigate whether the doses of magnesium sulphate routinely given to mothers reaches levels associated with harmful effects in the neonates. The current study was conducted to determine the levels of serum magnesium and the effects, if any, in the neonates born of these mothers.

PRIMARY OBJECTIVE

To determine the serum magnesium levels in neonates born of mothers who received magnesium sulphate during labour and compare the levels with neonates born of mothers who did not receive magnesium sulphate.

SECONDARY OBJECTIVES

1. To document the clinical abnormalities, if any, in the neonates
2. To relate the levels of magnesium to the observed clinical signs in the neonates

METHODOLOGY

Study area

The study was conducted in the new born unit and postnatal wards of Kenyatta National Hospital (K.N.H). The N.B.U offers level one, two and level three care to neonates. With a monthly admission of about 160 babies, K.N.H serves as the national referral and teaching hospital for the University of Nairobi. Neonates admitted are categorized and nursed according to their weights, with neonates of the same weight category being nursed together in the same nursery. Clinical care is provided by neonatologists, pediatricians, senior house officers and nurses.

Study population

Study subjects were defined as neonates born during the study period whose mothers had *severe pre-eclampsia / eclampsia* who received magnesium sulphate during labour. The *international standard is to give magnesium sulphate to all the mothers with severe pre-eclampsia / eclampsia* to treat and control convulsions

Controls were neonates born of mothers who had mild pre-eclampsia and so did not qualify to receive magnesium sulphate during labour.

Study design

This was a hospital based quasi-experimental study

Study period

The study was carried out between July and Dec 2008.

Inclusion criteria

- Neonates born within K.N.H
- Mother had severe pre-eclampsia / eclampsia
- Mother receiving magnesium sulphate during labour
- Consent given for the study by the parents/guardian

Exclusion criteria

- Neonates born before arrival or transfer in from other hospitals
- Neonates with significant congenital anomalies
- Parent/guardian not giving consent

Sampling Method

The principal investigator visited the new born unit and postnatal wards on weekdays between 8am and 8pm, checked the admission record in labour ward and recorded the names of the mothers admitted with either eclampsia or pre-eclampsia who were then traced to the respective postnatal wards. From the records, the neonates were traced to N.B.U or the postnatal wards. In the postnatal wards the investigator perused the mothers' files and the diagnosis of either eclampsia or pre-eclampsia made by the attending obstetrician was recorded on the data collection sheet.

Consecutive neonates born of mothers with severe pre-eclampsia/eclampsia who fulfilled the inclusion criteria were identified and recruited into the study until the desired sample size was achieved. For each neonate recruited for the study, there was a control matched for gestational age born of mothers with mild pre-eclampsia who did not receive magnesium sulphate during labour. Once a neonate who fulfilled the study inclusion criteria was identified, the parent/guardian was sought and an informed written consent obtained. Neonates who exhibited any of the factors on the exclusion criteria were excluded.

Neonates recruited into the study were examined daily for motor depression and respiratory depression for the first 72 hours of life.

Their birth weights were taken at admission using a top bar spring scale model ATZ that weighs to an accuracy of 50 grammes. The babies were assessed at birth by the senior house officers, mid wives or the principal investigator for Apgar score.

Neonatal gestational age was assessed using the modified Dubowitz scoring system by the principal investigator. The mode of delivery and the neonates' postnatal age were recorded in the data collection sheet and blood drawn for serum magnesium levels within the first 24 hours of life.

The total amount (dosage) of magnesium sulphate given to the mother was also recorded.

Sample size determination

Sample size was calculated using the formula for estimating the difference between two proportions in a quasi-experimental study

$$n = \frac{3.2}{d^2} [P_1(1 - P_1) + P_2(1 - P_2)]$$

Where;

n = Total required sample size;

P_1 is the proportion in one population and P_2 is the proportion in another.

$d = P_1 - P_2$, then samples would be taken in each population and the estimated difference is $\hat{d} = \hat{P}_1 - \hat{P}_2$.

Substituting the above values in the formulae above gave;

$$n = 71.18$$

$$n = 72$$

LABORATORY METHODS

Specimen collection and handling

Venous blood samples were drawn from the antecubital vein within the first 24 hours of life by the principal investigator. Once the vein was identified, the skin was cleaned with a spirit swab, then venepuncture done with a butterfly needle. Two milliliters of blood were drawn into a 5mls syringe and then transferred into a plain tube. Pressure was applied to the venepuncture site after withdrawing the needle until bleeding stopped. The sample was then labeled with a study number, put in a plain safe bag and taken immediately to the University of Nairobi clinical chemistry laboratory, where it was allowed to clot and then centrifuged at 3,000 revolutions per minute for ten minutes.

Serum magnesium and calcium levels were assayed using reagents from Chemlab.

Both serum magnesium and calcium levels were assayed using the photometric method. Half a milliliter of the reagent was put in a vial and 10 microlitres of the serum added and a control was also set. Both vials were incubated for 10 minutes at room temp (20-25 °C). The principle is that magnesium ions in alkaline medium form a coloured complex with xylidyl blue at wave length of 520nm. The absorbance is proportional to the magnesium concentration in the sample. Glycol ethylenetetracetic acid (GEDTA) is used as a chelating agent for calcium ions.

Calcium was assayed using the principle that calcium ions react with o-cresolphthalein complexone in an alkaline medium to form a purple coloured complex at wave length 570nm. The absorbance of this complex is proportional to the calcium concentration in the sample.

QUALITY ASSURANCE

All aspects of quality assurance were adhered to. *Standard operating procedures* were applied from specimen collection, handling and laboratory analysis. For every procedure set, internal quality control was set with either humatrol p or humatrol n. External quality assurance reagents from South Africa, National hospital laboratory services are usually run every month in the clinical chemistry laboratory, University of Nairobi .Study samples were only run if the controls were within acceptable limits.

DATA MANAGEMENT

Data collection

A standard data collection form was used to collect all the data generated in the study. See attached form -Appendix III.

Data analysis

Data was entered, verified and analyzed using the Stastical Package for Social Sciences (SPSS) version 12 .Independent sample t-test was used to determine whether the serum magnesium levels differed significantly in the magnesium exposed and the non-exposed neonates. P value below 0.05 was considered significant .The results were presented in graphs and tables.

ETHICAL CONSIDERATION

- The research proposal for this study was presented to the K.N.H. Ethics and research committee for review and approval prior to starting the study.
- The nature of the study was explained to the parents or guardians before recruitment
- A written consent was obtained from parents/guardians.
- Confidentiality of information obtained was maintained at all times.
- The results were availed to the clinicians managing the neonates
- The study had no adverse effects on the study subjects.

RESULTS

Baseline characteristics of the study population

Over a period of six months, a total of 98 neonates were recruited, 49 magnesium sulphate exposed and 49 controls. The study subjects were made up of, 23 males and 26 females while the controls consisted of 18 males and 31 Females. Gestational age ranged from 28 to 40 weeks with a median of 35.0 weeks in both study subjects and controls. Median birth weight in the study subjects and controls was 2284.7 grams and 2216.3 grams respectively. No significant difference was found between the mode of delivery and the gestational ages of the two populations with $p = 0.647, 0.078$ respectively (Table 1).

Table 1: Baseline characteristics of the study population (n=98)

Factor	Study Subjects, n = 49	Controls, n = 49	OR (95% CI)	p-value
Sex				
• Male ¹	23 (56.1)	18 (36.7)	1.5 (0.6-3.7)	0.306
• Female	26 (45.6)	31 (63.3)		
Mode of Delivery				
• SVD	12 (46.2)	14 (53.8)	0.8(0.3-2.2)	0.647
• C/S	37 (51.4)	35 (48.6)		
Gestational age				
Mean	34	34		
Median	35.0	35.0		
Range	28-40wks	28-40wks		

Birth weight distribution of the study population

The mean birth weight of the study subjects was 2,284.7 grams and for the controls was 2,216.3 grams. 57 % of the study population had low birth weight (<2500gms), with the controls contributing more (54.4%) to the low birth weight population, compared to 45.6 % contributed by the study subjects. (Fig 1).

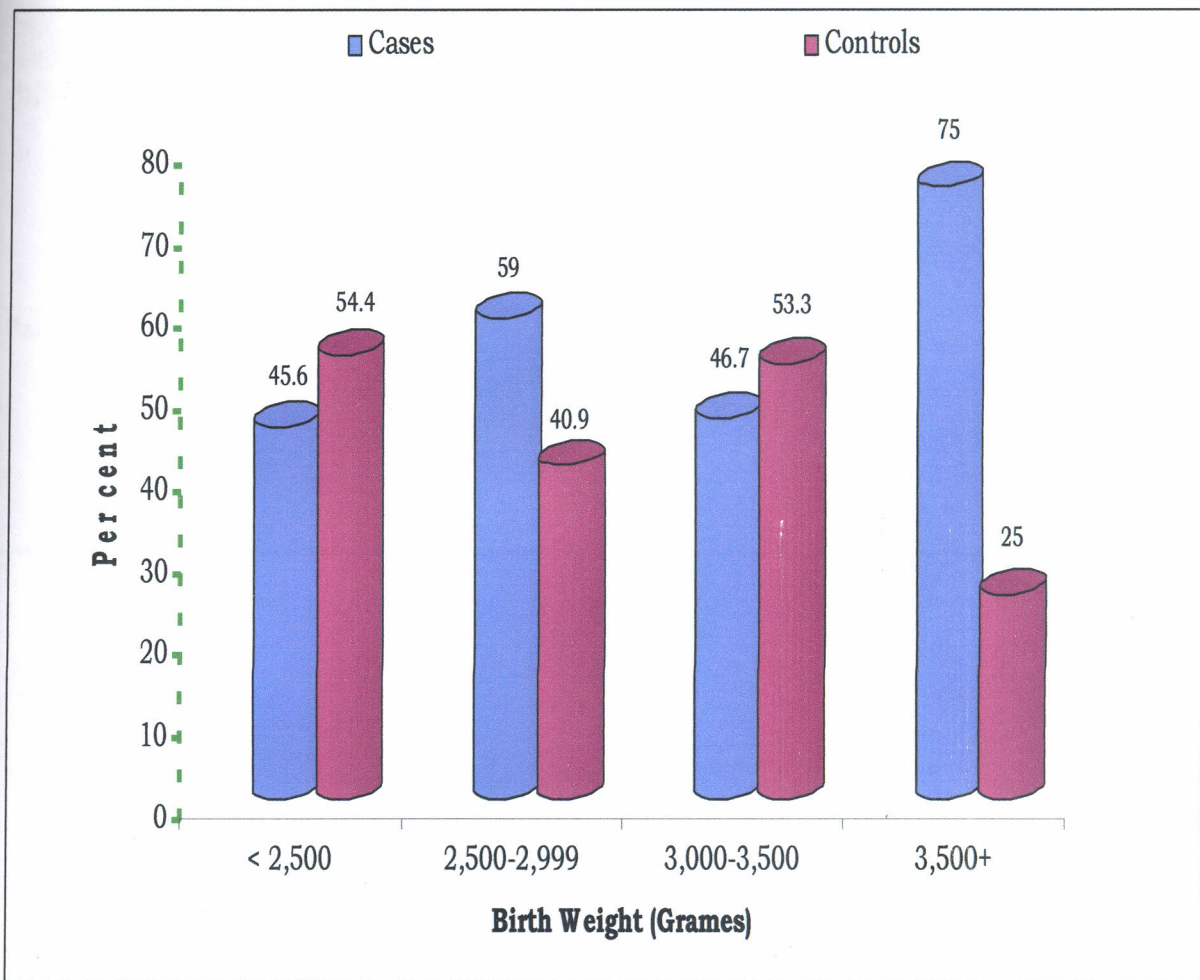


Figure 1: Birth weight distribution of the study population (n=98)

Baseline Characteristics of the Mothers

The mothers of the study subjects were relatively younger than the controls, the median age being 25 and 27 yrs respectively (Table 2).

Table 2. Baseline Characteristics of the Mothers (n=98)

Factor	Mothers of Study subjects, n = 49	Mothers of Controls, n = 49
Age (in years)	Study subjects	Controls
• Mean	24.9	28.3
• Median	25.0	27.0
• Range	15-39	17-42
Parity		
• Mean	1.0	1.0
• Median	1	1
• Range	0-5	0-6

The Distribution of Electrolytes in the neonates

The study subjects were found to have higher serum magnesium levels than the controls with means of 2.22mmol/l and 1.22mmol/l respectively $p < 0.001$, with a range of 1.1mmol/l - 4.0 mmol/l in the study subjects and 0.55 mmol/l - 2.9 mmol/l in the controls.

Serum calcium levels were not significantly different in the two groups, with a mean of 2.17 mmol/l in study subjects and 2.32mmol/l in the controls, $p = 0.116$. (Fig. 3).

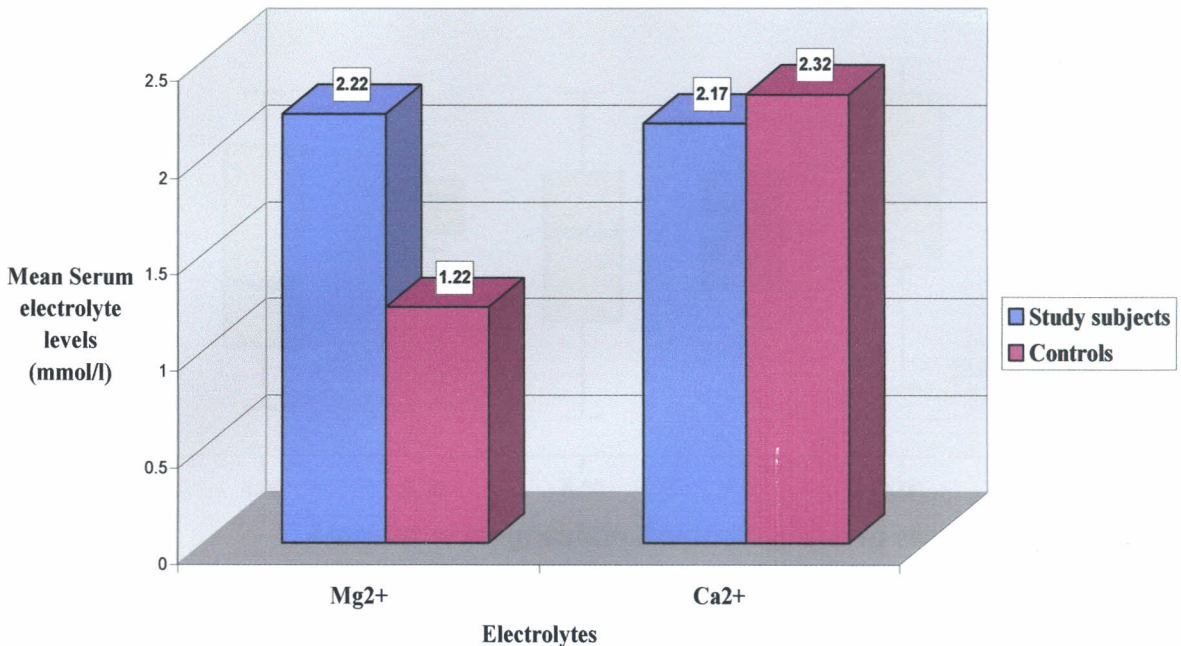


Figure 2: Distribution of Electrolytes in the Neonates

The Correlation between the amounts of magnesium sulphate received by the mothers and serum magnesium levels in the neonates

Neonates born of mothers who had received high levels of magnesium had high serum magnesium levels. However, the difference was not statistically significant, $p=0.285$ (Fig. 2).

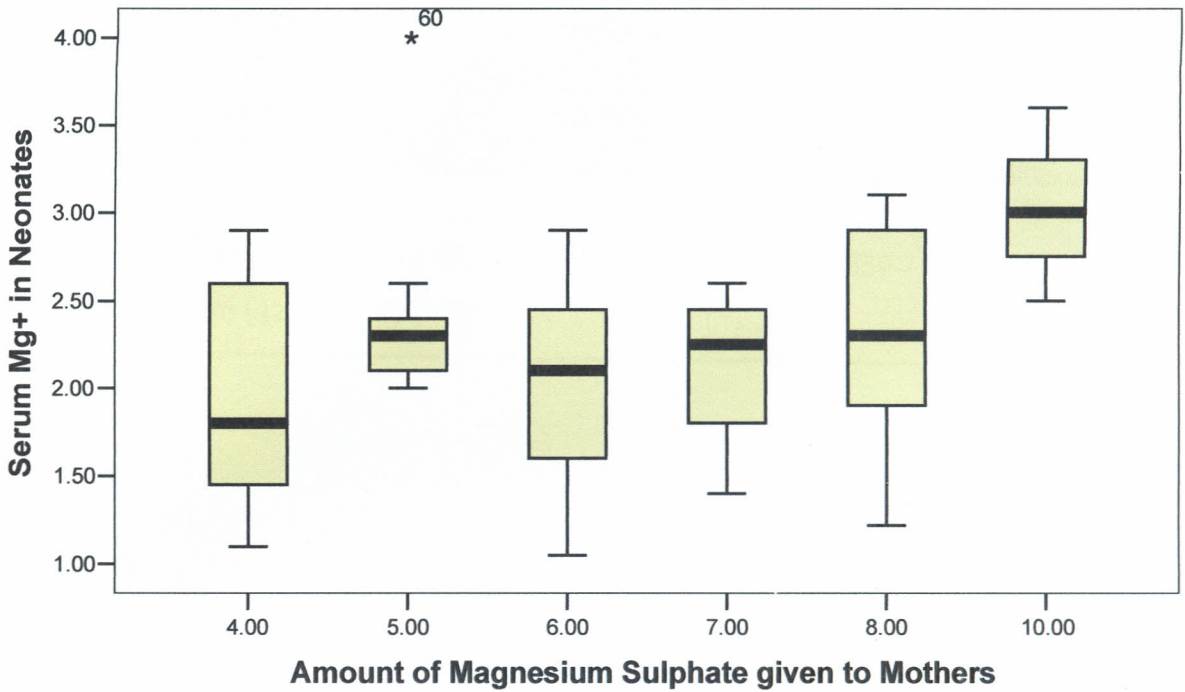


Figure 3: The relationship between the amounts of magnesium sulphate received by the mothers and serum magnesium levels in the neonates

The study population serum magnesium levels

In the Study population it was noted that, 33 (67.4%) of the study subjects had serum magnesium levels more than 2mmol/l as compared to 2 (4%) of the controls. This was stastically significant with $p < 0.001$. (Table 3).

Table 3: The Percentages of the study population with serum magnesium levels above and below 2 mmol/l.

	Study subjects, n = 49	Controls, n = 49	OR (95% CI)	p-value
Serum mg				
• > 2	33 (67.4)	2 (4.0)	48.5(9.6-330.2)	<0.001
• ≤ 2	16 (32.6)	47 (96)		

Apgar Scores of the Study population

The study subjects were found to have significantly lower Apgar scores at both one minute and five minutes when compared with the controls. The mean score at 1 minute was 6.8 and 7.5 for controls and study subjects respectively ($p=0.019$) while at 5 minutes it was 8.1 and 8.9, respectively, $p=0.010$ (Fig. 4).

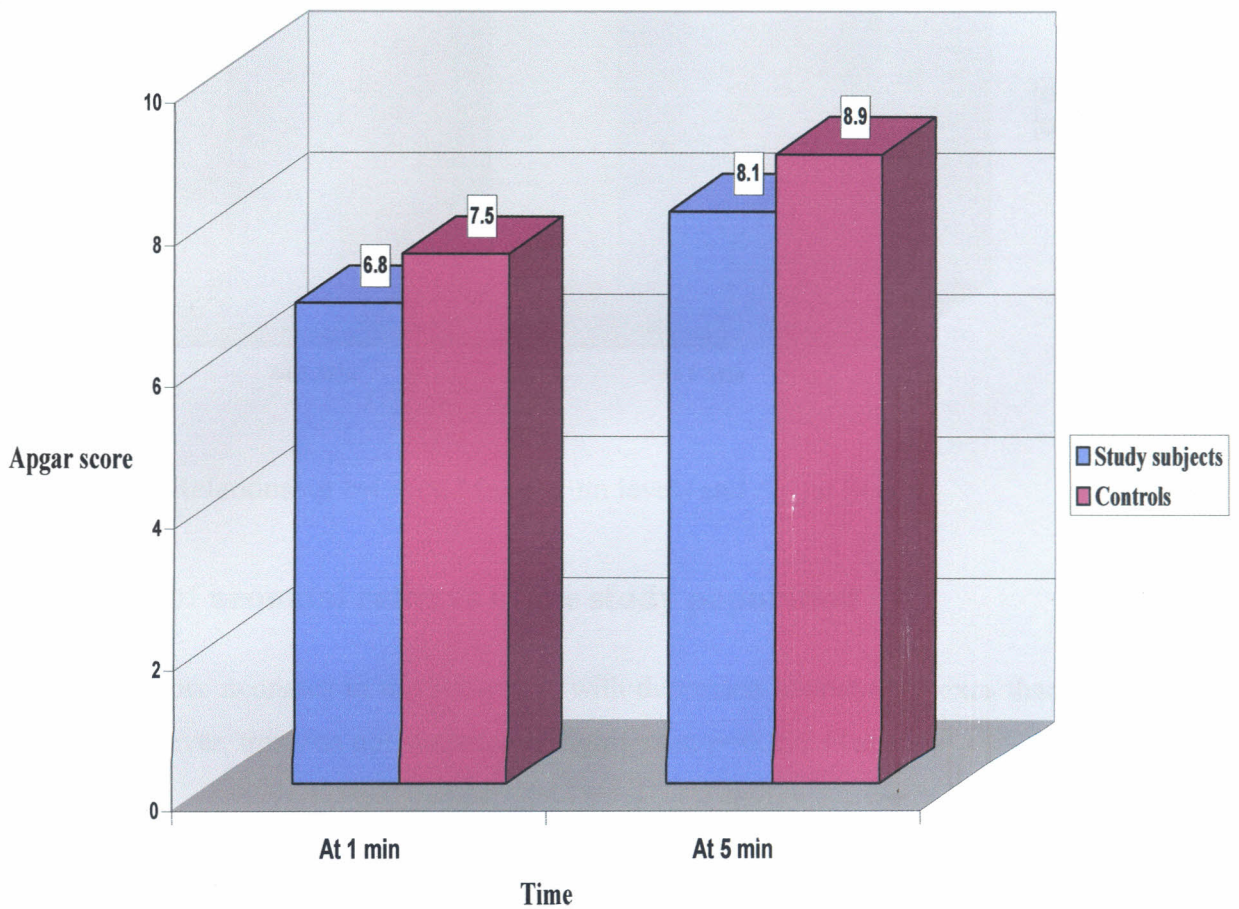


Figure 4: Mean Apgar Scores of the Study Population

The Relationship between Serum Magnesium levels and Apgar score

High magnesium levels were associated with significantly lower Apgar scores at both one and five minutes with $p=0.001$ and $p=0.002$ respectively (Fig 5).

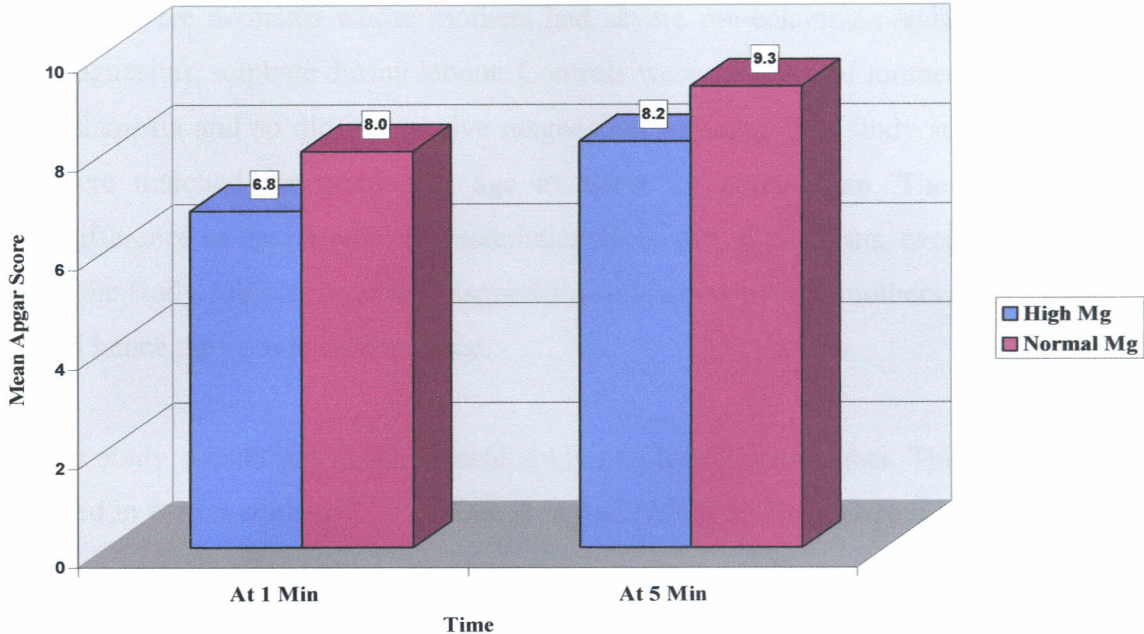


Figure 5: The Relationship between Magnesium levels and Apgar Scores

The Status of neonatal reflexes in the study population

There were more neonates in the study arm with depressed neonatal reflexes than in the controls. However, this was not statistically significant, $p=0.297$ (Table 4).

Table 4: Status of neonatal reflexes in the study population

NRR	Study subjects, n = 49	Controls, n = 49	OR (95% CI)	p-value
Status				
• Depressed	21 (56.8)	16 (42.2)	1.6(0.6-3.8)	0.297
• Normal	28 (45.9)	33 (54.1)		

DISCUSSION

This was a hospital based quasi experimental study which compared serum magnesium levels in neonates born of mothers who received magnesium sulphate during labour and neonates born of mothers who did not receive magnesium sulphate during labour. The study subjects were neonates whose mothers had severe pre-eclampsia /eclampsia and received magnesium sulphate during labour. Controls were neonates of mothers who had mild pre-eclampsia and so did not receive magnesium sulphate .The study subjects and controls were matched for gestational age to allow for comparison. There was no statistical difference in the baseline characteristics of the two populations, except that the mothers of the study subjects received magnesium sulphate while the mothers of controls did not, and hence they could be compared.

Most of the study population in the present study had low birth weights. This was also demonstrated in earlier studies^{14, 15, 51}. More than half (57%) of the total study population had low birth weights (less than 2500 gms), with the study subjects contributing 45.6% and 54.4 % contributed by the controls. This could probably be explained by the fact that, both the study subjects and the controls had been exposed to intrauterine hypoxia and therefore intrauterine growth retardation. This is comparable to the Magpie trial in which more than 53% of their babies had birth weight of less than 2500gms¹⁸.

The current study found serum magnesium levels in the magnesium exposed neonates to be significantly higher than in the non-exposed ones, with mean serum magnesium levels of 2.22 mmol/l and 1.22 mmol/l respectively ($P < 0.001$). All 49 study subjects were found to have serum magnesium levels above 1.04 mmol which is the upper normal limit in neonates. These findings are similar to other studies done previously which have found babies born to mothers with pre-eclampsia and eclampsia who receive magnesium sulphate to have higher serum magnesium levels than the controls^{45, 47, 49, 50}.

The high serum magnesium levels in the study subjects are unlikely to have been due to the severe pre-eclampsia /eclampsia in the mothers as previous studies done reported serum magnesium levels to be lower in women with pre-eclampsia /eclampsia than in controls.¹²⁻¹⁵. A study done by Harbans Lal et al in India reported that mean plasma magnesium concentrations were significantly lower in women with preeclampsia and eclampsia than the controls¹⁴. Similarly, a study done by Idogun E et al in Nigeria also found reduction in extracellular magnesium in patients with preeclampsia and eclampsia¹⁵.

In the current study, the serum magnesium levels of magnesium-exposed neonates were found to be 1.8 times higher than those of the controls. This compares well with a study done by Yavuz et al which reported magnesium levels of magnesium-exposed neonates to be 1.6 times higher than those of the controls⁴⁷. Both studies used photometric colour method in analysis of total serum magnesium concentrations, and hence were comparable. However, the studies differed in that, the current study used neonates of mothers with mild pre-eclampsia as controls while the Yavuz study used neonates of mothers with uncomplicated pregnancies as controls. The similar results despite the use of different controls suggests that magnesium levels in neonates born of mothers with mild pre-eclampsia and those with uncomplicated pregnancies are comparable.

Previous studies have shown symptoms of hypermagnesemia to manifest at serum magnesium levels above 2 mmol/l^{34, 35}. Our study results show that the study subjects had a higher percentage (94.3%) of neonates with serum magnesium levels above 2mmol/l compared to the controls who had 5.7%. It has been shown that, serious symptoms rarely occur at levels below 2.1mmol/l. Hypermagnesemia is associated with higher mortality and increased length of stay in ICU^{34, 35}. This suggests that the neonates with serum magnesium levels above 2.1 mmol/l should be monitored carefully by pediatricians to avoid or treat any clinical manifestations of hypermagnesemia.

In the current study, neonates born of mothers who had received higher amounts of magnesium sulphate had higher serum magnesium levels. The amount of magnesium sulphate given to the mothers before delivery ranged between 4 and 10 grammes. This difference was due to the fact that magnesium sulphate was started at the time the mothers presented, with some of them presenting in second stage of labour and therefore ending up receiving only the loading dose before delivery.

There were more neonates in the study arm with depressed neonatal reflexes than controls. The depressed neonatal reflexes in the study arm were probably due to the elevated serum magnesium levels, since it has been reported that, at high magnesium levels, the central nervous system is depressed and the infants have respiratory depression though the maternal severe pre-eclampsia/eclampsia could have also contributed^{31, 32, 33}.

A study done by Rasch et al, looked at the effects on the newborn infant of maternal magnesium therapy for treatment of pre-eclampsia. Cases were 36 hypermagnesemic infants born to pre-eclamptic mothers treated with magnesium sulphate. Controls were 18 neonates born to untreated pre-eclamptic mothers and 25 infants born to normal mothers. Impairment of neuromuscular transmission, as well as neurobehavioral differences when compared to controls, was found in hypermagnesemic infants⁵⁰.

In the current study, the cases were found to have statistically significant lower Apgar scores than the controls at both one minute and five minutes. This is similar to the findings in a prospective controlled study done at Albert Einstein medical centre in Philadelphia by Riaz M et al to evaluate the effects of maternal magnesium sulphate treatment on newborn outcomes⁴⁹. His study subjects were newborn infants delivered at ≥ 34 weeks of gestation whose mothers received a minimum of 12 hours of intravenous magnesium sulphate therapy before delivery. Control infants were the next born infants of similar gestational age. Outcome recorded at delivery included Apgar scores. Infants of mothers treated with magnesium sulphate were found to have lower Apgar scores at birth. The Riaz study just like our study matched the study subjects for gestational age and also had equal numbers of study subjects and controls.

Similarly, another study done in Japan which looked at the effects of magnesium sulphate administered to the mother on neonatal bone abnormalities, the cases were found to have low Apgar scores and high magnesium levels than the controls.⁴⁴ In this study, like the present study, the neonates were matched for gestational age and followed up prospectively.

The lower Apgar scores were probably due to the effect of the magnesium sulphate in the study subjects since magnesium has been associated with respiratory depression and hypotonia. The effects of the severe pre-eclampsia /eclampsia on the Apgar scores could not be ruled out since their mothers had severe disease than the controls though this is unlikely because the controls also had pre-eclampsia and so it is assumed that they also had intrauterine hypoxia and intrauterine growth retardation. It may also be possible that the statistical difference in the Apgar scores was not clinically significant and may disappear with a larger sample.

However, some studies have suggested that the lower Apgar score findings in neonates born of mothers who had received magnesium may be due to the effects of the disease itself rather than the administered magnesium sulphate. A study done by Constanza S. in Mexico reported that infants born of mothers with pre-eclampsia had lower Apgar at minute of birth despite not having received magnesium sulphate at birth¹²

Interestingly, other studies have suggested that there is little or no difference between neonates born of mothers with severe pre-eclampsia or eclampsia and those without these complications in the neonatal outcomes. There is a considerable debate on whether the effects seen in neonates after magnesium sulphate are due to the magnesium or the severe pre-eclampsia or eclampsia^{34, 35, 36, 47}.

Gul A, et al³⁶ compared perinatal outcomes in pregnancies complicated by severe pre-eclampsia or eclampsia with and without these complications. Clinical and laboratory findings and neonatal outcomes of all pregnancies with severe pre-eclampsia or eclampsia with and without complications were prospectively recorded. Analysis was

performed according to gestational age before and after 32nd gestational week. The difference of perinatal mortality between the two groups was not significant ($p = 0.644$ and $p = 0.250$), suggesting borderline difference³⁶.

Our study findings also contrast with the Magpie trial findings, that there was no significant difference in the Apgar scores between children born of mothers who received magnesium and those who did not. The different findings may be due to the different populations and methodology used in two studies. The Magpie trial which was a multicentre trial, carried out in 175 hospitals in 33 countries, differed from our study in that it was a much larger study with 10,141 participants compared to our study which had only 98 participants from one hospital only.

Magpie trial was a randomized controlled trial while our study was a quasi experimental study. In our study, the investigator neither administered magnesium to the patients nor decided who to give the drug (randomize) since the standard protocols of treatment of pre-eclampsia and eclampsia was used. It would have been unethical for the investigator to deny some mothers magnesium sulphate since it has been shown to be effective and adopted in the standard treatment guide lines of treatment of pre-eclampsia and eclampsia in KNH.

The Magpie trial also demonstrated no substantive harmful effects for the mother or baby, in the short term. It also reported that there was no clinically important effect on the risk of the baby dying before discharge from hospital or being in a special care nursery for more than 7 days¹⁸. However, the current study did not look at the pattern of mortality because the neonates were followed up for three days only.

In the current study, serum calcium levels were not significantly different between the magnesium exposed neonates and those not exposed. This differs from a study done by Rantonen et al in Finland in which he found hypermagnesemia in the neonates following magnesium sulphate exposure to be associated with neonatal hypocalcaemia²³. The

investigators explained these findings by noting that maternal magnesium sulphate treatment may cause an early neonatal hypermagnesemia that is associated with a prolonged blunted production of parathyroid hormone among exposed infants²³.

Awareness of the changes produced in the neonate by magnesium is important for accurate clinical assessment of the infant's condition, as well as for anticipating the postnatal interaction of magnesium with other drugs administered during labor and delivery⁵⁰.

There are many confounding factors that contribute to adverse neonatal outcome, and therefore make the evaluation of the neonatal outcome after magnesium sulphate therapy difficult, such as primigravidity, preterm delivery in preeclamptic and eclamptic women, respectively, and intrauterine growth restriction⁵¹.

CONCLUSION

Neonates whose mothers received magnesium sulphate were found to have statistically significant higher serum magnesium levels than those whose mothers did not.

Neonates exposed to magnesium sulphate were more likely to have a lower Apgar score on average when compared to the ones who were not exposed.

RECOMMENDATIONS

We recommend close monitoring of neonates whose mothers receive magnesium sulphate during labour

Further research that will follow up the neonates for a longer period to establish the pattern of morbidity and mortality and associate it with the serum magnesium levels is recommended.

STUDY LIMITATIONS

The manifestations of acute or chronic hypoxemia could account for some of these findings in the neonates.

The ideal controls for our study would have been neonates of mothers with severe pre-eclampsia / eclampsia who did not receive magnesium sulphate during labour but the standard management of severe pre-eclampsia /eclampsia is to give magnesium sulphate and so it would have been unethical to deny these mothers magnesium sulphate.

REFERENCES

1. Cunningham F.G, Gant N.F, Leveno K.J ,Larry C, Strap G, Hauth J.C . Hypertensive disorders in pregnancy. Williams obstetrics, 21st edition page 567-618.
2. World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. Geographic variation in the incidence of hypertension in pregnancy. Am J Obstet Gynecol. 1988;158:80–83.
- 3.The National Institute for Clinical Excellence, The Scottish Executive Health Department, The Dept of Health Social Services and Public Safety N. Ireland. Why mothers die 1997–1999: the fifth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. London: RCOG Press; 2001.
4. Department of Health, Welsh Office, Scottish Office Department of Health, Department of Health and Social Services NI. Why mothers die: Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 1994–1996 London: TSO. 1998.
5. Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. Br J Obstet Gynaecol. 1992; 99:547–53.
- 6 .Department of Health. Confidential Enquiry into stillbirths and deaths in infancy London: Department of Health. 1996.
7. Crowther CA. Eclampsia at Harare Maternity Hospital. An epidemiological study. S.Afr Med J.1985; 68:927–9
- 8 .Douglas KA, Redman CW. Eclampsia in the United Kingdom. BMJ. 1994; 309:1395–1400.

9. Wacker J, Schulz M, Fruhauf J, seasonal changes in the incidence of pre-eclampsia in Zimbabwe. *Acta Obstet Gynecol Scand.* 1988 Aug ;77 (7) :712-6]
10. Conde-Agudelo A, Kafury –Goeta AC . Epidemiology of Eclampsia in Colombia.int. *J. Gynaecol Obstet.* 1988 Apr. 61(1):1-8]
11. John Kiiru, M’Imunya Machoki, P. Olakhi Odongo .A review of the maternal and Perinatal outcome of pregnancies complicated by hypertensive disease at Kenyatta National Hospital. Mmed thesis 2005.
12. Sanchez-Carrillo Constanza , Ceron-Mireles Prudencia , Harlow Sioban D. Reyes-Zapata Hilda; Nunez-urquiza Rosa Maria ; Preeclampsia/eclampsia and its relation with adverse perinatal outcomes, *Boletín Médico del Hospital Infantil de México* 2003, vol. 60, n^o3, pp. 274-283 [10 page(s) (article)] (28 ref.)
13. Suka M, Sugimori H, Nakamura M, Haginiwa K, Yoshida K ; Risk factors of low APGAR score in Japanese full-term deliveries: a case-control study. *J Epidemiol.* 2002 Jul;12(4):320-3.
14. Harbans Lal , Nirmal Gulati, Saroj, Nidhi Sandooja and Kiran Chugh. Plasma and erythrocyte magnesium levels in patients with preeclampsia/eclampsia . *Indian journal of Clinical Biochemistry.* Volume 10, Number 2 / July, 1995.
15. Idogun, E.S; Imarengiaye, C.O, Momoh, S.M. Extracellular Calcium and Magnesium in Preeclampsia and Eclampsia. *African Journal of Reproductive Health*, Vol. 11, No. 2, 2007, pp. 80-85
16. Kimuhu S .M . The outcome of babies from pre-eclamptic and eclamptic pregnancies at Kenyatta National Hospital from 1st January 1980 to 1st December 1981. Masters of Medicine in Paediatrics and child health dissertation UON 1982.

17. Roberts J, Villar J, Arulkumaran S. Preventing and treating eclamptic seizures. Magnesium sulphate is effective and recommended for use, *BMJ* 2003;325: 609-610.
18. Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomized placebo-controlled trial. *Lancet*. 2002; 359:1877-1890.
19. Green K W, Key T C, Coen R ,Resnik R .The Effects of maternally administered magnesium sulphate on the Neonate .*American j. obstetric .Gynecol*,1983 May 1:146(1):29-33.
20. Donovan EF; Tsang RC; Steichen JJ ; Strub RJ; Chen IW; Chen M .Neonatal Hypermagnesemia :Effect on parathyroid hormone and calcium homeostasis. *J Pediatrics* 1980 Feb; 96(2):305-10
21. Rude R K, Singer FR: Magnesium deficiency and Excess ,*Annu Rev Med* 1981;32:245-259
22. Mc Guinness GA , Weinstein MM, Cruikshank DP, Pitkin RM. Effects of magnesium sulphate treatment on perinatal calcium metabolism .II. Neonatal responses. *Obstet Gynecol* 1980 ; 56: 595-600
23. Rantonen T , Jalonen J, Ekblad U, Peltola O,Kero P, Valimaki I ,kaapa P.Antenatal Magnesium sulphate exposure is associated with prolonged parathyroid hormone suppression in preterm Neonates. *Acta Paediatr* 2001;90: 278-281..
24. Mordes J P ,Wacker WEC, Excess magnesium .*Pharmacology Rev*.1978 ; 29 :273-91.

- 25 .Lipsitz PJ, English IC, Hypermagnesemia in the newborn infant. Paediatrics 1967; 40: 856-862)
26. Philip J. Lipsitz . The clinical and Biochemical Effects of Excess magnesium in the Newborn. Pediatrics Vol.47 No.3 March 1971,pp 501-509]
27. Rosen P, Barkin R.M, Sternbach G.L .Fluids and electrolytes in Essentials of Emergency Medicine .Philadelphia ;mosby Year Book ,1991 :483-504.
28. Bajpai P.C , Sugden D, Ramos A, Stern I .Serum magnesium levels in the newborn and older child. Arch .Dis Child.1996; 41:424-427
29. Whang R, Ryder K.W, Frequency of hypomagnesaemia and Hypermagnesemia Requested Vs Routine ,JAMA 1990;263:3063-4),
30. Wong E T, Rude R K, Singer FR, Shaw ST Jr. A High Prevalence of hypomagnesaemia and Hypermagnesemia in hospitalized patients .AM J Clin Pathol 1983 :79 :342-52)
31. Norwitz ER, Robinson JN . Neonatal side effects of preterm labour drugs. Clinical Obstetrics and Gynecology, Vol. 38, No. 4, December 1995, pp. 725-745.
- 32.Roth SC ,Edwards AD ,Cady EB, Delpy D.T, Wyatt JS .Relation between cerebral oxidative metabolism following Birth Asphyxia and neurodevelopment outcome and brain Growth at one Year. Dev .Med Child Neurol 1992;205:959-962.
- 33.Gathwala G ,Khera A, Singh I .magnesium therapy in birth asphyxia ,Indian J. pediatr 2006:73:209-212.
- 34 .Behrman RM, Kliegman R.M ,Jenson H .Nelson Text book of Pediatrics (17th Edition) ,WB Saunders company ,Philadelphia pp.610.

35. Broner CW , Stidham G L, Western Kirchner D.F, Tolley EA ,hypermagnesemia and hypocalcaemia as predictors of high mortality in critically ill pediatric patients. *Critical care med* 1990 ;18:921-7
36. Gul A, Cebeci A, Aslan H, Polat I, Ozdemir A ,Ceylan Y. Perinatal outcomes in severe pre-eclampsia-eclampsia with and without HELLP syndrome *Gynecol Obstet invest* 2005;59(2):113-8. Epub 2004 Dec 9.
37. Mehta R, Petrova A. Ionized magnesium and gestational age ,*Indian Journal pediatrics*,vol 74,number 11,November ,2007 pg 1025-1028
38. Wacker W.E.C , Altura B.M et al , ionized magnesium concentration in Biological samples, *Drugs* 28 (Suppl.I):120-142, 1984].
39. Ayoob Ali MD, Corinne Walentik,MD, Gregory J. Mantych,M,D, H. Farouk Sadiq, MD,William J.Keenan, M.D and Akhihiko Noguchi,MD ,Iatrogenic acute Hypermagnesemia after total parenteral nutrition infusion mimicking septic shock syndrome .*Paediatrics* vol.112 No.1 July 2003,pp.e70-e72 Cambridge, 1980
40. Rude R.K.Magnesium Metabolism ,in :Becker KL, ed .*Principles and Practice of Endocrinology and Metabolism* ,3 rd ed. Philadelphia Pa;lippincott 2001:673-678.
41. Weisinger J, Bellorin-Font E. Disorders of calcium ,phosphorus and magnesium metabolism. *Lancet* .1998; 352:391-396 .
42. Quamme G.A. Renal magnesium handling: New insights in understanding old problems .*Kidneys int.* 1997; 52:1180-1195
43. Mason BA, Standley CA, Whitty JE, Cotton DB. Fetal ionized magnesium levels parallel maternal levels during magnesium sulphate therapy for pre-eclampsia *Am J Obstet Gynecol.* 1996 Jul; 175(1):213-7.

- 44 .Matsuda Y, Maeda Y ,Sakamoto H, Masaoka N, Takada M, Sato K . Effects of magnesium sulphate administered to the mother on neonatal bone abnormalities..Gynecol obstetric invest. 1997; 44(2):82-8.
45. Robert Mittendorf, Robert Covert, Ronald Elin, Kwang-sun Lee et al .Umbilical cord serum ionized magnesium level and total paediatric mortality. Obstetrics and Gynecology 2001; 98:75-78.
46. Mittendorf R, Covert R, Boman J, Khoshnood B, Siegler M. Is tocolytic magnesium associated with increased total pediatric mortality? Lancet 1997; 350:1517-1518.
- 47 .Cord blood lipoprotein profile after magnesium sulphate treatment in pre-eclamptic patients Authors: Yavuz, Taner, Özlem; Ozdemir, Ismai; Afşar, Yilmaz: Acta Paediatrica, Volume 95, Number 10, October 2006, pp.1224-1227(4)
48. MagNET(Magnesium and Neurologic Endpoints Trial .Lancet 350[9090]:1517-18, 1997
49. Riaz M, Porat R,Brodsky N.L ,Hurt H. The effects of maternal magnesium sulphate treatment on Newborns, J .Perinatol. 1998 Nov-Dec; 18(6 pt 1):449-54.
- 50.Rasch DK, Huber PA, Richardson CJ, L'Hommedieu CS, Nelson TE, Reddi R; Neurobehavioral effects of Neonatal hypermagnesemia . J. Pediatr 1982 Feb;100(2
51. Omua A.E, Al-Harmi J., Vedi H.L., Mlechkova L., Sayed A.F., Al-Ragum N.S. Magnesium Sulphate Therapy in Women with Pre-Eclampsia and Eclampsia in Kuwait
- 52.Collaborative Eclampsia Trial: Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 1995; 345: 1455–1463.

53. Duley L, Gulmezoglu AM, Henderson- Smart DJ: Magnesium sulphate and other anticonvulsants for women with preeclampsia. Cochrane Database Syst Rev 2003; 2: CD000025.

54. Sibai BM: Magnesium sulphate prophylaxis in preeclampsia: Lessons learned from recent trials. Am J Obstet Gynecol 2004; 190: 1520–1526.

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APPENDICES

Appendix I

Study Subject Consent Information

Introduction

I am Dr Muviku, a post graduate student in the department of Paediatrics and child Health, University of Nairobi. I am required to do a research project as part of my post graduate studies. I intend to do a study on serum magnesium levels in neonates born to mothers with severe pre-eclampsia/ eclampsia who received magnesium sulphate during labour at K.N.H. I will also check other electrolytes which may be affected by the pre-eclampsia /eclampsia and also the administration of magnesium sulphate. Magnesium sulphate is a drug that is used to control and prevent convulsions in pregnant mothers with high blood pressure.

About The Study

Magnesium sulphate given to mothers is known to cross the placenta and enter into the babies system. This study will involve removing from your baby a sample of two milliliters of blood .This blood will be used to measure the serum magnesium, calcium, and potassium and sodium levels in the baby.

Removal of blood may be associated with mild occasional discomfort such as pain, bleeding or infection. However some of these are very rare complications e.g. infections but extreme care will be undertaken when doing the procedure to minimize the risks.

A sterile procedure will be performed with thorough cleaning and sterilization of the skin using spirit, prior to removing blood. After removal, gentle pressure will be applied to prevent / stop any bleeding.

Confidentiality will be maintained at all times. No names will be mentioned in the study. Any useful information which will improve the quality of care and outcome of the baby will be shared with the care giver for appropriate action.

It is important that you understand participation is voluntary and you can withdraw any time. This will not in any way affect the quality of care your child receives.

You are now free to ask questions relating to this study to get clarification on any issues that may not be clear to you.

You may therefore decide to participate or not.

Any questions about the study may be forwarded to the KNH-ERC, Kenyatta National Hospital ,P.O Box 20723,Nairobi,Tel 2726300-9.

APPENDIX II

CONSENT FORM

Participant's serial number ----- **Date**----- **Time**-----

I have been adequately explained about the study by Dr Muviku. I understand that my rights and the rights of my child will be respected and confidentiality maintained

I also understand participation is voluntary and I can withdraw at anytime and this will not compromise the quality of care my child is receiving. I therefore consent to be recruited into the study.

Guardian/mothers signature ----- **Date**-----

I have adequately explained to the mother/guardian of the baby about the study and she/he has accepted the child to participate in the study.

Dr Muviku

Investigators signature----- **Date**-----

For any issues you may contact

Dr muviku Virginia at 0722-668944

CC: Subject's file

Investigator's file

APPENDIX III

DATA COLLECTION FORM

Neonates Details

1. Hospital no -----

2. Study no. -----

3. Date of birth -----

Time of birth -----

4. Age in hrs -----

5. Gestation by Dates-----

Estimated gestational age-----

6 Sex male---

female ----

7. Weight in grammes -----

8. Date of admission -----

9. Apgar score -----

10. Mode of delivery-----CS / SVD

11. Respiratory rate ----- day 1----- , day 2-----, day 3-----

12. Neonatal reflexes -----
13. Serum Magnesium levels -----
14. Serum calcium levels-----
15. Serum potassium levels-----
16. Serum sodium levels-----































MOTHERS DETAILS

1. Total amount of magnesium sulphate received by the neonate's mother (Dosage used)
2. The duration of eclampsia /Pre-eclampsia (from the time of diagnosis)
3. Does the mother have severe pre-eclampsia or Eclampsia?

APPENDIX IV

Dubowitz scoring system for gestational age assessment

Table 11-2. Newborn maturity rating and classification.

	0	1	2	3	4	5	
Neuromuscular maturity							
Posture							
Square window (wrist)							
Arm recoil							
Popliteal angle							
Scarf sign							
Heel to ear							
Physical maturity							
Skin	Gelatinous, red, transparent	Smooth, pink; visible veins	Superficial peeling and/or rash; few veins	Cracking, pale area; rare veins	Parchment, deep cracking; no vessels	Leathery, cracked, wrinkled	
Lanugo	None	Abundant	Thinning	Bald areas	Mostly bald		
Plantar creases	No crease	Faint red marks	Anterior transverse crease only	Creases anterior two-thirds	Creases cover entire sole		
Breast	Barely perceptible	Flat areola; no bud	Stippled areola; bud, 1-2 mm	Raised areola; bud, 3-4 mm	Full areola; bud, 5-10 mm		
Ear	Pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna; soft; ready recoil	Formed and firm; instant recoil	Thick cartilage; ear stiff		
Genitalia (male)	Scrotum empty; no rugae		Testes descending; few rugae	Testes down; good rugae	Testes pendulous; deep rugae		
Genitalia (female)	Prominent clitoris and labia minora		Majora and minora equally prominent	Majora large; minora small	Clitoris and minora completely covered		

The following information should be recorded: Birth date and Apgar score at 1 and 5 minutes. Two separate examinations should be made within the first 24 hours to determine the estimated gestational age according to maturity rating. Each examination and the age of the infant at each examination should be noted.

Maturity rating:

Score	5	10	15	20	25	30	35	40	45	50
Weeks	26	28	30	32	34	36	38	40	42	44

Reproduced, with permission, from Ballard JL et al: A simplified assessment of gestational age. *Pediatr Res* 1977;11:374. Figures adapted from Sweet AY: Classification of the low-birth-weight infant. In: *Care of the High-Risk Infant*, 3rd ed. Klaus MH, Fanaroff AA (editors). Saunders, 1986. This form is available from the Mead Johnson Nutritional Group, Evansville, IN 47721.



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17th June 2008

Ref: KNH-ERC/ 01/ 517

Dr. V.M. Muviku
Dept. of Paediatrics & Child Health
School of Medicine
University of Nairobi

Dear Dr. Muviku

RESEARCH PROPOSAL: "SERUM MAGNESIUM LEVELS IN NEONATES BORN TO MOTHERS WHO RECEIVED MAGNESIUM SULPHATE AT K.N.H AND PUMWANI MATERNITY HOSPITAL"(P17/2/2008)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your revised research proposal for the period 17th June 2008 – 16th June 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH-ERC

- c.c. Prof. K.M.Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Paediatrics & Child Health, UON
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Dr. A. Amayo, Dept. of Human Pathology, UON