UNIVERSITY OF THE WITSWATERSRAND

THE EFFECT OF MAGNESIUM SULPHATE ON CLINICAL OUTCOMES OF LOW-BIRTH-WEIGHT BABIES AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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This research report is submitted in the submissible format in partial fulfilment of the requirements for the degree of Master of Medicine in the Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

September 2022

Declaration

I declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in Paediatrics at the University of the Witwatersrand, Johannesburg in the submissible format for Frontiers in Paediatrics (Neonatology). It has not been submitted before for any degree or examination at any other University.

Temitope Olawale Oluwadare Odubunmi

Signed at Johannesburg on 11th September 2022

Co- authors declarations:

We, the co-authors and supervisors of this paper, Dr F.L Nakwa, Prof K Thandrayen and Dr L Sepeng; declare that this research report was completed by Dr Temitope Olawale Oluwadare Odubunmi, as the first author in completion of his Masters in Medicine in the Division of Paediatrics and Child Health.

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Dr Letlhogonolo Sepeng _____

Date: 12/09/2022

Dedication

To Fortune and Iyanuoluwa.

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Presentations

This research has been presented at:

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2. Paediatric Research Day at the University of the Witwatersrand on 20th November 2020.
3. South African Paediatric Association (SAPA) Conference as an e-Poster on 14th August 2021.

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THE EFFECT OF MAGNESIUM SULPHATE ON CLINICAL OUTCOMES OF LOW-BIRTH-WEIGHT BABIES AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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Abstract

Introduction

Magnesium sulphate ($MgSO_4$) has been used for neuroprotection in the management of pre-eclamptic toxaemia (PET) and eclampsia in mothers of neonates at a lower gestational age and its' use is recommended in preterm deliveries less than 30-32 weeks of gestation. There may be greater effects at an earlier gestational age, with no associated long term adverse foetal or maternal effects; resulting in increased survival of preterm babies. The aim of the study was to assess if the administration of $MgSO_4$ improved the neonatal outcomes in low birth weight (LBW) infants whose mothers received magnesium sulphate.

Methods

This was a retrospective descriptive study of neonates, whose mothers' received $MgSO_4$ (as indicated by $MgSO_4$+ group) admitted to the neonatal unit within a two-year period (January 2016 – December 2017). The demographics and outcome at hospital discharge were collected and analysed.

Results

A total of 485 (7.5%) of 6510 LBW neonates' mothers received MgSO4. Pre-eclamptic toxaemia (PET) [n=235 (48%)], eclampsia [n=90 (19%)] and Haemolysis, Elevated Liver enzymes, Low platelets (HELLP) syndrome [n=28 (6%)] were the main indicators for the administration of $MgSO_4$. Mothers in the $MgSO_4$+ group were older and had a higher parity. Seventy percent received antenatal steroids in the $MgSO_4$+ group and 30% of these were HIV positive. Neonates in the $MgSO_4$+ group had a lower gestational age ($p < 0.001$) and birthweight ($p<0.001$). A smaller number of neonates in the $MgSO_4$+ group required resuscitation and had higher oxygenation ($p=0.005$) on admission. A higher proportion of neonates in the $MgSO_4$+ group had lethargy, hypotonia ($p<0.001$), asphyxia ($p<0.001$), early onset sepsis (EOS) ($p<0.001$), intraventricular haemorrhage (IVH) ($p<0.001$), respiratory distress syndrome (RDS) ($p<0.001$), required respiratory support ($p<0.001$) and died ($p<0.001$).

In the multivariate logistic regression analysis; PET, asphyxia and hypotonia were associated with mortality.

Conclusion

There was an increase in neonatal morbidities and mortality in neonates whose mothers received $MgSO_4$+. Monitoring of these neonates, in addition to monitoring MgSO4+ levels to document a dose effect, is essential.

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Introduction

Magnesium sulphate ($MgSO_4$) has been used predominantly as a tocolytic agent in obstetrics especially in women in preterm labour. It was found to have a role in the management of pre-eclamptic toxaemia (PET) and eclampsia. Its role as a neuroprotective agent became more evident in the early eighties following randomised control trials (RCTs) done on its effects in infants with a lower gestational age (GA) at delivery and is currently recommended for use in preterm deliveries less than 30-32 weeks of gestation (1). An estimated 5% of all pregnant women in the United States receive eclampsia prophylaxis each year and magnesium sulphate is the most frequently administered pharmacological agent (2).

The prevalence of preterm birth is increasing, and it was reported that every year, one in ten babies, equivalent to 15 million babies worldwide will be born preterm. Of these, approximately one million will die and many will suffer from lifelong disability (2). Advances in neonatal care have improved the survival of infants born preterm, particularly those born at a very low birth weight (VLBW) or gestational age (GA). Despite this improved survival rate, the prevalence of neurodisability, even in high income countries is increasing (3). The survival of infants born preterm has also improved with the introduction of magnesium sulphate ($MgSO_4$) in women at risk of early preterm imminent birth especially with regards to neuroprotection. The risk of evolution and development of cerebral palsy has declined in most centres (4). Furthermore, there appears to be fewer articles regarding the effects of magnesium sulphate on other co-morbidities in at risk and preterm infants.

Magnesium ions are essential for most cellular processes, most especially glycolysis, protein synthesis, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) aggregation and oxidative phosphorylation. Magnesium also influences mechanisms implicated in apoptosis or dysfunction by decreasing pro-inflammatory cytokines and free radicals that are produced during hypoxic ischaemic reperfusion as well as in other inflammatory diseases of pregnancy (1). Magnesium provides a non-competitive voltage-dependent inhibition of the N-methyl-D-aspartic acid (NMDA) receptor to glutamate, reducing calcium entry into cells by inhibiting presynaptic excitatory amino-acid release (5). Hence, preventing excitotoxic calcium-induced injury (6).

The haemodynamic effects of magnesium are to stabilise the changes in maternal blood pressure and cause an increase in cerebral flow in preterm neonates. The administration of magnesium sulphate before delivery is associated with protection of gross motor function in infants born preterm. The effect may be greatest at early gestational ages and is not associated with adverse long-term foetal or maternal outcome (7).

Despite the widespread use of antenatal $MgSO_4$ for preterm pre-eclampsia, eclampsia and foetal neuroprotection; there is no consensus on its effect on neonatal outcomes (8).
The aim of the study was to evaluate the impact of the antenatal administration of

$MgSO_4$ on LBW neonates whose mothers received magnesium sulphate ($MgSO_4$+) and to compare the outcomes with LBW neonates whose mothers did not receive magnesium sulphate ($MgSO_4$-).

Methodology

The study was conducted in the Neonatal Unit at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto. The hospital is the 3rd largest hospital in the world and has the capacity of approximately 3,200 beds. It is a tertiary care teaching hospital for the University of the Witwatersrand. The neonatal unit has a bed capacity of 185 beds with 18 neonatal intensive care beds, 42 high care beds, 100 standard care beds and 19 kangaroo mother care (KMC) beds. The CHBAH delivers more than 20000 and admits on average of about 4000 babies yearly.

Objectives of the study

- To identify the prevalence of neonates whose mothers received $MgSO_4$ that were referred and admitted to the neonatal unit.
- To determine the indication for prescribing $MgSO_4$ in the mothers
- To determine and compare the characteristics of both LBW neonates and their mothers whom received and did not receive $MgSO_4$.
- To compare the mortality, morbidity and outcomes of LBW neonates whose mothers received with those whom did not receive $MgSO_4$.

Study subjects and methods

This study is a retrospective descriptive review of the outcomes of LBW neonates whose mothers received magnesium sulphate antenatally either for treatment for preeclamptic toxaemia (PET) or for tocolysis.

The patients were identified through the neonatal Research Electronic Data Capture (REDCap) database of the University of the Witwatersrand, Human Research Ethics Committee (HREC) and clearance number is M151196. HREC provided clearance for this study (M190501) (Appendix B).

All LBW neonates (≤2500g) delivered during the period January 2016 - December 2017 were included in the study. The birthweight of <2500g was utilised as the proxy for preterm neonates. Magnesium sulphate has been administered for neuroprotection in mothers at risk of seizures with an estimated gestational age of less than 36 weeks (EGA) and for neuroprotection in at risk babies. The protocol has been used in the hospital since 2010 in neonates. The database was then

mined for those LBW neonates whose mothers received MgSO4+ and those whom did not receive $MgSO_4$- to make comparisons between the two groups.

The information was extracted, and data collected. Information was inclusive of maternal and infant demographics, obstetric history, maternal medical conditions, indication for receipt of $MgSO_4$, mode of delivery, gestational age, indication for delivery if delivered by C-section, Apgar scores, need for resuscitation, an arterial blood gas in the first hour of life, birth weight, interventions, complications, and outcome in the neonatal unit prior to discharge.

The exclusion criteria were if the neonate was out born, had congenital abnormalities, chromosomal abnormalities and incomplete data or records.

Morbidities that were included are listed below and these were stratified based on the classification where applicable.

- Respiratory diagnoses and interventions such as ventilatory support i.e. intermittent positive pressure ventilation (IPPV), nasal continuous positive pressure (nCPAP), high frequency oscillator ventilation (HFOV)
- Seizures
- Intraventricular haemorrhage (IVH) (all grades as defined by Papile) (9)
- Necrotising enterocolitis (NEC) (defined by modified Bell's staging) (10)
- Retinopathy of Prematurity (defined by the ETROP study) (11)
- Neurological compromise e.g., lethargy and Apgar score < 7 at 5 mins

Statistical Analysis

The data was exported into an excel spreadsheet from REDCap and data was analysed using the Statistica (Statsoft, USA, version 14) and STATA package (version 16.1). Means and standard deviations were used to describe continuous variables with normal distribution, and medians and interquartile ranges were utilized when not normally distributed. Categorical variables were described as frequencies and proportions. To compare the characteristics between the 2 groups; $MgSO_4$+ and $MgSO_4$-; the Student t-test was used when comparing parametric data and a Mann-Whitney U test to compare non-parametric data. The Pearson Chi-square or Fischer exact test was used to compare categorical variables. A p-value less than 0.05 was regarded as statistically significant. Logistic regression analyses (both univariate and multivariate) were run to assess for the risk factors associated with mortality in this cohort. Variables with a p- value of <0.1 was considered for the multivariate analyses.

Results

Overall

A total of 6510 LBW neonates were identified and admitted during the study period (Figure 1). There were 485 (7.5%) neonates whose mothers received magnesium sulphate ($MgSO_4$+).

Maternal characteristics

The mothers who received $MgSO_4$+ were older and had a higher parity as compared to those whom did not receive $MgSO_4$-;(29.0±6.4 vs 27.9±6.6 years of age);p<0.001(Table 1).

There were more HIV positive mothers in the group that received $MgSO_4$+ as compared to those whom did not receive $MgSO_4$-; (144 (30%) vs 809 (13%); p<0.001).

Maternal hypertension and its complications were the commonest indications for receipt of MgSO4; (182 (38%) vs 21 (0.4%); p<0.001). Pre-eclamptic toxaemia (PET) [n=235 (48%)], eclampsia [n=90 (19%)] and HELLP syndrome [n=28 (6%)] were the main indicators for the administration of $MgSO_4$, as shown in Table 1.

Neonatal characteristics

Neonates born to mothers whom received $MgSO_4$+ were younger (31.2±3.3 weeks vs 32.6±3.3 weeks of gestation; p<0.001) and smaller (1471±487 vs 1722 ±503 g; p<0.001) as shown in Table 2. There were no differences in the mode of delivery and proportion of neonates with Apgar score < 7 at 5 minutes between the 2 groups.

More neonates in the $MgSO_4$- group required resuscitation (44% vs 37%; p=0.06), but this was marginally significant.

Acid- Base Status

Overall 23% of the neonates had an arterial blood gas drawn (27% $MgSO_4$+ vs 23% $MgSO_4$-). There were higher partial pressure of oxygen (PaO_2) (126 vs 112 mmHg; p=0.005) and a lower partial pressure of carbon dioxide ($PaCO_2$) (36 vs 39 mmHg; p <0.001) in the $MgSO_4$+ group as shown in Table 3.

Neonatal morbidity

In Table 4, more neonates were admitted with respiratory distress syndrome (RDS) in the $MgSO_4$+ group [436 (90%) vs 2834 (47%); p <0.001]. Sixty-one percent of neonates in the $MgSO_4$+ group required respiratory support, with a higher proportion who required non-invasive (40% vs 16%; p<0.001) and invasive (21% vs 8%; p<0.001) respiratory support.

Neonates in the $MgSO_4$+ group were significantly more lethargic (p <0.001), hypotonic (p<0.001) and had a higher number of neonates with asphyxia (p<0.001), EOS (p<0.001), IVH (p<0.001) and ROP (p<0.001) (Table 4).

Neonatal mortality

In univariate analysis for the entire cohort, those who received $MgSO_4$+ were 3.5 times at a greater risk of dying (Table 5). Hypertension (4.46, p-0.001), HELLP syndrome (6.6, p-0.000), PET (3.47, p-0.000), resuscitation at birth (2.39, p-0.000), RDS (1.68, p-p0.008), seizures (5.22, p-0.007), asphyxia (17.01, p-0.000) and hypotonia (9.59, p0.000) were associated with mortality in the MgSO4+ group. An increase in Apgar scores at 1, 5 and 10 minutes showed a 54%, 53% and a 49% reduction in mortality respectively. However, in the adjusted multivariate logistic regression analysis, neonates whose mothers had PET (3.15, p-0.006), neonates with asphyxia (6.13, p0.000) and hypotonia (4.49, p-0.000) were more likely to die. A higher GA had a 31% reduction in mortality. In addition, RDS and being managed with CPAP were not associated with mortality.

No other maternal or neonatal factors such as hypertension, parity, gestational age, birth weight, asphyxia and hypotonia were associated with mortality in the adjusted multivariate logistic regression analysis.

Discussion

This study described the effects of antenatal administration of magnesium sulphate on LBW neonates and compared neonates whose mothers received magnesium sulphate compared to those LBW neonates whose mothers did not receive magnesium sulphate. The main findings were that a smaller number of neonates in the $MgSO_4$+ group required resuscitation however a higher proportion of these neonates had lethargy, hypotonia, asphyxia, EOS, IVH, RDS requiring respiratory support and death. Despite an increase in RDS and NICU admissions, there were no risk factors affecting mortality during admission.

The maternal characteristics indicated that mothers in our study who received $MgSO_4$+ were older and had a lower parity, with 1945 (30%) of our cohort being primigravida and 3631 (56%) multiparous. This is similar to a study by Crowther et al. who reported a lower parity and an average maternal age of 28.4±5.8 years in those whom received $MgSO_4$ (12). However, Ambadkar et al. described the administration of MgSO4 (40%) in younger mothers 22- 26 years

(40%) whom were primigravidae (55%) (13). Girsen et al. also reports that $MgSO_4$ exposed mothers were younger and more likely to be of African American origin (14). The majority of our patients are of African descent.

A higher proportion of mothers were HIV positive in the $MgSO_4$+ group (30% vs 13%, p<0.001). This is in keeping with previously described studies reporting a high prevalence of HIV in Soweto with a third of our patients being HIV positive in the group that received $MgSO_4$ (15–17). The existence of a potential association between HIV and PET has been investigated in the literature. It has been suggested that immunological abnormalities may be responsible as HIV is an immune-dysfunction disorder. The impaired immunity associated with HIV could lower the risk of pre-eclampsia (18). The HIV rate in the study by Kalumba et al. was significantly lower in women with PET than in normotensive pregnant women (15). Hall et al. in their prospective study done in the Western Cape, South Africa; found that HIV infection was less common in women with PET with no evidence of a relationship between the two (19). There was no association found between HIV and eclampsia or pre-eclampsia.

Duley et al. concluded that the administration of $MgSO_4$ is the commonest intervention to mothers at risk of the complications of hypertensive disorders and decreases the risk of eclampsia by more than half (20). It has been reported that 10% of pregnant women have elevated blood pressure in pregnancy and 2-8% developed preeclampsia (21). Systematic reviews and clinical practice guidelines support its use when given for neuroprotection in pre-eclampsia as well as eclampsia (22). Our findings were in keeping with hypertensive disorders and its complications being the commonest indications for the administration of $MgSO_4$ (48% for preeclampsia and 19% for eclampsia). This is in keeping with other studies reporting on the indications for administration of $MgSO_4$. Ambadkar et al. reported that 91.5% of patients with severe preeclampsia had received $MgSO_4$ (13). In the meta-analysis by Crowther et al., preeclampsia was the primary reason for the administration of $MgSO_4$ (23).

In our study, neonates whose mothers received $MgSO_4$ were of lower gestational age (31.2 ±3.3 vs 32.6 ±3.3 weeks; p-value < 0.001) and birthweight (1471 ± 487 vs 1722 ± 503grams; p-value < 0.001). Elimian et al. in their study reported $MgSO_4$+ neonates having lower gestational age compared to the unexposed neonates (28.2 ±30 vs 29.3 ±3.1 weeks; p = 0.001) (24). A meta-analysis by Crowther et al. had comparable gestational ages between the controls and the $MgSO_4$+ group (23). This is in keeping with the guidelines on the use of $MgSO_4$ for gestational ages <32 weeks. Thus, we are prescribing $MgSO_4$ as per protocol.

Magnesium sulphate is known to depress respiration, thus there is a concern that the neonates may have depressed breathing and lower Apgar scores. In this study, $MgSO_4$ did have an effect on the Apgar scores with lower Apgar scores in the MgSO4+ group at 1 minute, 5 minutes and 10 minutes. Pruett et al. reported that the administration of $MgSO_4$ in women with pregnancy-induced hypertension (PIH), did not result in lower Apgar scores (25). The dose administered in the Pruett study was 6g of $MgSO_4$, given intravenously over 20mins and 2g of $MgSO_4$ given intravenously per hour thereafter (25). Our study dose was

4g of $MgSO_4$ given as a rapid infusion and a maintenance dose of 10g into 200ml normal saline run at 20ml/hour, which is equivalent to 1g/hour.
Thus, a lower dose of $MgSO_4$ was administered to the mothers in the current study. There is evidence to highlight that there exists a dose dependent relationship following the administration of $MgSO_4$ and the occurrence of lower Apgar scores which is in keeping with elevated circulating maternal levels (26). Increased neonatal levels have been associated with lethargy and respiratory compromise. We did not consistently monitor levels in both mothers and neonates.

There was no increase in the need for resuscitation in the $MgSO_4$+ group (37% vs 44%, p=0.06). Many studies have come to the same conclusion in terms of the need for resuscitation in the neonates whose mothers received $MgSO_4$ (12,27,28). Drassinower et al. found no effects of magnesium sulphate on the need for oxygen, resuscitation and intubation (28). In a retrospective Canadian cohort, no increase in delivery room resuscitation was found; however, information on timing, duration of exposure or dose of MgSO4 was lacking (29).

This study had neonates in the $MgSO_4$+ group with a higher median PaO_2 and a lower $PaCO_2$ on arterial blood gas (ABG) at the time of birth. $MgSO_4$ has a vasodilatory effect on the brain and lungs, as well as reducing vascular instability and helping in tissue protection against free radical activity. It further has an inhibitory effect on the inflammatory cascade and contributes to an improved brain tissue oxygenation index by at least 34% (23,30,31). This mechanism assists in improving oxygenation and reducing
CO_2 accumulation. The higher PaO2 levels seen in the MgSO4+ group need to be further investigated as the delivery room resuscitation practices and the concentration of oxygen during resuscitation has not been documented.

In our study, the neonates had an increased risk of RDS, respiratory support and NICU admission with mechanical ventilation despite high antenatal corticosteroid exposure (70.5% vs 8.2%; p<0.001). Antenatal corticosteroids are known to decrease the risk of RDS and decrease mechanical ventilation (32). In our study, the time points at which antenatal corticosteroids and whether a full course was administered was not documented. Studies had shown similar rates of RDS in both groups (23,30,31).

We found a higher proportion of neonates with lethargy, hypotonia and asphyxia in the $MgSO_4$+ group. Many studies reported lower Apgar scores, increased delivery room intubation, admission to a special care nursery and hypotonia in neonates whose mother received MgSO4 at higher concentrations or with higher circulating levels in the maternal circulation (23,33,34). A Cochrane review found no difference in admission to a special care nursery nor delivery room intubation between the groups.(35) In our study, magnesium levels were not reported, as only 32 (6.6%) of the infants had magnesium levels drawn. The unit protocol is to administer a low dose of $MgSO_4$, and this could account for the low rates of hypotonia. We reported 48 (10%) neonates to have hypotonia; of which only 11 (2.2%) had their magnesium levels drawn and 4 (0.8%) had levels trending towards toxicity.

The prevalence of NEC was low in the $MgSO_4$+ group. This is in keeping with studies and a meta-analysis that found no indication that the administration of $MgSO_4$ increases the risk of NEC (36–38). In retrospective studies, there were no increases in NEC in neonates exposed to $MgSO_4$. However, Rattray and Kamyar report a concern regarding NEC in the earlier gestational ages (39,40).

The current study reported an increase in IVH in the $MgSO_4$ exposed neonates (2.7% vs 0.7%; $p<0.001$). Crowther et al. reported no difference in the prevalence of IVH and cPVL between the 2 groups in their study (12). In addition, the meta-analysis by Crowther et al. reported no difference in these outcomes (23). Petrova et al. found a lower risk of IVH, whereas Mittendorf et al. concluded that the risk of IVH was associated with higher maternal magnesium levels (41,42). We had a small number of magnesium levels measured in our cohort. It can be postulated that the rate of IVH may be related to higher magnesium levels in both mothers and neonates in our cohort.

Death was higher in the $MgSO_4$+ group (5% vs 1.5%; $p<0.001$) in the current study. This is in contrast to studies reporting that $MgSO_4$ reduced the incidence of death (11,27)**.** There were 121 (2%) missing data for death in the $MgSO_4$- unexposed group in our cohort and thus the results are to be reviewed with reserve. However, the multivariate adjusted logistical regression analysis indicated that neonates with asphyxia and lethargy in the MgSO4+ group were more likely to die. This is in contrast to Shepherd et al. and Crowther et al. who conclude that there are no clear associations between mortality and other adverse neonatal outcomes when $MgSO_4$ is given for the beneficial indications of maternal neuroprotection in preeclampsia/eclampsia and foetal neuroprotection**.** A reduction was found in the rates of cerebral palsy (3,23,27). It is thus important to establish if any cofounders are present to streamline possible causes for the increased numbers in death.

Limitation of the study

This was a retrospective study with missing or incomplete records. We recorded 121 (2%) missing data on death outcome in the $MgSO_4$- unexposed group. Birthweight as a proxy for gestational age led to 17 (3.5%) term small for gestational age (SGAs) being included in the MgSO4+ group. The serum levels of magnesium were not consistently drawn in both mothers and neonates exposed to $MgSO_4$ hence the correlation between the levels and outcomes were not possible. We did not access the maternal records to document the duration and the cumulative dosing of $MgSO_4$. This would have assisted in observing the early effect and risks of increased circulating maternal levels and the attendant interventions that are required.

Conclusion

The risk factors for mortality in neonates whose mothers received antenatal administration of $MgSO_4$ was PET in mothers; hypotonia and asphyxia in the neonates. Despite increased RDS and NICU admissions, there was an associated reduction in mortality. A prospective study monitoring the magnesium serum levels in both neonates and mothers are essential as some co morbidities have been reported with higher serum levels. In addition, documenting the neurodevelopmental outcomes in neonates exposed to antenatal $MgSO_4$ is warranted in our setting.

TABLE 1 Characteristics of mothers who received ($MgSO_4$+) and did not receive magnesium sulphate ($MgSO_4$-)

Maternal characteristics	All Mothers 6510 n(%)	$MgSO_4$ + n = 485 n(%)	$MgSO_4$ - n = 6025 n(%)	p-value
Age (years)*	28.1±6.6	29.0±6.4	27.9±6.6	< 0.001
Parity**	2.0 (1-3)	2.0 (1-2)	2.0 (1-3)	0.037
Gravidity**	2.0 (1-3)	3.0 (1-3)	2.0 (1-3)	0.126
HIV positive	953 (15)	144 (30)	809 (13)	< 0.001
Antenatal corticosteroids	836 (12.8)	342 (70.5)	494 (8.2)	< 0.001
Maternal indications for $MgSO_4$				
Hypertension	203 (3)	182 (38)	21 (0.4)	< 0.001
HELLP syndrome	38 (0.6)	28 (6)	10 (0.2)	< 0.001
PET	299 (5)	235 (48)	64 (1)	< 0.001
Eclampsia	100 (1.5)	90 (19)	10 (0.2)	< 0.001
Diabetes Mellitus	40 (1)	26 (5)	14 (0.2)	< 0.001
Cardiac diseases	8 (0.1)	4 (0.8)	4 (0.1)	< 0.001

*Mean (SD); ** Median (± IQR)

LBW – low birth weight, $MgSO_4$ – did not receive magnesium sulphate, $MgSO_4$ + received magnesium sulphate, HELLP – Haemolysis; Elevated Liver Enzymes; Low Platelets, PET- Pre Eclamptic-Toxaemia

TABLE 2 Characteristics of neonates whose mothers received and did not receive magnesium sulphate ($MgSO_4$)

Neonatal characteristics	All LBW n (%)	$MgSO_4$ + n (%)	$MgSO_4$ - n (%)	p-value
C-section	6080 (93)	458 (94)	5622 (93)	0.34
NVD	429 (7)	27 (6)	402 (7)	0.34
GA (weeks)	32.5±3.8	31.2±3.3	32.6±3.3	< 0.001
Birthweight	1703.8±506	1471.0±487	1722.0±503	< 0.001
Apgar's**				
1 min	8 (6 - 9)	7 (5 - 9)	8 (6 - 9)	< 0.001
5 min	9 (8 - 10)	9 (8 -10)	9 (8 -10)	< 0.001
10 min	10 (9 - 10)	9 (9 - 10)	9 (9 - 10)	< 0.001
Resuscitation	2808 (43)	179 (37)	2629 (44)	0.06

*Mean (SD), ** Median- IQR

C-section- Caesarean section, NVD – normal vaginal delivery, GA – gestational age, LBW – low birth weight, $MgSO_4$+- received magnesium sulphate, $MgSO_4$- - did not receive magnesium sulphate, min = minutes

TABLE 3 Arterial blood gas (ABG) parameters on admission

Acid-Base Parameter	All LBW N=1505	$MgSO_4$ + (n = 131)	$MgSO_4$ - (n = 1374)	p -value
pH*	7.24 (7.18 -7.34)	7.26 (7.18 -7.34)	7.24 (7.18 -7.34)	0.075
PaO_2 mmHg**	114.8 (81.4 -141.0)	126 (94.5 -150)	112 (79- 143)	0.005
$PaCO_2$ mmHg**	40.5 (31.5 - 47.2)	36 (30 -43)	39 (31- 47)	0.001
Lactate mmol/l**	6.4 (2.3 -8.3)	5.40 (2.7 – 9.7)	4.0 (2.3- 8.3)	0.087
BD mmol/l**	9.1 (4.7 – 11.9)	8.0 (5.4 – 12.1)	7.5 (4.7-11.9)	0.219

*Mean (SD), **Median (IQR)

LBW – low birth weight, $MgSO_4$ + - received magnesium sulphate, $MgSO_4$- – did not receive magnesium sulphate, PaO_2 - partial pressure of oxygen, $PaCO_2$- partial pressure of carbon dioxide, BD – base deficit.

TABLE 4 Admission diagnosis and morbidities of neonates whose mothers received and did not receive $MgSO_4$

Neonatal diagnosis and morbidities	All LBW n (%) n = 6510	$MgSO_4$ + n (%) n = 485	$MgSO_4$ – n (%) n = 6025	p-value
RDS	3270 (50)	436 (90)	2834 (47)	< 0.001
Respiratory support				
nCPAP	1130 (17)	193 (40)	937 (16)	< 0.001
IPPV	602 (9)	103 (21)	499 (8)	< 0.001
HFOV	5 (0.1)	1 (0.2)	4 (1)	0.280
Lethargy	106 (2)	38 (8)	68 (1)	< 0.001
Hypotonia	238 (4)	48 (10)	190 (3)	< 0.001
Asphyxia	108 (2)	38 (8)	70 (1)	< 0.001
Seizures	35 (0.5)	1 (0.2)	34 (0.6)	0.301
Sepsis	151 (2)	15 (3)	136(2)	0.230
EOS	36 (0.6)	10 (2)	26 (0.4)	< 0.001
LOS	115 (2)	5 (0.1)	110 (1.7)	0.206
NEC	113 (2)	9 (2)	104 (2)	0.824
IVH	57(0.9)	13 (2.7)	44 (0.73)	< 0.001
ROP	34 (0.5)	34 (0.6)	0 (0)	0.097
Death*	115 (2)	25 (5)	90 (1.5)	< 0.001

* 121 (1.9%) missing variable in the $MgSO_4$- group.

LBW – low birth weight, $MgSO_4$+ - received magnesium sulphate, $MgSO_4$- – did not receive magnesium sulphate, RDS – respiratory distress syndrome, nCPAP – nasal continuous positive ventilation, IPPV – intermittent positive pressure ventilation, HFOV - high frequency oscillatory ventilation, EOS – early onset sepsis, LOS – late onset sepsis, NEC – necrotizing enterocolitis, IVH- intraventricular haemorrhage.

Table 5: Logistic Regression Analysis for Mortality as the Primary Outcome

Death	Unadjusted OR (95% CI)	p – value	Adjusted OR (95% CI)	p - value
$MgSO_4$	3.5 (2.23-5.52)	0.000	1.44 (0.59-3.49)	0.415
Age	1.02 (0.99-1.05)	0.145		
Parity	0.79 (0.67-0.93)	0.004	0.88 (0.73-1.06)	0.168
Gravidity	1.02 (0.88-1.18)	0.743		
Antenatal care	0.76 (0.18-3.11)	0.700		
HIV	0.66 (0.37-1.22)	0.187		
Steroids	1.20 (0.72-1.99)	0.481		
Diabetes mellitus	1.40 (0.19-10.26)	0.740		
Hypertension	4.46 (2.50-7.95)	0.000	1.97 (0.77-5.03)	0.159
Eclampsia	2.3 (0.84-6.42)	0.105		
HELPP syndrome	6.6 (2.31-18.95)	0.000	1.06 (0.23-4.83)	0.932
PET	3.47 (2.02-5.97)	0.000	**3.14 (1.39-7.07)**	**0.006**
Resuscitation at birth	2.39 (1.59-3.59)	0.000		
Apgar 1 min	0.46 (0.41 - 0.51)	0.000		
Apgar 5 min	0.47 (0.44 - 0.52)	0.000		
Apgar 10 min	0.51 (0.46 - 0.57)	0.000		
Gender	0.66 (0.45-0.96)	0.029	0.88 (0.56-1.37)	**0.578**
GA (weeks)	0.75 (0.71 - 0.79)	0.000	**0.69 (0.64-0.74)**	**0.000**
Birth weight (g)	0.99 (0.99 - 0.99)	0.000		
RDS	1.68 (1.15-2.49)	0.008	**0.34 (0.19-0.58)**	**0.000**
CPAP	0.59 (0.33-1.05)	0.073	**0.26 (0.12-0.55)**	**0.000**
IPPV	1.02 (0.54-1.90)	0.959		
NEC	0.99 (0.24-.06)	0.991		
Sepsis	0.73 (0.18-2.98)	0.657		
Seizures	5.22 (1.58-17.31)	0.007	0.41 (0.06-2.67)	0.352
Asphyxia	17.01 (10.2-28.37)	0.000	**6.15 (2.31-16.3)**	**0.000**
Hypotonia	9.59 (6.12-15.01)	0.000	**4.49 (1.98-10.19)**	**0.000**

$MgSO_{4+}$ – magnesium sulphate received, RDS – respiratory distress syndrome, nCPAP – nasal continuous positive ventilation, IPPV – intermittent positive pressure ventilation, HELLP – Haemolysis; Elevated Liver Enzymes; Low Platelets, PET- Pre Eclamptic-Toxaemia, NEC – necrotizing enterocolitis, min- minutes, GA- gestational age, g- grams

Due to collinearity in Apgar scores, resuscitation at birth and asphyxia, asphyxia remained in the model; and similarly for GA and birth weight, GA remained in the model.

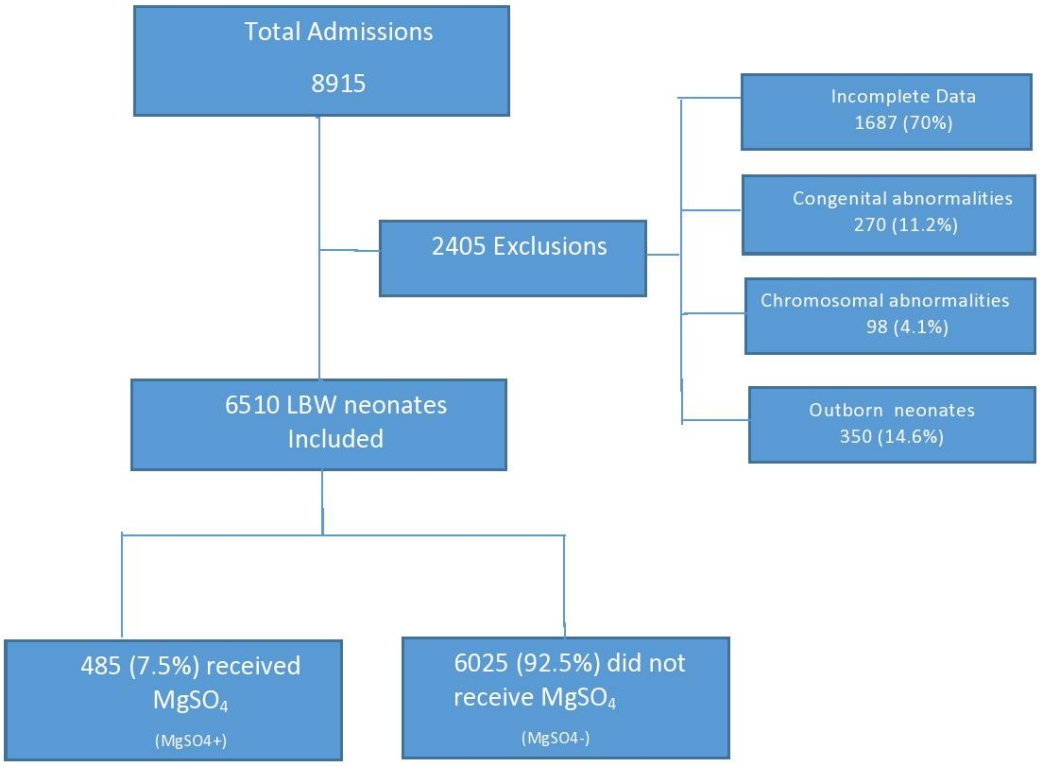

Figure 1: Consort diagram of patients included into the study over a 2-year period.

Conflicts of interest

None

Authors' contributions

All authors contributed equally to the manuscript. All authors reviewed and approved the current manuscript for submission.

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APPENDIX A: Protocol

UNIVERSITY OF THE WITSWATERSRAND.

DEPARTMENT OF PEADIATRICS AND CHILD HEALTH.

THE EFFECT OF MAGNESIUM SULPHATE ON CLINICAL OUTCOMES OF LOW BIRTH WEIGHT BABIES AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL.

CANDIDATE: TEMITOPE ODUBUNMI.

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SUPERVISOR: DR.F.L. NAKWA

CO- SUPERVISOR: DR.L. SEPENG

DATE: 27th August 2019.

TABLE OF CONTENTS:

ABBREVIATIONS:

- **ACTOMgSO$_4$- Australasian Collaborative Trial of Magnesium Sulphate**
- **ATP – Adenosine Triphosphate**
- **BEAM- Beneficial Effects of Antenatal Magnesium Sulphate**
- **CNS – Central Nervous System**
- **cPVL – cystic Periventricular leukomalacia**
- **DNA – Deoxyribonucleic acid**
- **EGA – Estimated Gestational age**
- **LBW – Low Birthweight**
- **MagNET- Magnesium and Neurological Endpoints Trial**
- **MAGPIE- Magnesium Sulphate for prevention of Eclampsia**
- **MDG – Millennium Development Goals**
- **NEC – Necrotising Enterocolitis**
- **RDS – Respiratory Distress Syndrome**
- **RNA – Ribonucleic acid**
- **ROP – Retinopathy of Prematurity**
- **VLBW – Very Low Birthweight**
- **NMDA – N-Methyl-D-Aspartic acid**
- **BPD – Bronchopulmonary Dysplasia**
- **EGA – Estimated Gestational Age**

1. INTRODUCTION.

The World Health Organization (WHO) defines preterm birth as delivery before 34 weeks gestation with sub-categories including very preterm birth (28 to 32 weeks), extreme preterm birth (less than 28 weeks gestation) and moderate to late preterm (32 to 37 weeks). Worldwide, it is estimated that more than I in 10 neonates were born preterm in 2013, accounting for approximately 15 million premature babies. Among these 1 million children younger than age 5, die annually because of complications relating to preterm birth.(1)

Preterm delivery accounts for a large percentage (5 to 18%) of low birthweight (LBW) and Very Low Birthweight (VLBW). About 42% of under-five mortality is caused by neonatal deaths. This is increased from 37% in the year 2000 when the Millennium development goals (MDGs) were proposed. MDG 4 targets reduction in Under- 5 deaths.(2)

Conditions as well as complications associated with preterm birth are multi-systemic and include chronic lung disease, interventricular haemorrhage (IVH), cystic periventricular leukomalacia (cPVL), growth retardation, respiratory distress Syndrome (RDS), necrotizing enterocolitis (NEC) and retinopathy of prematurity (ROP), all of which have a significant impact on long-term development and outcome. (3)

Conde-Agudelo, A and colleagues also considered preterm birth as a risk factor for poor neurological outcomes and emphasized that the risk increases with decreasing gestational age. (4)

The resultant neurological sequelae may manifest as seizures, interventricular haemorrhage, and presenting as cerebral palsy in later years. This necessitates the importance of neuroprotection in the preterm infant.

Usman et al, reported that magnesium sulphate had a modest neuroprotective effect which is greater the in the infants with a lower gestational age at delivery and is currently recommended for use in preterm deliveries less than 30-32 weeks of gestation.(5)

Magnesium sulphate has been extensively prescribed in obstetrics for decades for the prevention of seizures in patients with eclampsia. Its mechanism of action involves depressing the CNS, blocking neuromuscular transmission, and produces an anticonvulsant effect as well as decreasing the amount of acetylcholine released at the motor nerve endplate.

Despite its widespread use for the treatment of preeclampsia, there is a lack of consensus regarding dosage, standard regimen, and therapeutic window. (6)

The initial interest in the use as well as effectiveness of magnesium sulphate dates to the early eighties, as experimentally there were reports of a neuroprotective effect. However, the role of its effect in other neonatal co-morbidities such as respiratory distress syndrome, chronic lung disease, congenital heart conditions have not been fully elucidated.

There remains a huge knowledge gap in understanding how magnesium sulphate acts as a neuroprotective agent. Magnesium sulphate is a good candidate for neuroprotection of very preterm children for several reasons; magnesium ions are essential for key cellular processes, including glycolysis, oxidative phosphorylation, protein synthesis, DNA and RNA aggregation, and maintenance of plasma membrane integrity. It can influence mechanisms implicated in cell death or dysfunction by decreasing pro-inflammatory cytokines or free radicals produced during hypoxic-ischaemic reperfusion and inflammatory diseases of pregnancy. It can also act by preventing excitotoxic calcium-induced injury.(7)

The neuroprotective effect of magnesium sulphate is cited to be related to blocking of the calcium processes and thus acting as a vasodilator, it may inhibit or delay ischaemic cell death during and after cerebral ischaemic events.

Magnesium sulphate may reverse the harmful effects of hypoxic/ischaemic brain injury by blocking N-methyl-D-aspartic acid (NMDA) receptors, acting as a calcium antagonist and reducing calcium influx into the cells. This in turn protects the cell from the deleterious effects of calcium and prevents apoptosis and necrosis from occurring. (8)

The results from five randomised control trials (RCTs) from 1997-2008, were published in a meta-analysis. These studies are of key significance because of their impact on establishing the role of magnesium sulphate and neuroprotection. The results of these studies do not uniformly report that there is an improved outcome with the use of magnesium sulphate. The short-term outcome was aimed at assessing if the infant died or if on discharge there was existent sequelae of IVH, seizures, NEC, bronchopulmonary dysplasia (BPD), as well as the need for mechanical ventilation. The long-term outcome was to assess for the presence and severity of cerebral palsy.

The MagNet trial, the first RCT done in 1997 published interim safety data because of high adverse outcomes found in foetuses exposed to magnesium sulphate. A loading dose of 4g magnesium sulphate was given in this trial. Further findings published in 2002 suggested that in women administered magnesium sulphate, the higher the umbilical cord magnesium sulphate levels in the neonate, the more severe the perinatal outcome. The ACTOMgSO_4 trial reported a non-significant reduction in cerebral palsy and death {RR-0.85, 95% C.I- 0.55-1.31}. A 4g bolus of magnesium sulphate over 20 minutes, followed by 1g/hour until birth was given in the ACTOMgSO_4 trial. However, a significant reduction in the prevalence of gross motor dysfunction was noted. The PREMAG trial, in which a 4g bolus of magnesium sulphate given over 30 minutes was a French study that reported on primary outcomes of infant death or white matter injury on cranial ultrasound.(9) Cerebral palsy and gross motor dysfunction was evident in patients.

Secondary outcomes which included follow-up of children at 2 years of age did not show a significant difference in rates of cerebral palsy {RR-0.80, 95% C.I-: 0.63-1.22} gross motor dysfunction or combined death and cerebral palsy between the control and treatment groups.

The BEAM study, which was done in the United States of America (USA) used a different prescribing regimen; 6 g loading dose as compared to 4 g loading dose. The study reported a significant difference in outcome between the placebo and magnesium sulphate for the occurrence of severe cerebral palsy [148/1,188 (12.5%) vs 173/1,256 (13.8%), RR-0.91; C.I; 0.85-1.05] but not for the milder forms of cerebral palsy. The primary outcome in the MAGPIE trial looked at mortality of the baby before hospital discharge and a combined outcome of death or neurosensory disability at 18 months of corrected age. Analysis of secondary outcome reported a lower risk of death or cerebral palsy [182/785 (23.2%); RR-1.07{0.90- 1.28}] at 18 months of age. (10)

The outcomes from the use of magnesium sulphate were varied in these trials. These studies do not comment on the measures put in place for the measurement of magnesium levels. When magnesium sulphate is administered at recommended dosages and with proper monitoring, it is not associated with more harmful outcomes.

The reference ranges of serum magnesium levels that are accepted as normal ranges are between 0.7-1.0mmol/l. However, there is no clarity on the optimal serum magnesium range.

Magnesium sulphate has a narrow therapeutic range; therefore, caution is necessary when deciding on the dose administered. During magnesium sulphate infusion foetal monitoring is continuous via the use of a cardiotocography (CTG) because of the risk of respiratory depression in the mother which may affect the foetus. However, adverse outcomes of the neonate have not been conclusively proven.

Das and Chauduri et al observed that the neonatal effects of magnesium in their study occurred primarily within the therapeutic ranges and were not solely attributable to excessive levels of magnesium in the maternal circulation. (11)

There is currently a paucity of data relating to the immediate clinical outcomes of magnesium sulphate given antenatally to mothers especially with regards to other co-morbidities that a preterm is predisposed to. There is limitation in assessing the possible effects of toxicity related to magnesium sulphate.(12)

The current protocol for the administration of magnesium sulphate at the Chris Hani Baragwanath Academic Hospital is for the prevention of seizures in mothers with pre-eclampsia/eclampsia as well as for neuroprotection in the at-risk population and not routinely for tocolysis. The protocol in operation entails the use of magnesium sulphate at a dosage of 4g into 200mls normal saline, which is administered as a stat dose and the infusion can run over 30 minutes.

The maintenance dose of 10g magnesium sulphate into 200mls of normal saline @20mls/hour, equivalent to 1g/hr is then given until delivery.

This regimen is usually given to mothers at the risk of seizures with an estimated gestational age of less than 36 weeks (EGA) and for neuroprotection in at risk babies. This protocol has been in use in the hospital since 2010. The administration of magnesium sulphate requires intensive monitoring. The high care in the obstetrics unit can house 6 patients at a time. Thus, not all at risk moms will receive magnesium sulphate. There will be a subset of neonates who are born to at risk moms who would not have received magnesium sulphate.

The alternate regimen often used is to dilute magnesium sulphate 4g (8ml) into 12ml normal saline and given intravenously over 4 minutes, with 5g intramuscularly into each buttock, with 1ml 1% lignocaine. The maintenance dose is 5g intramuscularly 4 hourly in alternate buttocks.

The measures put in place to monitor toxicity of magnesium sulphate in the mother include the clinical monitoring of respiratory rate, urine output > 100mls in the preceding 4hrs, as well as the presence of deep tendon reflexes, most especially the patella reflex. It could also result in pulmonary oedema and cardiac arrest in overdose.

The rationale of the study is to evaluate the impact of the antenatal administration of magnesium sulphate on low birth infants whose mothers received magnesium sulphate. The study will be conducted in the Neonatal Unit at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto. The hospital is the 3rd largest hospital in the world and has the capacity of approximately 3,200 beds. It is a tertiary care teaching hospital for the University of the Witwatersrand. The neonatal unit has a bed capacity of 180 beds with 18 neonatal intensive care beds.

This study also aims to bridge the knowledge gap between the effectiveness and safety profile of magnesium sulphate in preterm and small for gestational age infants; the GA below which this therapy should be offered as well as the optimal loading and maintenance doses. (13)

2. AIM OF THE STUDY

The aim of this study is to assess if magnesium sulphate improves the neonatal outcome in LBW infants whose moms received magnesium sulphate as part of clinical care.

3. OBJECTIVES OF THE STUDY

- To identify the prevalence of patients whose mothers received magnesium sulphate, that were referred to the neonatal unit.
    - The proportion of these patients who were LBW
- To identify the maternal characteristics of the mothers who received $MgSO_4$
- To determine the indication for prescribing MgSO4 in the mothers who received $MgSO_4$;
- To determine the characteristics of LBW neonates born to mothers who received magnesium sulphate and compare it to the LBW neonates born to moms who did not receive $MgSO_4$.
- To compare the morbidity of LBW infants whose mothers were given $MgSO_4$ with those infants of similar weight who did not receive $MgSO_4$.

Morbidities as identified by-:

- Respiratory diagnosis and interventions such as ventilator support
- Seizures
- IVH (grade as defined by Papile)
- Post haemorrhagic hydrocephalus (PHH)
- NEC (defined by modified Bells staging)
- ROP (defined by the ETROP study)
- Other neonatal comorbidities e.g., BPD
- Thrombocytopaenia (defined as a platelet count < $150X10^9$/l)
- The time to normalisation of the platelet count
- Neurological compromise e.g., lethargy

- To describe the magnesium levels of the LBW infants born to mothers who received $MgSO_4$.
- To determine the number stillbirths (macerated and fresh stillbirths) born to mothers who received $MgSO_4$.
- To compare the short-term outcome in terms of death or discharge and length of stay for the LBW infants whose mothers received $MgSO_4$ compared to those LBW infants whose moms did not receive $MgSO_4$.

4. STUDY POPULATION

- **Inclusion criteria:** will be inclusive of all;
  - LBW New-born/Infants admitted to CHBAH
  - Mothers who received magnesium sulphate antenatally according to the CHBAH protocol
- **Exclusion criteria:** will include.
  - Out born infants whose mothers received $MgSO_4$
  - LBW infants with congenital abnormalities whose mothers received $MgSO_4$
  - LBW infants with chromosomal abnormalities whose mothers received $MgSO_4$
  - Infants with incomplete data

4. STUDY METHODS.

5.1 STUDY DESIGN

This is a retrospective case-control record review to describe the outcome of babies whose mothers received magnesium sulphate antenatally; either as treatment for pre-eclamptic toxaemia or for tocolysis as well as babies whose mothers did not receive magnesium sulphate. Neonatal information is collected prospectively for clinical audits and entered into a

Redcap database. Patients will be identified through the REDCap database. All LBW infants delivered during the period January 2016 - December 2017 with a birthweight ≤ 2500g will be included in the study. As the gestational ages are not always correctly captured the birthweight will be used as a proxy for the gestational age. Thus, for the purpose of the study we will use the birthweight ≤2500g as a proxy for preterm. This cohort will be filtered according to the LBW infants who received $MgSO_4$ and those LBW infants who did not receive $MgSO_4$. Data will be collected according to Appendix B. Information will be checked for completeness and verified.

5.2 DATA COLLECTION

The data collected will be over a period of two years from January 2016 to December 2017. The Recap Neonatal database will be mined to identify the preterm patients that were admitted to the Neonatal unit during the study period. The patients that received Magnesium sulphate who were admitted to the Neonatal unit will be identified. These will be the cases. The neonates that were preterm (LBW) who did not receive $MgSO_4$ will be the controls. The data will be anonymized, and the identifiers will be kept separately from the variables collected.

5.2.1 Sample Size:

There was a total of 5266 low birthweight infants reviewed in the neonatal unit during the study period. Of these 1805 LBW infants were admitted to the neonatal unit. Two hundred and sixteen (216) of the LBW infants received magnesium sulphate (cases) 1589 with a birthweight ≤ 2500g did not receive magnesium sulphate (controls). Three thousand four hundred and sixty-one (3461) LBW infants who were reviewed in the neonatal unit were discharged from the labour ward nursery.

5.3 DATA ANALYSIS

The data will be entered into an excel spreadsheet and imported into STATA for analysis. Categorical variables will be reported as proportions. Comparison between categorical variables will be done using the Chi-squared or Fishers' exact test where appropriate. Continuous variables will be reported as means or medians depending on the distribution of the data. The Students t-test will be used to compare means whereas the Mann-Whitney U

test will be used to compare medians. Logistic regression analysis will be undertaken to analyse variables associated with outcomes and complications in the two groups. A p-value of <0.05 will be considered statistically significant.

6. ETHICS

Permission to conduct the study will be obtained from the CEO of Chris Hani Baragwanath Academic Hospital; the National Department of Health (NDoH); the Heads of Departments of Obstetrics; Paediatrics; Head of Unit- Neonates as well as the matrons of the Maternity wards and neonatal unit.

The study will be approved by the Human Ethics Committee (HREC) of the University of Witwatersrand prior to its commencement.

The data will be anonymized with a study number. Identifiers will be kept separately from the populated dataset.

Data will be available to principal investigator and the supervisors.

7. Gant chart.

	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Literature review	■	■										
Preparing protocol	■	■										
Protocol assessment		■	■	■								
Ethics application				■								
Collecting data					■	■	■					
Data analysis								■				
Writing up thesis									■	■		
Writing up paper											■	■

8. FUNDING.

Minimal cost is anticipated, and the research will be self-funded.

9. LIMITATIONS

This is a retrospective study, so it is expected that not all maternal and neonatal information is complete and readily available.

A possible limitation is also that the timing of magnesium sulphate administration as well as a detailed documentation of the indication for the administration of magnesium sulphate might not be succinctly stated.

Appendix A: - CHBAH PROTOCOL FOR MAGNESIUM SULPHATE.

GIVING MAGNESIUM SULPHATE*

Loading dose: Add magnesium sulphate 4 g to 200 mL normal saline and run the infusion rapidly.

Maintenance dosage: Add magnesium sulphate 10 g to 200 mL normal saline and run the infusion at 20 mL/hour, equivalent to 1 g/hour.

Alternative regimen: Dilute magnesium sulphate 4 g (8 mL) in 12 mL saline and give IV over 4 minutes, with 5 g IM in each buttock with 1 mL 1% lidocaine (total 14 g). Maintenance is 5 g IM 4 hourly, in alternate buttocks, with lidocaine.

Precautions during magnesium sulphate infusion

Maintenance doses should only be continued if the following hourly observations are made and confirmed:

Presence of patellar reflexes, the respiratory rate is 12 breaths/minute, and Urine output is 100 mL in the last 4 hours

Treatment of suspected overdose

The symptoms and signs of overdose are a feeling of extreme weakness, decreased respiratory rate, and absent tendon reflexes. Take blood for magnesium level. Give 10% calcium gluconate 10 mL IV slowly, then observe closely.

Blood magnesium levels:

Normal range 0.7-1.0 mmol/L, therapeutic at 1.25-3.25, absent reflexes at 4-5, respiratory depression at 6-8, cardiac arrest at >15 mmol/L

Appendix B: Data collection form

Study no: _____

Maternal details

Age_____ Parity_____ Gravidity_____

Maternal medical condition:

Antenatal care: yes____, no___ _; HIV status: _____; Steroids: yes_____, no_____;

Hypertension: _____, Diabetes: _____, Cardiac_____,

Eclampsia: _____, HELLP Syndrome: _____, Pre-Eclampsia _____

Magnesium sulphate: yes_____, no_____, if no reason:

_____

Loading Dose: _____mg, Infusion dose: _____mg, Duration: _____hours

Infant details:

Place of birth: inborn/other hospital/clinic/BBA, Mode of delivery: NVD/C/S/ Breech/Vacuum

If C/S indication:

_____

Resuscitation at birth: yes_____, no_____

BMV_____, CPR_____, Intubation_____, _Adrenaline

ABG: pH_____, pO_2_____, pCO_2_____, lactate_____, HCO_3_____, BE_____

APGAR score: 1 min _____, 5 min _____, 10 min _____

Age at admission: _____/_____/_____

Gestational age: _____ weeks, Gender Male/Female/Ambiguous

Birth weight: -_____g, HC: _____cm, Length: _____cm

Main diagnosis: RDS; yes_____, no, ____, NEC yes_____, no, _____, IVH yes_____, no, _____

if Yes Grade _____; Seizures: yes_____, no, _____, Asphyxia yes_____, no, _____, BPD yes_____, no, _____; ROP yes_____, no, _____, lethargy yes_____, no _____, hypotonia yes____, no _____.

Other Diagnosis 1) _____, 2) _____, 3) _____

4) _____, 5) _____, 6) _____

Sepsis: yes_____, no, _____ Date of Sepsis: _____/_____/_____

Early onset sepsis: _____, late onset sepsis: _____,

Organism cultured: _____

Initial FBC: WCC_____ $X10^9$/L, Hb _____g/dl, Platelets: _____ $X10^9$/L,

Repeat FBC date _____/_____/_____ (within the first week) WCC_____ $X10^9$/L, Hb _____g/dl, Platelets: _____ $X10^9$/L,

Magnesium: _____ mmol

Intervention:

Ventilated: yes_____, no_____. Type of ventilation: HFOV, _____IPPV_____, CPAP_____,

Surfactant: yes_____, no_____.

Fluid boluses: yes_____, no_____, Saline -_____, FFP_____, Blood_____

Hypotension: yes_____, no_____; Inotropes: yes_____, no_____

Dopamine _____, Dobutamine_____, Adrenaline_____, Hydrocortisone _____

Complications:

Seizures: yes____, no____, Antiepileptic drugs: phenobarbitone/Keppra/dormicum/phenytoin/lidocaine

Maintenance treatment: _____, _____

Outcome:

BPD: Grade _____, Discharged Home on oxygen: Yes_____, No_____

IVH Grade: _____, Post haemorrhagic hydrocephalus (PHH) Intervention VSG_____, VPS ____

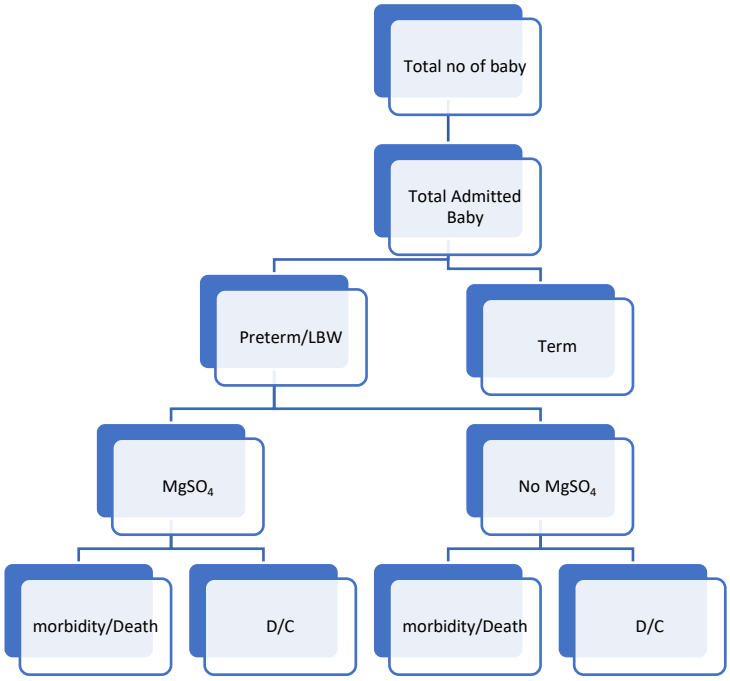
ROP Stage _____

NEC Grade _____, Interventions pencil drain _____, laparotomy _____

Discharge_____, Death_____. Date of outcome: _____/_____/_____

Length of Stay _____ days

FLOW DIAGRAM.



***Morbidity-: inclusive of;**

- Seizures

-IVH (grade as defined by Papile)

- Post haemorrhagic hydrocephalus

- Thrombocytopenia (platelets <150 x 10^9/l)

- NEC

- ROP

- Neurological compromise e.g., lethargy

-Respiratory diagnosis and interventions

- Other neonatal comorbidities e.g., BPD, etc

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Appendix B: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Temitope Olawale Odubunmi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190501

NAME: (Principal Investigator)	Dr Temitope Olawale Odubunmi
DEPARTMENT:	Peadiatrics and Child Health Chris Hani Baragwanath Academic Hospital Diepkloof, Soweto
PROJECT TITLE:	The effect of magnesium sulphate on clinical outcomes of low birth weight babies at the Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	31/05/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Firdose Nakwa and Dr Letlhogonolo Sepeng
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/07/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

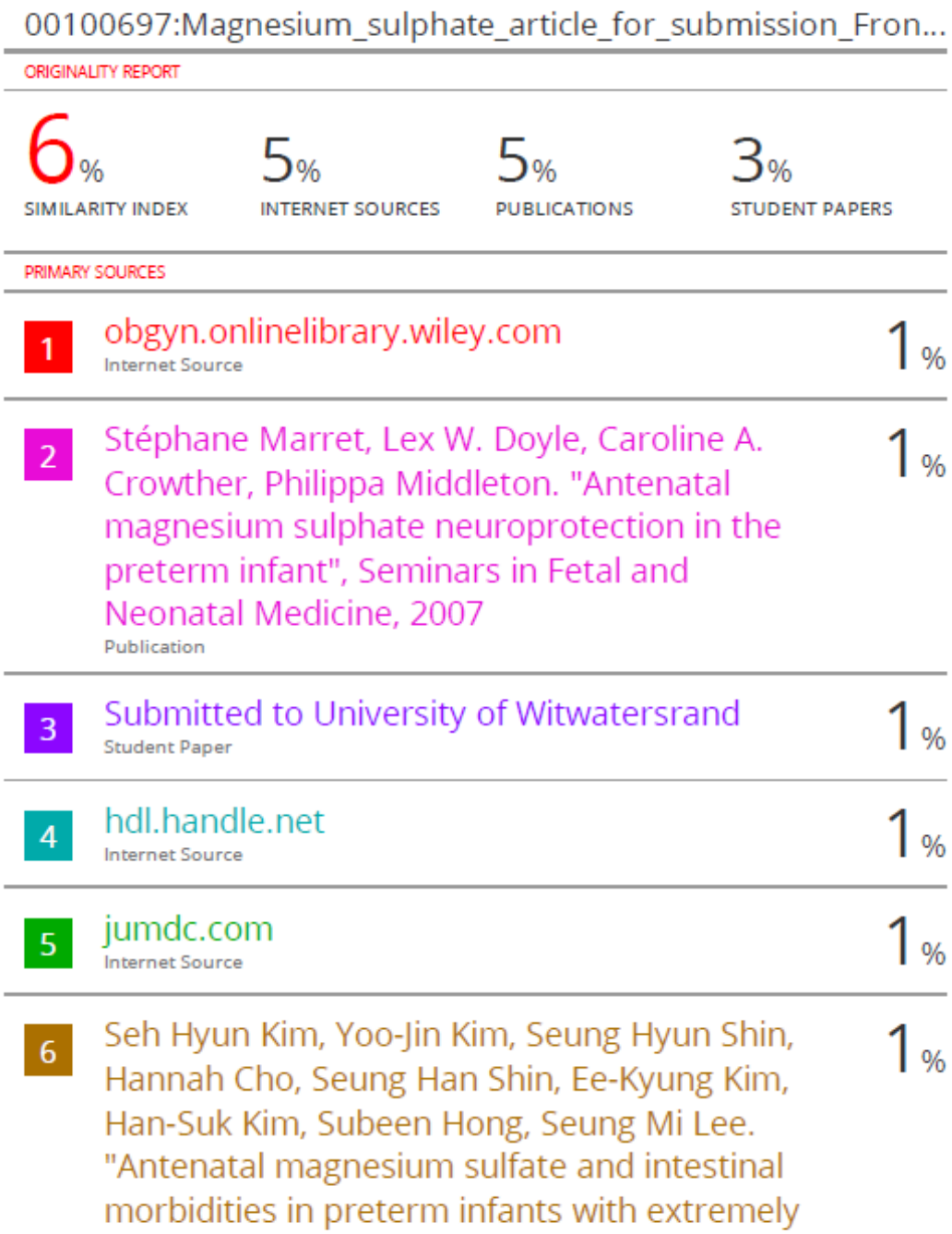
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 219 University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed May and will therefore be due in the month of May each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

08/07/2019.
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Plagiarism report



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