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Tiivistelmä – Referat – Abstract <p>The risk for a very preterm child to develop cerebral palsy is significantly higher than for child born at term or later than 32 weeks of gestation. Doyle et al. published an updated systematic review of five RCT's in 2009 in which they proved, that antenatal magnesium sulfate administration markedly decreased the risk of cerebral palsy and substantial gross motor dysfunction in preterm infants. In a research of Magee et al. it was noted, that the NNT to prevent 1 CP or death was 43 and NNT to prevent one CP only was 50 at 32 weeks of gestation.</p> <p>The use of antenatal magnesium sulfate for fetal neuroprotection was launched in HUCH on June 7 th, 2012. After the pilot period of approximately two months, the implementation was evaluated and the decision to set-up the upper gestational age of 31+6 weeks for the fetal neuroprotection has been done (August 21st , 2012).</p> <p>Our main objective was to compare the implementation of antenatal magnesium sulfate for fetal neuroprotection, the proximity of the magnesium exposure to delivery and the determination of the delivery-related blood loss in those that received MgSO4 compared to the cohort of the same gestational age that have not received MgSO4. Pregnancy characteristics and fetal neuroprotection data were collected retrospectively and retrieved from the hospital records.</p> <p>The overall implementation rate during both periods was 83,7%. The rate of 86.2% in period 2012-2016 was higher than expected with an increase of 8,56% compared to the period A. To determine the accurate implementation rate (83,0%) we excluded those with elective CS. The implementation rate was found very successful and higher than that in any of the previous published study. Mean duration of magnesium administration was 7,13 hours and mean dose of MgSO4 was 17,61g. There was a decrease of 33% in women who did not receive magnesium sulfate even though indicated from period A to period B. The decrease of 77,9% from period A to period B with those who did not receive magnesium sulfate for an unknown reason is a huge accomplishment. We found the proximity of the magnesium exposure to delivery to be on a very satisfying level. Altogether 68,0% of women gave birth <12 hours after the exposure to MgSO4 had ceased, and as much as 58,4% delivered <6 hours after the exposure to magnesium.</p> <p>With 29,6% of those eligible for magnesium treatment, magnesium administration time was miscalculated (maintenance dose shorter 30 minutes). This non-adherence to the local guidelines has been noted and an auditing with midwives will be made. In conclusion, MgSO4 administration for fetal neuroprotection has been successfully and safely implemented in our institution.</p>			
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Implementation of antenatal magnesium sulfate for fetal neuroprotection in the third-level teaching university hospital

The retrospective analysis in period 2012-2016

Ritva Mettänen, LK

ritva.mettanen@helsinki.fi

Student no. 013862769

Thesis

Supervisor: Vedran Stefanovic

Adjunct Professor, Senior Consultant in Obstetrics, Gynecology and Fetal Medicine

HUCH Department of Obstetrics and Gynecology

Medical faculty, University of Helsinki

Helsinki 20/3/2017

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1. Introduction

1.1 Preterm Birth – Definition, Etiology, Morbidity

Premature birth is one that occurs at $\leq 36+6$ weeks of gestation or less than 258 days of gestation.¹ World Health Organization (WHO) classifies premature infants in three sub-categories by gestational age: extremely preterm (< 28 weeks), very preterm (< 32 weeks) and moderate to late preterm (32 to < 37 weeks).²

Altogether, there were 55759 children born in Finland in 2015. Of these 3316 were preterm birth (5,9% of all deliveries, gestational age < 37 weeks); 608 (1,09%) very or extremely prematurely born.¹ The overall prevalence of preterm births in developed countries in 2010 was 8,3%.²

The major risk factors for a preterm birth are: multifetal pregnancy, intrauterine (intraamniotic) infections (IAI), acute maternal infections, chronic maternal diseases with poor therapeutic equilibrium, a previous preterm birth or miscarriage, history of cervical surgery, genital malformations, a very young (< 18 years) or advanced (> 40 years) maternal age, lower socioeconomic status, use of alcohol and drugs, smoking and antenatal bleeding.³

Most of the cases of preterm birth occurs as a spontaneous preterm labour with or without premature rupture of membranes or as iatrogenic preterm delivery for various medical and obstetrical indications (chorioamnionitis, severe intrauterine growth restriction with deteriorating fetal status).

In a recently published research Raba et al. investigated a possibility to predict a preterm labor within 7 days of enrollment by evaluating the predictive value for known risk factors, such as: smoking before pregnancy, low socioeconomic status, frequent contractions during pregnancy, bleeding during pregnancy and urinary tract infections in a cohort of 622 women hospitalized for the threatened preterm labour. They found out that the accumulation of these five risk factors have ability to predict a preterm labor within a week of enrollment with a positive predictive value of 98%.⁴

In addition to high risk of perinatal mortality, a very preterm infant has a major risk of developing severe neurological problems, such as damage of developing brain, cerebral palsy, cognitive dysfunction and cerebral hemorrhage. The risk decreases considerably after 32 gestational weeks.⁵ The risk for a very preterm child to develop cerebral palsy is significantly higher than for child born at term or later than 32 weeks of gestation. For example in Australia and New Zealand of all the patients diagnosed with cerebral palsy, 40% are related to preterm birth.⁶

Cerebral palsy (CP) is a syndrome which includes neurodevelopmental disabilities, such as permanent defects in movement, postural maintenance and function. It is caused by a single damage in developing brain in the area of motoric regulations. The brain is most commonly damaged during fetal period, either during first trimester e.g. due to an infection or exposure to toxic items, or during 26 to 34 gestational weeks when the matter surrounding cerebral ventricles is most vulnerable.⁷ Another known cause of CP is hypoxic–ischemic encephalopathy (HIE). It is suggested that 14.5% of children with CP would have been damaged by ischemia or hypoxia during labour at term.⁸ Additionally gastrointestinal and nutritional problems, orthopedic problems, sensory disabilities, intellectual disabilities, trouble in cognition and behavior, limited life expectancy and epilepsy are in some cases, depending on the size and precise spot of damage, associated with CP.^{7,8} In Finland

100-120 children are diagnosed with CP each year possessing a significant burden to the children, their families and the society.⁷ It is not only the most common syndrome which requires long term and regular rehabilitation all through life, but it is also one of the most expensive syndromes for our society. In 2003 lifelong direct and indirect costs for a person with CP were estimated to be US\$921 000 per person.⁸ Approximately the same results were achieved by a Danish group of researchers in 2008, where estimated costs rose up to 861 000€, with only 7.6% of this amount related to the medical costs.⁹

1.2 Use of Magnesium Sulfate in Obstetrics

Magnesium sulfate ($MgSO_4$) is widely used in obstetrics for three main indications: 1) prevention and treatment of eclampsia-related seizures, 2) fetal neuroprotection and 3) tocolysis associated with preterm labour. Rarely, the fetal intrauterine resuscitation during intrapartum distress may be attempted by magnesium sulfate.¹⁰

$MgSO_4$ has been used for more than a century for pre-eclampsia-related seizures and prevention of eclampsia and has been a drug of choice for this indication for decades with a reduction in maternal deaths and reoccurrence of seizures.¹¹ In RCT's it has been proved to be a better anticonvulsive drug than diazepam or phenytoin, wherefore it has already been used for a century and continues to be used as a main drug in prevention and treatment of eclampsia.¹²

Since late 1960's it has been known, that magnesium sulfate impairs myometrial contractility *in vitro*. Therefore magnesium was introduced into clinical practice for decades as a tocolytic drug. The initial enthusiasm has diminished after the first RCTs in mid 80's that failed to prove the effectiveness of $MgSO_4$ as a tocolytic drug.¹²

Despite of the proven ineffectiveness of $MgSO_4$ as a tocolytic (even in delaying labour for the short time needed to administer corticosteroids), still ten years ago almost 45% of obstetricians in the United States still used it as the first-line tocolytic agent.¹³

In a retrospective study of a long-term burden of hypoxic-ischaemic encephalopathy, Eunson et al. suggested, that continuous administration of magnesium sulfate for women with severe early-onset preeclampsia would have a favourable effect in fetal outcome by postponing deterioration of preeclampsia, alleviating decreasing maternal platelet count and prolonging pregnancy with approximately 7 days.⁸ However, it is well-known that long-term infusion of magnesium sulfate has several adverse effects, such as a higher incidence of pulmonary edema, an increasing proteinuria and possible fetal and neonatal demineralization and fractures when administrated continuously for more than a week.⁸

The prognosis of preterm infants has markedly improved since 1992, when Kuban et al. found in their research that maternal receipt of magnesium sulfate decreased the risk of germinal matrix hemorrhage, even in infants born to mothers who did not evidently have preeclampsia.¹⁴

In 1995 Nelson et al. showed in their study that children who had been exposed to antenatal magnesium sulfate had less cerebral palsy syndrome as in controls. Although their study consisted only of children with very low birth weight (VLBW, <1500g) it was rather evident that magnesium sulfate had a protective effect against CP.¹⁵

Doyle et al. published an updated systematic review of five RCT's in 2009 in which they proved, that antenatal magnesium sulfate administration markedly decreased the risk of cerebral palsy and substantial gross motor dysfunction in preterm infants. There was no remarkable increase in major maternal complications, but a little higher amount of maternal adverse effects, e.g. tachycardia and hypotension was noted. Also no effect on other neurological impairments was found.¹⁶

These five trials (Table A) were included in a Cochrane systematic review, which confirmed benefit, showing that 63 mothers need to be given magnesium sulfate prior to very preterm birth to prevent one case of cerebral palsy.¹⁶ In a research of Magee et al. it was noted, that the NNT to prevent 1 CP or death was 43 and NNT to prevent one CP only was 50 at 32 weeks of gestation.¹⁷

Study	Country; no. of location centers; no. of countries; no. of subjects	Inclusion	No. of infants	Regimen; initial dose; maintenance	CP RR (95% CI): combined perinatal death & CP RR (95% CI)
MagNET Mittendorf et al.	US 1 1 149	25 – 33 weeks PTL	165	4 g 2-3 g/hr*	Not significant (of n=3 in both treated and placebo group) n/a
ACTO MgSO₄ Crowther et al.	Australia 16 2 1062	< 30 weeks Delivery expected < 24 hrs	1255	4 g / 20 mins 1 g / hr (not to exceed 24 hrs)	0.85 (0.56 – 1.31) 0.83 (0.66 – 1.03)
Magpie Trial Duley et al.	International 125 19 1544	<37 weeks Severe pre-eclampsia	1593	4 g / 10-15 mins 1 g / hr (for 24 hrs)	0.66 (0.11 – 3.94) 1.06 (0.09 – 1.25)
PREMAG Marret et al.	France 13 1 573	< 33 weeks PTL	688	4 g / 30 mins No maintenance	0.70 (0.41 – 1.19) 0.86 (0.55 – 1.34)
BEAM Rouse et al.	US 20 1 2241	24 – 31 weeks High risk of spontaneous birth	2444	6g per 20-30 mins 2 g/hr (for 12 hrs)	0.59 (0.40 – 0.85) 0.97 (0.77 – 1.23)

Table A. Randomized controlled trials: effect of magnesium sulfate treatment for expected premature birth risk of perinatal death or cerebral palsy (CP)¹⁸

*36% of subjects were more than 4cm dilated and received only the loading dose.

In each trial, evaluators of perinatal outcomes were blinded to treatment and all outcomes were based on intention to treat. ACTOMgSO₄, Australasian Collaborative Trial of Magnesium Sulfate; BEAM, Beneficial Effects of Antenatal Magnesium Sulfate; CI, confidence interval; MagNET, Magnesium and Neurologic Endpoints Trial; PTL, preterm labor; RR, relative risk

The same conclusion was drawn by Conde-Agudelo et al., who used the same five RCT's in their systematic review in 2009, although the results were even better with both cerebral palsy (RR 0.69, 95% CI 0.55–0.88) and substantial gross motor dysfunction (RR 0.60, 95% CI, 0.43–0.83).¹⁹ Although the neuroprotective mechanism of magnesium sulfate remains unclear, two main effects are suggested: first, MgSO₄ prevents glutamate binding with NMDA-receptors, which prevents the calcium uptake into damaged neurons preventing apoptosis of those cells, respectively. Second, magnesium is also suggested to serve as a vasoactive substance, which dilates cerebral arteries and veins, thus reducing the risk of HIE. Furthermore, it seems that magnesium sulfate itself has a direct anti-apoptotic effect on neurons.²⁰

However, there is no definite evidence regarding minimum effective dose, optimal timing or repeated use of magnesium sulfate regarding fetal neuroprotection.

1.3 Implementation of the New Guidelines

Several obstetrical societies have issued guidelines on MgSO₄ fetal neuroprotection but the implementation has not been as easy as it was expected.

Bain et al. recently conducted a research considering the implementation of a new health care guideline among doctors and nurses in Australia and New Zealand by one-to-one interviews with health care professionals.²¹ The new guidelines were first published in 2010 in Australia and it was anticipated that some sort of implementation would be required for the new guidelines to be put into operation. The implementation project called WISH (Working to Improve Survival and Health for babies born very preterm) was planned and taken into action. Today it offers large amount of useful strategies to help with implementation and integration of a new guideline, to ensure the optimal uptake of magnesium sulfate therapy for very and extremely preterm infants. The main barriers and enablers in implementing a new guideline were associated mainly to theoretical domains. Education of health care professionals and common knowledge were emphasized as well as the importance of memory and attention, before coming into use routinely. The main barriers mentioned were related to environmental context and resources. The use and knowledge of magnesium therapy seemed to increase convincingly throughout the first three years of implementation.

Since preterm birth remains often very difficult to predict, it was suggested that pre-drawn syringes should be taken into use as an enabler.²¹ More knowledge to predict a preterm labor such as published in Raba et al. research is needed to help us target magnesium therapy in the future for mothers who are in the highest risk to give birth in a very short period of time.⁴

There have been five publications on the magnesium sulfate implementation in the existing literature²²⁻²⁶ and the implementation rate varied between 62 and 81.7%. However, these studies included quite small number of patients (71-274).

1.4 Implementation of Magnesium Sulfate in Department of Obstetrics and Gynecology, Helsinki University Central Hospital (HUCH)

The use of antenatal magnesium sulfate for fetal neuroprotection was launched in HUCH on June 7th, 2012. After careful examination of the literature and the current guidelines of the respectable obstetrical societies, the proposal for the implementation was displayed to the hospital staff and accepted by chief obstetricians and neonatologists.

The written guidelines were published at the hospital intranet. Midwives were briefed with special attention, since the treatment execution is performed by midwives once the MgSO₄ neuroprotection has been commenced by attending obstetrician.

The upper gestational age for the pilot period of two months was chosen to be 29+6 weeks due to the uncertainty of the population size and antenatal ward space sufficiency.

The eligible women were those with threatened or imminent preterm birth on $\leq 29+6$ weeks of gestation. "Imminent preterm birth" is defined as a high likelihood of birth due to one or both of the following conditions: a) active labour with ≥ 2 cm of cervical dilation, with PPROM or intact membranes, and b) a planned preterm birth for fetal or maternal indications on $\leq 29+6$ weeks of gestation.

Contraindications for MgSO₄ treatment are set to be: fetal lethal anomaly, maternal myasthenia gravis or other neuromuscular disease, renal insufficiency, maternal or fetal distress with the need for urgent delivery, and maternal refusal.

When fetal neuroprotection has been commenced by the attending obstetrician, two midwives prepare the MgSO₄ solutions (double check) and infuse a loading dose of 4-g within 30 minutes, followed by maintenance dose of 2g/hour for 12 hours or until birth. Repeated doses were not allowed if undelivered after the maintenance dose of 12 hours has been received. Maternal and fetal follow-up during the MgSO₄ treatment has been performed according to the existing guidelines. After the pilot period of approximately two months, the implementation was evaluated and the decision to set-up the upper gestational age of 31+6 weeks for the fetal neuroprotection has been done (August 21st, 2012).

The data regarding the implementation of antenatal magnesium sulfate in 6/2012-12/2013 was collected and analyzed by Ulla Isoranta in her graduation study in 2014.²⁰

It was observed that only 79,4% of the mothers giving birth at less than 31+6 weeks of gestation in HUCH Dept of Obstetrics and Gynecology received magnesium sulfate prior birth according to the published international guidelines, mainly due to the lower gestational age upper limit in the pilot phase of the MgSO₄ implementation.²⁰

2. Objective of research

Our main objective was to compare the implementation of antenatal magnesium sulfate for fetal neuroprotection in HUCH Department of Obstetrics and Gynecology in 01/2014-06/2016, later referred as period B with the previous published period, referred as period A.

We aimed also to identify patients that have not received magnesium sulfate despite of their eligibility for the fetal neuroprotection.

The secondary outcome we have searched for were the proximity of the magnesium exposure to delivery and the determination of the delivery-related blood loss in those that received MgSO₄ compared to the cohort of the same gestational age that have not received MgSO₄.

3. Patients and Methods

Pregnancy characteristics and fetal neuroprotection data were collected retrospectively and retrieved from the hospital records. We have identified all deliveries \leq 31+6 gestational weeks in both periods A and B.

Women who gave birth in some other hospital, home or anywhere else outside of hospital were excluded. To integrate the two implementation periods, some exclusions of patients were made from period A raw data, resulting in minor changes.

Since fetal neuroprotection was introduced as a part of standard clinical care, no ethical permission was necessary. The research permission was obtained by the HUCH Research Board, (extension of the previous permission on the same issue, § 1, 9.1.2014)

All data received were listed in an excel file for further analyzing. Analyzing was made with IBM SPSS Statistics 24, Helsinki University license for 2017-2018, Chi-Square Test as a main statistic test.

4. Results

The study population consists of 485 women, of which 180 were included on period A and 305 on period B. On period A the total number of patients treated with MgSO₄ was 143 (79,4% of all births ≤ 31+6 gestational weeks) whereas on period B the number of women receiving fetal neuroprotection was 263 (86,2% of all births ≤ 31+6 gestational weeks) (Figure 1). The overall implementation on periods A and B was 83,7% (table B).

There were altogether 423 (87.2%) singleton pregnancies, 49 (10.1%) twin pregnancies, 2 (4.1%) set of triplets and one quadriplet pregnancy (2.1%) with total of 531 fetuses. There were 188(38.8%) vaginal deliveries and 297 (61.2%) cesarean sections including elective, emergency and crush cesareans.

	Period A	Period B	Period A+B
Participants (N)	180	305	485
Gestational age, mean (days)	200	202	201
MgSO₄ implementation rate, all patients (%)	79.4	86.2	83.7
MgSO₄ implementation rate, elective CS excluded (%)	78.5	85.6	83.0
MgSO₄ treatment duration, mean (hours)	6.97	7.22	7.13
MgSO₄ treatment, total dose, mean (g)	17.13	17.90	17.61
MgSO₄ full dose 28 g, N (%)	56 (31.1)	80 (26.2)	136 (28)
MgSO₄ load + partial dose, N (%)	84 (46.7)	167 (81.0)	251 (51.8)
MgSO₄ load dose only, N (%)	3 (1.7)	16 (5.2)	19 (3.9)
Blood loss volume, patients treated with MgSO₄, mean (ml)	671.8	592.9	621.1
Blood loss volume, patients not treated with MgSO₄, mean (ml)	625.8	598.5	610.7

Table B. Main characteristics of the results in implementing new guidelines in Helsinki University Central Hospital (HUCH) in period 2012-2016

abv. MgSO₄ = magnesium sulfate; CS = Cesarean section

Although there was an increase of 8,6% on period B compared to period A (95% CI 0,995-1,184; p = 0.057), the use of MgSO₄ for fetal neuroprotection has not reached statistical significance. The number of women who did not receive magnesium although indicated was decreased by 33,0% (95% CI 0,448-1,001).

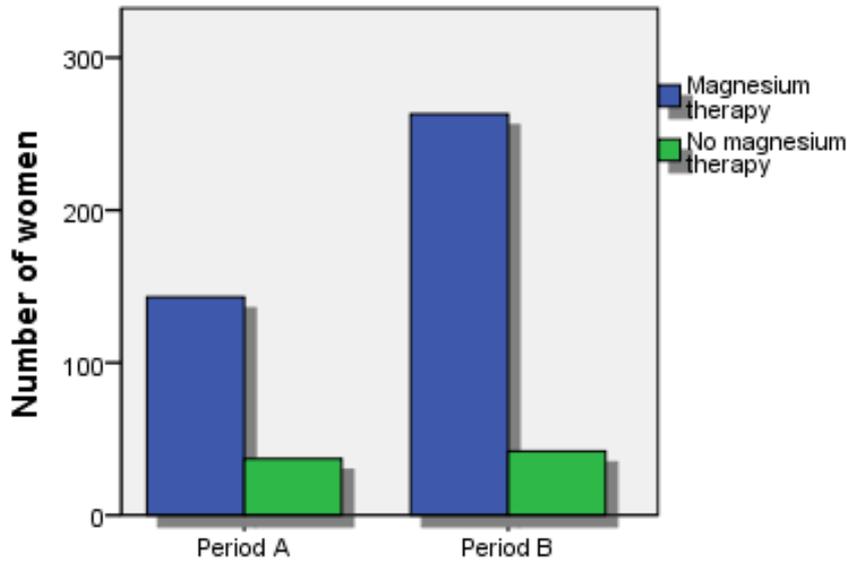


Figure 1. Number of women medicated with magnesium therapy on periods A and B.

Mean gestational age in periods A and B was 201 days (28+6 weeks). The mean duration of MgSO₄ administration on period B was 7,22 hours (p <0,001; 95% CI 6,65-7,80) and mean dose of magnesium was 17,90 grams (p <0,001; 95% CI 16,66-19,14) (table B). Compared to period one there is a 4,5% increase in mean MgSO₄ dose.

There was a minor decrease in patients who received full dose of magnesium on period B. There are also significant number of women who received almost a full dose of magnesium (28-g), but because of miscalculated administration time the dose was only partial, p = 0,025 (Table B). In some cases magnesium administration was ceased. The main reason for this was a need for emergency cesarean section (CS) for maternal or fetal indication (39,9%). Almost one third (29,6%) of all ceased magnesium administrations were ceased 30 minutes before a full administration of twelve hours would have been reached without any specific reason.

	No. of women (%)
Imminent delivery	52 (19,3)
Need for emergency Cesarean section (within 30 minutes)	105 (38,9)
Maternal side effects*	14 (5,2)
Miscalculated time	80 (29,6)
Other reasons	19 (7,0)

Table C. Reasons for ceasing MgSO₄ administration

*Significant blood pressure drop, nausea, pain in cannulated arm, flushing symptoms and palpitations. Other reasons: e.g. obstetrician's orders, switch to oxytocine, fully dilated cervix, anuria, patients request. The main reasons for not receiving MgSO₄ though indicated were rapid delivery (within 2h from arrival to the hospital), a need for emergency CS (within 30 minutes) and a crash section (table D). In 11 patients there was no information on why magnesium wasn't administered (2,3% of all). During period A there were eight women (4,4%) with no information, whereas on period B there were only three women (1,0%) with no information, with a total decrease of 77,9%.

	No. of women (%)
Rapid delivery	17 (21,5)
Need for emergency Cesarean section (within 30 minutes)	21 (26,6)
Crash Cesarean section	21 (26,6)
Contraindication	9 (11,4)
No information	11 (13,9)

Table D. Reasons for not receiving magnesium though indicated.

During period B as much as 35,4% of patients who received magnesium gave birth < 1 hour after termination of MgSO₄ administration and a total of 55,9% gave birth < 6 hours after magnesium treatment had ended (table E).

		Period A N (%)	Period B N (%)	Period A+B N(%)
Time gap between magnesium administration and birth	<6 hours	90 (62.9)	147 (55.9)	237 (58.4)
	<12 hours	13 (9.1)	26 (9.9)	39 (9.6)
	<24 hours	9 (6.3)	35 (13.3)	44 (10.8)
	>24 hours	31 (21.7)	55 (20.9)	86 (21.2)
Total		143 (100.0)	263 (100.0)	406 (100.0)

Table E. Proximity of magnesium exposure to delivery, p = 0,168.

Comparison of the implementation rate in this study to other international published studies (Table F).

Study	No. of women	Uptake	Repeated dose	Regimen
Bouet, P.E. (2015) Implementation of an antenatal magnesium sulfate protocol for fetal neuroprotection in preterm infants ²²	119	68.1%	No	≤33 weeks of gestation Load dose of 4g i.v. in 30 min Administration 1g / h, max. 12 hours
Ow, L.L.et al. (2012) Feasibility of implementing magnesium sulfate for neuroprotection in a tertiary obstetric unit ²³	168	73,2%	Yes	≤32 weeks of gestation Load dose of 4g i.v. in 15 min. Administration 2g / h, reduced to 1g / h in the event of significant maternal side effects
Siwicki, K. et al. (2015) Nonreceipt of antenatal magnesium sulfate for fetal neuroprotection at the Women's and Children's Hospital, Adelaide 2010–2013 ²⁴	245	62,0%	No	23+0 - 29+6 weeks of gestation. Load dose of 4g i.v..Administration 1g / h, max. 24 hours
Tan, Y.H. et al. (2014) A prospective audit of the adherence to a new magnesium sulfate guideline for the neuroprotection of infants born less than 30 weeks' gestation ²⁵	71	81,7%	No	24+0 - 29+6 weeks of gestation. Load dose of 4g i.v. Administration 1g / h
Gibbins, K.J. (2013) Evaluation of the clinical use of magnesium sulfate for cerebral palsy prevention ²⁶	274	71,9%	No	≤32 weeks of gestation Load dose of 6g i.v. Administration of 2g / h
Mettänen, R. (2017) Implementation of antenatal magnesium sulfate for fetal neuroprotection in the third-level teaching university hospital; The retrospective analysis in period 2012-2016	485	83,7%	No	≤ 31+6 weeks of gestation Load dose of 4g i.v. in 30 min Administration 2g / h, max. 12 hours

Table F. Comparing published international studies to the latest Finnish research of implementing a new protocol.

No. = number; g = grams; i.v. = intravenous; h = hour

We collected the data of total blood loss during birth to see if there was any correlation between magnesium administration and delivery-related blood loss in those that received MgSO₄ compared to those who did not receive MgSO₄. Data of delivery-related blood loss in 14 women was missing.

There was no difference in the mean blood loss among the women who did received MgSO₄ for fetal neuroprotection and those who did not received MgSO₄ (621.1 vs 610.7 ml) (Figure 2, Table B).

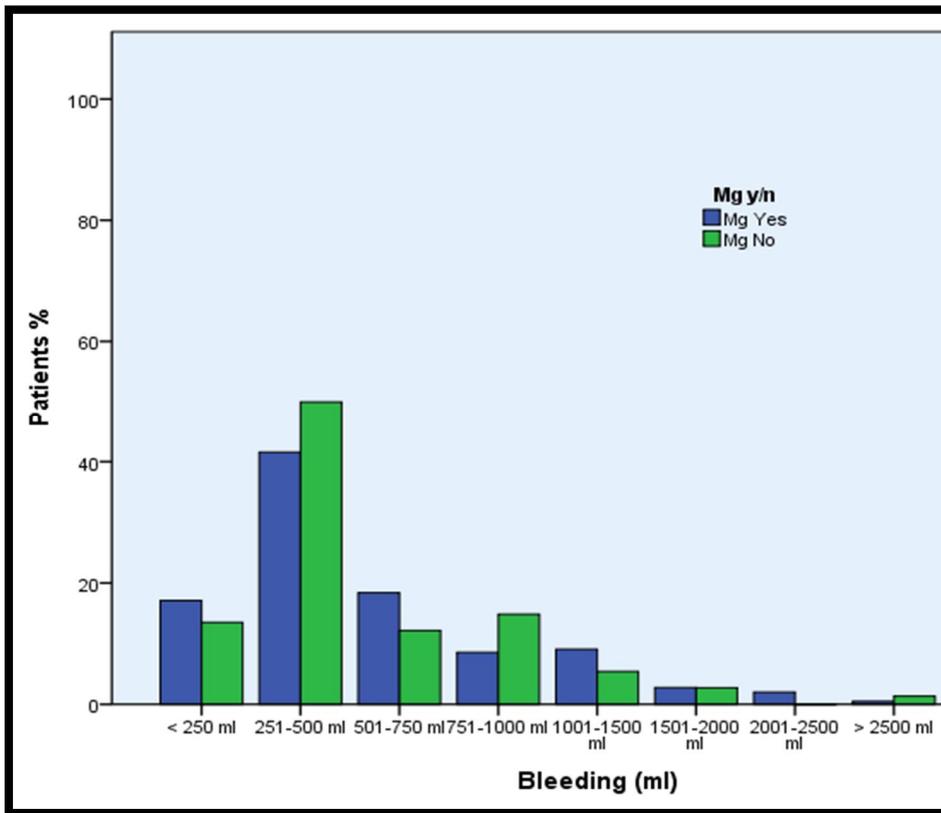


Fig 2. Correlation between magnesium administration and total bleeding volume, periods A and B. Mg = magnesium; ml = milliliters; y = yes; n = no

There was no correlation between total magnesium dose and bleeding volume, $p = 0,48$ or magnesium administration and bleeding volume, $p = 0,87$. Instead a rather strong correlation between delivery mode and blood loss was observed, $p < 0,001$.

5. Discussion

This research focused on the implementation rate of antenatal MgSO₄ administration for fetal neuroprotection during two periods, proximity of the MgSO₄ exposure to delivery and the comparison of blood loss among women with premature birth with and without administration of MgSO₄.

The overall implementation rate during both periods was 83,7%. The rate of 86.2% in period 2012-2016 was higher than expected with an increase of 8,56% compared to the period A.

The implementation rate of full dose MgSO₄ regimen (28g) of women with elective cesarean section was almost 100%. We calculated the implementation rate by excluding those with elective CS to determine the accurate implementation rate in those, whose delivery time was unpredictable. We found the implementation rate of 83.0% as very successful and is higher than that in any of the previous published study. Additionally, the number of pregnancies that received MgSO₄ for the fetal neuroprotection is the highest ever reported

Mean duration of magnesium administration was 7,13 hours and mean dose of MgSO₄ was 17,61g. In some cases magnesium was given not only for fetal neuroprotection but for pre-eclampsia too. In those cases total magnesium dose was frequently more than the maximum dose (4g + 24g), but for statistical analyzes those patients were considered as patients who received full dose of magnesium (28g).

There was a decrease of 33% in women who did not receive magnesium sulfate even though indicated from period A to period B. The decrease of 77,9% from period A to period B with those who did not receive magnesium sulfate for an unknown reason is a huge accomplishment. A major impact in decreasing the percentage of patients who did not receive magnesium though indicated was an alteration in practice of administrating magnesium in emergency situations. During period A, patients who gave birth relatively quickly upon admission or who gave birth by an emergency CS within 30 minutes from decision did not generally receive magnesium even though there would have been time for at least a loading dose administration. During period B there was an alteration in the matter; patients were more often administrated at least a load dose (4g), were there no contraindications and the predicted time preceding birth was estimated to be at least one hour.

The proximity of the magnesium exposure to delivery was also on a very satisfying level. Altogether 68,0% of women gave birth <12 hours after the exposure to MgSO₄ had ceased, and as much as 58,4% delivered <6 hours after the exposure to magnesium. The data of those who delivered <1 hour after the exposure to MgSO₄ was collected only during period B being as high as 35,4%. Turitz et al. recently published a study of proximity of magnesium sulfate exposure to neonatal outcomes. A strong association was noted between maternal exposure to magnesium sulfate less than 12 hours before delivery and a significant decrease in CP, as compared with a maternal exposure to magnesium sulfate \geq 12 hours prior to delivery (OR 0,41; CI 95% 0,18-0,91; p = 0,03).²⁷ Hence we may conclude that the proximity of MgSO₄ exposure to delivery in HUCH has been at the “therapeutic” level.

McPherson et al. searched for a difference in fetal outcomes with different durations of magnesium administration. Statistically there was no difference between duration of <12 hours, 12 to 18 hours and more than 18 hours. They also found no evidence of greater fetal morbidity between the three groups.²⁸

The guidelines need constant updating, whilst midwives and gynecologist need regular audit and feedback on hospital guidelines and new research data. It has been suggested that a higher concentration of magnesium sulfate in fetuses may result in possible adverse effects, such as necrotizing enterocolitis, intraventricular haemorrhage and increased mortality. Morag et al. recently published a research, where magnesium concentration was measured of both mother and a newborn infant after magnesium administration. They found that there was a remarkable correlation ($p = 0,001$) between maternal magnesium concentration (mMgC) and infant magnesium concentration (iMgC).²⁹ Accordingly, higher or repeated doses of magnesium sulfate should be considered only with extra caution.

We could not demonstrate any statistical and clinical difference in blood loss during delivery among women with or without MgSO₄ administration which is in line with previous reports. However, a strong correlation between mode of delivery and blood loss was noted, being higher in cesarean deliveries, as expected. The same conclusion was made by Sangkomkamhang et al. in their research of mode of delivery and outcomes in preterm births.³⁰

Our research data was collected retrospectively, out of obstetrical electronic patient data records. Therefore the probability for an error is exclusively caused by handwork in collecting the data into an Excel file.

The implementation rate and proximity of MgSO₄ exposure to delivery were at a very high level during both periods. Nevertheless, there is always something to improve. Detailed and explicitly described guidelines of magnesium administration for fetal neuroprotection are written in Haikarakansio, a Handbook of obstetric guidelines used by midwives and obstetricians in HUCH. Therefore, there is no rational explanation why magnesium administration time was miscalculated with 29,6% of those eligible for magnesium treatment (maintenance dose shorter 30 minutes). This non-adherence to the local guidelines has been noted and an auditing with midwives will be made. Fortunately, this miscalculation did not influence significantly total MgSO₄ dose that fetuses received.

Had the administration time been calculated correctly with every patient, the percentage of those receiving full dose of magnesium could have been as high as 44,3%. Statistically there is a huge difference between 26,2% and 44,3%. Certainly, there is only a small or no clinical difference between the patients and the outcome of their prematurely born children with 27g or 28g dose²⁸, but guidelines do exist for a good reason and they are an outcome of many, long term researches dealing with sufficient dose of magnesium sulfate in fetal neuroprotection.

In conclusion, MgSO₄ administration for fetal neuroprotection has been successfully and safely implemented in our institution. This is to our best knowledge the largest study with the highest implementation rate ever reported.

Although not straightforward, taking into consideration the fact that the mean gestational age of our cohort was 28+6 gestational weeks, with the NNT to prevent one CP in this group being 30, we have theoretically prevented 17.7 CP cases (531 fetuses/30).

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