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Evaluation of the Fetal Neuroprotection Protocol with Magnesium Sulphate in a University Hospital in Burkina Faso

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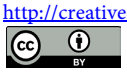

Abstract

Introduction: Prematurity continues to stand as a major public health issue worldwide and more particularly for low incomes countries like Burkina Faso. Indeed, it is the main cause of high death rate and infant morbidity, neurologic deficiencies being one of them. **Objective**: From March 1st to September 30th, 2020, evaluate the fetal neuroprotection protocol using sulfate magnesium during births before thirty-three (33) weeks of amenorrhea at the University Health Centers (UHC) of Yalgado Ouedraogo and Bogodogo in Ouagadougou, Burkina Faso. **Patients and Methods:** It was a prospective cohort survey, exposed or unexposed. The exposed ones are from the UHC of Yalgado Ouedraogo, while the unexposed ones are from the UHC of Bogodogo. Analysis of the results showed 87 newborns from the exposed and 180 from the unexposed. The mortality rate, as well as neonatal neurologic complications, was higher with unexposed than with exposed. Although antenatal exposure to magnesium sulfate was not statistically associated with mortality and morbidity in newborns at a threshold of 0.05%, it has shown an overall good neurological prognosis in newborns exposed. **Conclusion:** A survey of a large sample of the population would be relevant in order to better assess the determinants of this influence. **Proposition:** In light of the results, the use of magnesium sulfate for neuroprotective purposes could be considered in our countries.

Keywords

Premature Delivery, Fetal Neuroprotection, Sulfates Magnesium, UHC of Yalgado Ouedraogo, UHC of Bogodogo, Burkina Faso

1. Introduction

Preterm birth is a source of great morbidity, such as neurological deficits and a predisposition to long-term chronic illnesses, and thus represents an important cause of loss of human potential in survivors [1].

In low-income countries such as Burkina Faso, half of all babies born at 32 weeks of amenorrhoea die due to a lack of feasible and affordable care [2]. Infant mortality and morbidity due to prematurity can be reduced by providing appropriate interventions to the mother who is at risk of imminent preterm delivery [3]. Magnesium sulphate given in imminent preterm delivery has been shown to be effective in preventing the neurological sequelae [4] [5] [6]. In sub-Saharan Africa, few studies have been conducted on this subject, and we have undertaken this study in Burkina Faso.

2. Patients and Methods

We conducted a multicentre study in the Department of Gynaecology-Obstetrics of the Yalgado Ouédraogo University Hospital, the Department of Gynaecology-Obstetrics and Reproductive Medicine of the Bogodogo University Hospital, and the Neonatology Department of the UHC-YO. This was a prospective exposure-non-exposure cohort study that took place over a period of seven (07) months from 1 March 2020 to 30 September 2020. Our study population consisted of all patients with imminent preterm delivery between 28 and 32 SA and 6 days and their newborns in the Yalgado Ouédraogo and Bogodogo University Hospitals of Ouagadougou between 1 March 2020 and 30 September 2020. Thus, they were included in our study.

2.1. For the Exposed Group

Patients at the Yalgado Ouédraogo University Hospital (where the brain maturation protocol is applied) who presented an imminent risk of preterm delivery between 28 SA and 32 SA + 6 days, whether it was a single or multiple fetal pregnancy, who received $MgSO_4$ for the purpose of fetal neuroprotection and in whom we collected informed consent to participate in this study.

Newborns born to mothers who did not present malformations and whose delivery took place at the UHC Yalgado Ouédraogo.

2.2. For the Unexposed Group

UHC-Bogodogo patients (where the brain maturation protocol is not yet applied) who presented an imminent risk of preterm delivery between 28 SA and 32 SA + 6 days, whether single or multiple fetal delivery, who did not receive $MgSO_4$ for the purpose of fetal neuroprotection and in whom we collected informed consent to participate in this study.

Neonates from the mothers, who did not have any known chromosomal or genetic abnormalities or malformations and whose delivery took place at the

Bogodogo University Hospital.

Magnesium sulphate-exposed patients were progressively recruited from the UHC-YO to be matched with unexposed patients from the UHC of Bogodogo. For each exposed patient, two unexposed patients of the same type were recruited according to matching criteria such as female age and gestational age at 05 days interval.

Patients who were at imminent risk of preterm delivery between 28 and 32 SA and 6 days with fetal death in utero and those with a contraindication to the use of magnesium sulphate [7] were not included in our study. The study was conducted according to the following protocol.

2.3. For the Exposed Group

Administration of magnesium sulphate to patients:

- Initial dose: 04 gr or 8 ml of 50% $MgSO_4$, administered intravenously (IVL) slowly over 30 minutes;
- maintenance dose: then 04 gr or 8 ml of $MgSO_4$ 50% diluted with 1 ml of xylocaine 2% intramuscularly (IM) every 4 hours for 12 hours.

2.4. Maternal Monitoring [7]

Post-delivery: The neonates were examined at birth, at day 7, and at day 28. At D7 and D28, this examination was performed by a paediatrician, looking for neurological disorders, and was completed with a transfontanellar ultrasound, performed by a radiologist. This follow-up was performed for all newborns included in the cohort.

For the unexposed group: the process was the same, except for the administration of magnesium sulphate.

We studied the following dependent variables: neonatal mortality (during the first 28 days of life of the newborn) and neonatal morbidity: Neurological abnormalities of the newborn observed at day 7 and day 28: tonus anomaly, archaic reflex anomaly, consciousness anomaly.

We had a single exposure variable, which was magnesium sulphate, coded yes for children who received it antenatally and no for children who did not.

Epidemiological, clinical, therapeutic, and neonatal parameters were used as covariates to control for their effect on the occurrence of our events of interest and thus isolate the true effect of antenatal magnesium sulphate administration.

The odds ratio (OR) was the measure of association used in this analysis by examining the direction of association, strength, precision, and significance. The bottom-up stepwise method was used for the inclusion of independent variables in the model. All variables that had a p-value of less than 0.2 in the univariate analysis were included progressively in the multivariate model with an assessment of the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). The significance level retained in multivariate was $p < 0.05$.

Ethical and deontological considerations were respected in our study.

3. Results

3.1. Epidemiological Aspects

3.1.1. Frequency

3491 women gave birth at the CHU-YO during our study period, which lasted from 1 March 2020 to 30 September 2020. Of these, 189 gave birth between 28 and 36 weeks' gestation + 6 days, *i.e.*, a preterm birth rate of 5.4%. During the same period, 3824 women gave birth at the CHU-Bogodogo and 219 between 28 SA and 36 SA + 6 days, *i.e.*, a preterm delivery frequency of 5.7%.

3.1.2. Socio-Demographic Characteristics

The average age of exposed women (Table 1) was 26.4 years, with extremes of 15 and 39 years, and that of unexposed women was 25.9 years, with extremes of 16 and 43 years. The majority of exposed and unexposed women were housewives (54.3% and 63.6%); married (78.6% and 77.1%); not in school (31.4% and 28.6%); and living in urban areas (61.4% and 76.4%).

Table 1. Distribution of patients according to socio-demographic characteristics.

Socio-demographic characteristics	Exposed (n = 70)		Unexposed (n = 140)	
	Number	Percentage	Number	Percentage
Age range				
<25	29	41.4	68	48.6
[25 - 35[	32	45.7	57	40.7
≥35	9	12.9	15	10.7
Profession				
Housewife	38	54.3	89	63.6
Tradeswoman	14	20.0	16	11.4
pupil	4	5.7	9	6.4
Student	4	5.7	10	7.1
Informal	4	5.7	6	4.3
Farmer	3	4.3	2	1.4
Civil servant	3	4.3	8	5.7
Educational level				
Primary	13	18.6	37	26.4
Secondary	11	15.7	42	30
superior	9	12.9	11	7.9
Literate	15	21.4	10	7.1
Not in school	22	31.4	40	28.6
Marital status				
Married	55	78.6	108	77.1
Free Union	10	14.3	20	14.3
Divorced	3	4.3	1	0.7
single	2	2.8	11	7.9
Origin				
Urban	43	61.4	107	76.4
Rural	27	38.6	33	23.6

3.2. Clinical Aspects

The most frequent reason for admission was the threat of premature delivery (PAD), 51.4% in exposed women and 62.1% in unexposed women. Both exposed and unexposed women were admitted by referral (68.6% and 80%), were pauci-gravida (37.1% and 42.9%) or nulliparous (32.9% and 38.6%). Pregnancy was monofetal in both exposed and unexposed women (77.1% and 74.3%). The distribution of patients according to clinical aspects is presented in Table 2.

3.3. Therapeutic Aspects

3.3.1. Treatment with Magnesium Sulphate$_4$

Of the exposed women, 75.7% received magnesium sulphate administration in the delivery room, 14.3% received a course of treatment for severe pre-eclampsia or eclampsia, 91.4% were monitored, and 67.1% had minor side effects (Table 3).

Table 2. Distribution of patients according to clinical aspects.

Clinical aspects	Exposed (n = 70)		Unexposed (n = 140)	
	Number	Percentage	Number	Percentage
Reason for admission				
threat of premature delivery	36	51.4	87	62.1
Premature rupture of membranes	14	20	25	17.9
Metrorrhagia	3	4.3	5	3.6
Other*	17	24.3	23	16.4
Number of gestures				
Primigest	19	27.1	46	32.9
Pauci gest	26	37.1	60	42.9
Multigest	19	27.1	31	22.1
Large Multigest	6	8.6	3	2.1
Parity number				
Nulliparous	23	32.9	54	38.6
Primiparous	22	31.4	49	35
Multiparous	21	30	35	25
Large multiparous	4	5.7	2	1.4
Preterm delivery				
Yes	8	11.4	10	7.1
No	62	88.6	130	92.9
Pregnancy type				
Single fetal	54	77.1	104	74.3
Twin	15	21.4	32	22.9
Trimellar	1	1.4	4	2.9

Continued

Gestational age				
[28SA - 29SA[	1	1.4	7	5
[29SA - 30SA[	4	5.7	10	7.1
[30SA - 31SA[	18	25.7	26	18.6
[31SA - 32SA[	15	21.4	26	18.6
[32SA - 33SA[	32	45.7	71	50.7
Etiologies of prematurity				
Premature rupture of membranes	22	31.4	56	40
Placenta previa	5	7.1	5	3.6
Intrauterine growth retardation	4	5.7	1	0.7
Gestational hypertension	1	1.4	7	5
Pré-éclampsia	8	11.4	0	0
HELLP Syndrome	2	2.9	0	0
Retroplacental Hematoma	2	2.9	1	0.7
Fetal heart rhythm abnormality	0	0	5	3.6
Not found	**12**	17.1	22	15.7
other*	14	20	43	30.7

Table 3. Distribution of patients according to aspects of magnesium sulphate treatment (n = 70).

$MGSO_4$ Treatment	Number	Percentage
Place of administration of $MgSO_4$		
Pre-labour room	4	5.7
Delivery room	53	75.7
Pathological Pregnancy Unit	13	18.6
Cures for cerebral maturation		
Total number of complete cures	22	31.4
Total number of incomplete cures	38	54.3
Cure for severe pre-eclampsia/eclampsia	10	14.3
Monitoring		
Yes	64	91.4
No	6	8.6
Side effects		
Minor	47	67.1
Moderate	3	4.3
management of side effects and signs of overdose		
Symptomatic treatment	46	65.7

3.3.2. Delivery Route

The route of delivery (Table 4) was mostly low in the exposed (71.4%) and unexposed (83.6%) women.

Other treatments received besides $MGSO_4$.

Corticosteroids were administered in 92.9% of cases (Table 5).

3.4. Neonatal Results

Comparison of neonate sexes, birth weights, and anthropological parameters.

A total of 87 neonates were born to exposed women and 180 to unexposed women. They were predominantly female in the exposed group (56.3%) and male in the unexposed group (56.1%). The average birth weight was 1544.1 g in the exposed group and 1401.7 g in the unexposed group. Table 6 shows the distribution of newborns according to sex, birth weight, and anthropological parameters.

Table 4. Distribution of patients by route of delivery.

Delivery route	Exposed		Unexposed	
	Number	Perrcentage	Number	Percentage
vaginal delivery	50	71.4	117	83.6
Caesarean section before labour	15	21.4	11	7.9
Caesarean section during labour	5	7.1	12	8.6
Total	**70**	**100.0**	**140**	**100.0**

Table 5. Distribution of exposures according to other treatments received outside $MGSO_4$ (n = 70).

Other treatments	Number	Percentage
Corticosteroids	65	92.9
Tocolytics	35	50
antihypertensive drugs	15	21.4
Antibiotics	14	20
Spinal anaesthesia	10	14.3
Blood transfusion	5	7.1
Oxytocics	5	7.1
General anesthesia	2	2.9
Anti-malaria	2	2.9
Analgesics	1	1.4
Misoprostol	1	1.4
Anti-anemics	1	1.4

Table 6. Distribution of newborns according to sex, birth weight, and anthropological parameters.

Characteristics of newborns	Exposed (n = 87)		Unexposed (n = 180)	
	Number	Percentage	Number	Percentage
Gender				
Femal	49	56.3	79	43.9
Male	38	43.7	101	56.1
Birth weight (grams)				
Moyen	1544.1		1401.7	
<1500	27	31.1	96	53.3
[1500 - 2500]	60	68.9	84	46.7
Anthropological parameters (centimeter)				
Middle cranial perimeter	28.3		28.3	
Middle thoracic perimeter	26.1		25.9	
average size	41.9		41.1	

The Apgar score at the 10th minute was greater than or equal to seven in 96.6% of the exposed and 92.8% of the unexposed, and we did not observe any significant difference in the Apgar score according to the use or not of $MgSO_4$ when it was greater than or equal to seven. We also did not find significant differences in the resuscitation of neonates at birth. Indeed, newborns were resuscitated in 21.8% of the exposed and 21.2% of the unexposed.

Hospitalization after transfer to pediatrics was necessary for 35.6% of exposed and 54.5% of unexposed patients.

On day 7, neurological disorders were reported in 4.6% of exposed patients and 10.6% of unexposed patients.

At day 21, neurological problems were reported in only 1.1% of unexposed individuals.

The outcome of the management of newborns was favourable for 77% of the exposed and 63.9% of the unexposed. The mortality rate was 19.5% in the exposed and 30% in the unexposed.

Effects of antenatal exposure to magnesium sulphate on preterm newborns in univariate analysis.

Antenatal exposure to magnesium sulphate was not statistically associated with neonatal mortality at a threshold of 0.05%. However, gestational age between 28 and 32 weeks' gestation and the existence of morbidity were risk factors for mortality.

In multivariate analysis, antenatal exposure to magnesium sulphate was not statistically associated with morbidity in preterm newborns at a threshold of 0.05%. However, having divorced parents, a gestational age between 28 and 32 SA, and a birth weight of 1500 g were risk factors for morbidity in our cohort, whereas having been resuscitated reduced the risk of morbidity (Table 7).

Table 7. Factors associated with morbidity in preterm newborns in multivariate analysis.

Variable	OR	IC à 95%		P
Marital status				
Single	1.19	0.31	4.75	0.798
Divorced	2.3E+08	2.3E+08	2.3E+08	**<0.001**
Free union	1.21	0.41	3.51	0.732
Gestational age (Weeks of Amenorrhea)				
[28 - 29[	6.4E+08	1.3E+08	3.0E+09	**<0.001**
[29 - 30[	6.2E+08	1.2E+08	3.1E+09	**<0.001**
[30 - 31[	3.9E+08	7.9E+07	1.9E+09	**<0.001**
[31 - 32[	1.9E+08	1.9E+08	1.9E+08	**<0.001**
Delivery weight < 1500 g				
Yes	1.27	1.12	3.56	**0.001**
No				
APGAR score < 7				
Yes	2.4E-15	0	nd	0.997
No				
Intensive care				
Yes	0.35	0.15	0.85	**0.021**
No				

4. Discussion

The aim of our study was to evaluate the protocol for fetal neuroprotection with magnesium sulphate before 33 weeks of amenorrhea. During the course of the study, a number of limitations and biases were encountered, namely: its hospital-based nature compared to the general population; the low rate of complications and mortality in the sample, making it more difficult to draw statistical inferences about the influence of the fetal neuroprotection protocol with magnesium sulphate before 33 weeks of amenorrhoea on pregnancy outcomes; Despite these limitations and biases, we have arrived at results that we have commented on and compared with the literature.

4.1. A Descriptive Study of the Sample Base

4.1.1. Frequency

During our study period, the frequency of preterm delivery was 5.4% and 5.7% of deliveries at UHC-Yalgado Ouédraogo and UHC-Bogodogo, respectively. Our frequency is lower than that of Mokuolu *et al.* [8] in Nigeria in 2010, Hounpkonou *et al.* [9] in Benin in 2017 and Muchie *et al.* [10] in Ethiopia in 2020, which were respectively 11.8%, 17.9% and 10.5%. This difference in frequency could be explained by under-reporting of preterm births in our working context.

4.1.2. Socio-Demographic Characteristics of the Study Population

Socio-demographically, our results reflect the data of the general population in Burkina Faso, which is very young and fertile, with a low socio-economic and educational level [11]. According to the findings of Chang *et al.* [12], there is a consistent relationship between low education and preterm delivery. According to Ferrero DM *et al.*, who conducted work on preterm births through an individual participant analysis of 4.1 million births, the increased risk of preterm birth was associated with poverty and low education [13].

4.2. Clinical Aspects

4.2.1. Reasons for Admission

The patients in the study population were selected on the basis of having had a preterm birth. This explains why the most frequent reason for admission was the threat of preterm delivery: 51.4% of exposed patients and 62.1% of unexposed patients. Our results are in line with those of Crowther *et al.* [4], in whom the main reason for delivery was preterm labour (63%).

4.2.2. Parity

In our study, the majority of patients (exposed and unexposed) were nulliparous (32.9% and 38.6%). Our result is comparable to that of Mcpherson *et al.* [14] in 2014 in the USA, who reported a majority of nulliparous women (51.1%). Other authors consider nulliparity as a risk factor for prematurity [15] [16].

4.2.3. Etiology of Preterm Delivery

Premature rupture of membranes was the most common cause of prematurity in both exposed and unexposed women (31.4% and 40%, respectively). One of the main causes of spontaneous preterm delivery is the presence of intra-amniotic inflammation, with a prevalence of about 30% in women with preterm labour and intact membranes and up to 60% in women with preterm rupture of membranes before the onset of labour [17] [18].

4.3. Therapeutic Aspects

4.3.1. Treatment of $MGSO_4$

During our study, 85.7% received a course of magnesium sulphate in the context of brain maturation, and the majority (75.7%) in the delivery room. In the study by Millochau J-C, *et al.* [19], magnesium sulphate was prescribed for 91.5% of patients, 82.4% of whom received it in the delivery room. Our results corroborate this data. The tolerance of magnesium sulphate administered according to the protocol in our study was excellent since no serious side effects (maternal death, cardiac arrest, or prolonged assisted ventilation) were observed. Our data on tolerability are consistent with those of Gibbins *et al.* [20] and Bouet *et al.* [21], who found no maternal morbidity attributable to treatment.

4.3.2. Other Treatments Received Outside of $MGSO_4$

Apart from $MGSO_4$, 50% of cases received tocolysis; Marret *et al.* [22] found

68% of women tocolysed in the $MgSO_4$ group. Gibbins *et al.* [20], who also analysed this criterion, found that 49.4% of eligible patients were tocolysed.

In contrast to tocolysis, antenatal corticosteroid therapy should be of interest to all patients at risk of delivery before 34 SA. A standard course of treatment consists of 2 injections.

Corticosteroids were administered in 92.9% of the patients in our study. These results are in agreement with the literature [22] [23].

The delivery route was mostly low in exposed (71.4%) and unexposed (83.6%) women. The obstetrical protocols in force in Burkina Faso codify the choice of delivery route. Apart from vital emergencies for the mother and/or the newborn, all public health facilities are equipped to carry out vaginal delivery under optimal conditions. In our study, a low rate of situations required the use of caesarean section.

4.3.3. Neonatal Outcomes

The average birth weight was 1544.1 g in the exposed group and 1401.7 g in the unexposed group. Neonates born to the unexposed had a lower mean birth weight. The main risk of prematurity is low birth weight. The main risk of prematurity is low birth weight, since the pregnancy is not full term and the organs of the fetus are not sufficiently matured, thus justifying a low birth weight. We did not observe any significant difference in the Apgar score according to the use or not of $MgSO_4$ when it was greater than or equal to seven. We also did not find significant differences in the resuscitation of neonates at birth. Indeed, newborns were resuscitated in 21.8% of the exposed and 21.2% of the unexposed. Our results are in line with the meta-analysis of 04 neuroprotection trials which stated that no significant effect on Apgar score, need for assisted ventilation at birth was observed and that maternal exposure to magnesium sulphate did not affect neonatal resuscitation in the short term [24]. They agree with Marret *et al.* [22] where the rate of APGAR score and ventilation support was not different between treated and untreated groups.

4.3.4. Mortality and Morbidity

The exposed group had a mortality rate of 19.5%, while the unexposed group had a mortality rate of 30%. On the seventh day of life, neurological disorders were reported in 4.6% of the exposed group and 10.6% of the unexposed group. Neurological disorders were reported in 1.1% of unexposed individuals on the 28th day of life. Neonatal outcomes were less favourable in patients who did not receive $MgSO_4$, although we cannot attribute this to the effect of $MgSO_4$ alone. We note that neonates with previous exposure to magnesium sulphate had fewer neurological complications than those without exposure.

4.4. Effects of Antenatal Magnesium Sulphate Exposure on Preterm Newborns

4.4.1. Neonatal Mortality

In our study, the neonatal mortality rate was higher in the unexposed than in the

exposed group. Indeed, antenatal exposure to magnesium sulphate was not statistically associated with neonatal mortality at a threshold of 0.05%. Our results are comparable to those of Rouse *et al.* [23] in 2008, Maged *et al.* [24] in 2009, and Mcpherson *et al.* [14] in 2014. However, Crowther *et al.* [25] in 2017 reported a significant reduction in mortality.

4.4.2. Neonatal Morbidity

In our study, we found that neonates with previous exposure to magnesium sulphate had fewer neurological complications than those without exposure. Chang *et al.* [12] in 2012, Mcpherson *et al.* [14] in 2014, and Crowther *et al.* [25] in 2017 reported that magnesium sulphate significantly reduced the risk of neurological and hemorrhagic complications in preterm newborns and even into infancy. Gestational age between 28 and 32 days' gestation, birth weight less than 1500 g, and resuscitation were identified as risk factors for neonatal morbidity.

5. Conclusions

Our study shows that although prematurity is a real problem in newborns because of its high morbidity and mortality, the administration of magnesium sulphate to pregnant women between 28 and 32 weeks' gestation is a real asset in reducing these neonatal complications. However, a study on a larger population is necessary to better appreciate the determinants of this influence **(proposition: à suprimer).**

A generalisation of the use of magnesium sulphate for neuroprotective purposes could even be envisaged in our countries.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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