Predictive factors for Cerebral Palsy: a cohort study

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Keywords

Cerebral Palsy, Magnesium sulphate, Neuroprotection, Prematurity, Periventricular leukomalacia.

Abstract

Objective

Antenatal administration of magnesium sulphate (MgSO4) is recommended worldwide for imminent preterm birth due to its proven protective effect on Cerebral Palsy (CP). The aim of this study was to identify predictive factors for (suspect) CP, for neonates born between 24 and 32 weeks' gestation, who are dismissed from the Neonatal Intensive Care Unit (NICU).

Methods

Cohort study of neonates born between 2012 and 2018 in Ghent University Hospital at a gestational age between 24 and 32 weeks. Predictive and risk factors for (suspect) CP described in literature were examined through modelling using generalized estimating equations.

Results

The study population consisted of 474 neonates, of which 293 were antenatally exposed to MgSO4. The composite outcome (suspect CP or CP) was present in 44 (9.3%) neonates. The final model consisted of the following variables: neuroprotection (odds ratio (OR): 0.38 (95% confidence interval (CI): 0.19, 0.75); p = 0.005), periventricular leukomalacia (OR: 2.41 (95%CI: 1.20, 4.82); p = 0.013), smoking (OR: 2.57 (95%CI: 1.21, 5.44); p = 0.014) and reason of preterm delivery (placental insufficiency versus SPL (OR: 0.34 (95%CI: 0.11, 1.08); p = 0.068), PPROM versus SPL (OR: 1, 23 (95%CI: 0.60, 2.52); p = 0.567) and other causes of preterm delivery versus SPL (OR: 0.70 (95%CI: 0.17, 2.99); p = 0.633)).

Conclusion

Neuroprotection is shown to be a protective factor. Periventricular leukomalacia and smoking are negatively associated with CP.

Introduction

Cerebral Palsy (CP) is described as a heterogeneous group of non-progressive motor disorders caused by chronic brain injury which occurs in the developing brain of the foetus or infant (1). Cerebral palsy is the main cause of disability at young age. The incidence amounts to 2 to 3 per 1000 live births worldwide; in Belgium it is estimated at 1.48 per 1000 live births (2). This number increases to 40 to 100 per 1000 live births when the neonate is born at less than 27 weeks or with a birth weight less than 1000 grams (3). Preterm birth is thus an important risk factor for CP. There are numerous other risk factors, both maternal and foetal, such as maternal smoking and periventricular leukomalacia (PVL) (4, 5). The consequences of CP not only affect the individual but also the family. Furthermore it has a high socio-economic burden (6, 7).

One of the preventive measures is prenatal administration magnesium sulphate (MgSO4) as a neuroprotective agent to mothers at risk of delivering preterm. Five randomized controlled trials (RCT) were performed evaluating the effect of MgSO4 on the occurrence of CP (8-12). Only one of these trials showed that the administration of MgSO4 results in a significant decrease of patients with mild or severe CP (relative risk (RR): 0.55 (95%CI: 0.32 - 0.95)) (11). Meta-analyses and an individual participant data meta-analysis, however, showed a significant reduction of CP in the MgSO4 group (13-18). As a result, several guidelines recommend the intravenous use of MgSO4 as neuroprotection for imminent preterm birth at less than 32 weeks' gestation (19, 20). Major maternal and foetal side effects are limited with the recommended MgSO4 dosing schemes (10, 13, 14, 21-23).

Considering the burden of disease and the absence of a cure, the prevention of CP is important. The aim of this study was to identify predictive factors for (suspect) CP, for neonates born between 24 and 32 weeks' gestation, discharged from the neonatal intensive care unit (NICU).

Methods

This study was performed in the context of the PRETURN-project at the Ghent University Hospital (PREdiction in preTerm birth meets caUsal infeReNce). In this project, one of the aims is to provide clinical risk predictions. Informed consent was obtained from the parents of included neonates. The approval of the Medical Ethics Committee of Ghent University Hospital was obtained on 22/10/2019 with following registration numbers: B670201941300 and B670201941301.

From 2012 until 2017, data were collected retrospectively from the patient records. Prospective data collection began in mid-2017. Data were collected and managed using REDCap® (Research Electronic Data Capture) (24, 25).

The primary outcome of this study was to identify predictive factors for (suspect) CP. These factors could be used for counselling parents

whose neonates are born before 32 weeks' gestation and are discharged from the NICU.

The diagnosis of CP is not based on a single diagnostic tool. It is recommended to use a combination of clinical history, neurological imaging and a standardized neurological examination to make an early and accurate diagnosis of CP (5). Based on the neurological examination, a distinction can be made between a normal result, suspect psychomotor problem, suspect CP and confirmed CP. The following neurological test results indicate suspect CP: hyperreflexia, problems with muscle coordination, muscle control, muscle tone, balance and posture (26, 27). For evaluation of motor development between birth and 10 months (corrected age), the Alberta Infant Motor Scale (AIMS) is used. To classify the various categories of CP, the Flemish Centres for Developmental Disorders use Flemish norms of the Bayley-III scales for cognition, gross motor skills, fine motor skills, language comprehension, and language expression. The assessment is conducted from 10 months (corrected age) to 36 months of age. The centre consistently collaborates with an experienced paediatric neurologist, who also reviews imaging, and a specialized physical therapist trained in Bobath therapy. At a post-term age of 4 months (corrected age), there may still be uncertainty, especially if the patient shows only hypertonia without pyramidal reflex or imaging abnormalities. In these cases, the term 'suspect CP' is used. From a post-term age of 10 months (corrected age), CP can definitively be diagnosed.

Participants

Neonates born between 2012 and 2018 in Ghent University Hospital (Belgium), were included in this study. Only neonates born at less than 32 weeks' gestation, discharged from the NICU, followed-up in the Centre for Developmental Disorders and without missing data of the composite outcome (CP or suspect CP) were included.

Instruments

Neonates born before 2015 were offered long term follow-up at the Centre for Developmental Disorders if they were born at less than 30 weeks and/or if their birth weight was less than 1250 grams. From the year 2015 onwards, follow-up was provided at a gestational age of less than 32 weeks and/or a birth weight of less than 1500 grams. Four follow-up appointments are scheduled at the corrected age of 4 months, the corrected age of 10 months, and at the age of 2 and 4 years old.

In Ghent University Hospital, MgSO4 has been given for imminent preterm delivery since 2014. However, neonates born before 2014 were also included in the dataset. The indication for MgSO4 before 2014 was preeclampsia. Both for neuroprotection and eclampsia prevention, a bolus of 4g MgSO4 followed by a maintenance dose of 1 g/h is administered intravenously. Neuroprotection is started when birth is expected within the following 24 hours at a gestational age less than 32 weeks.

Model and modelling strategy

Risk and protective factors for CP were identified by literature review and the evidence for the neuroprotective effect of MgSO4 was studied based on published RCT data (10-14). A search was performed via Pubmed and Embase with the following search terms: 'premature birth', 'parturition', 'prematurity', 'premature labor', 'neurodevelopmental disorders', 'motor dysfunction', 'cerebral palsy', 'infant mortality', 'neuroprotection', 'magnesium sulfate' and 'brain protection' (The literature search is detailed in the appendix).

The following factors associated with CP were identified in literature: neuroprotection with MgSO4, smoking, PVL, gestational age at birth, mode of delivery, reason for preterm delivery, intracerebral haemorrhage (ICH), birthweight, foetal growth restriction (FGR), antenatal administration of corticosteroids (ACS), gender and number of foetuses.

All statistical analyses were performed using IBM SPSS version 26. Generalized estimating equations were used to account for the non-independence of multiples. As a first step, a descriptive analysis of the database was performed (Table 1).

Table 1: Descriptive statistics.

Variable		Number	%
Gender	Male	262	55.3
Smoking	Never smoked or quit before/during pregnancy	404	85.2
	Smoking during pregnancy	65	13.7
	Missing values	5	1.1
Gestational age	24 weeks	18	3.8
	25 weeks	21	4.4
	26 weeks	38	8.0
	27 weeks	36	7.6
	28 weeks	67	14.1
	29 weeks	85	17.9
	30 weeks	91	19.2
	31 weeks	118	24.9
Reason preterm delivery	SPL	164	34.6
	PPROM	158	33.3
	Placental insufficiency (preeclampsia or FGR)	124	26.2
	Others	28	5.9
Birth weight	500 -1000 grams	144	30.4
	1001 – 1500 grams	211	44.5
	1501 – 2000 grams	108	22.8
	2001 – 2500 grams	11	2.3
Neuroprotection	Yes	293	61.8
FGR	Yes	61	12.9
CP or suspect CP	Yes	44	9.3

Results

Before combining multiple predictors, every variable identified as a risk or protective factor for CP was tested individually for an association with the composite outcome (suspect CP or CP) using univariate analysis. A significant association was observed for five out of the 12 factors described above: neuroprotection ($p < 0.001$), smoking ($p = 0.012$), PVL ($p = 0.017$), gestational age at birth ($p = 0.022$) and reason for preterm delivery ($p = 0.036$). In the next step, both forward and backward selection of variables, significantly associated in univariate analysis, were used ($\alpha = 0.05$). In the forward model the most significant variable was added first. For backward selection, the variable with the highest p-value was removed from the model in each step, to end with only significant variables (5 variables). For variables with multiple categories the lowest

Table 2: Overview of included predictors in the final model.

Predictor	B	95% Wald Confidence interval for B		Exp(B)	Standard Error	95% Wald Confidence interval for Exp (B)		P-value
		Lower	Upper			Lower	Upper	
Intercept	-2.090	-2.696	-1.485	0.124	0.309	0.068	0.227	< 0.001
Neuroprotection = yes	-0.973	-1.656	-0.290	0.378	0.349	0.191	0.748	0.005
Neuroprotection = no	0	.	.	1	.	.	.	.
PVL = yes	0.879	0.185	1.573	2.409	0.354	1.204	4.821	0.013
PVL = no	0	.	.	1	.	.	.	.
Smoking = Smoked during pregnancy	0.942	0.190	1.694	2.565	0.384	1.209	5.440	0.014
Smoking = Never smoked or quit before/during pregnancy	0	.	.	1	.	.	.	.
Reason for preterm delivery = placental insufficiency	-1.068	-2.217	0.080	0.344	0.586	0.109	1.084	0.068
Reason for preterm delivery = PPROM	0.209	-0.507	0.925	1.233	0.365	0.602	2.522	0.567
Reason for preterm delivery = others	-0.353	-1.801	1.094	0.702	0.739	0.165	2.987	0.633
Reason for preterm delivery = SPL	0	.	.	1	.	.	.	.

Table 3: Incidence of (suspect) CP according to gestational age. N (%).

	24	25	26	27	28	29	30	31	Total
CP or suspect CP = no	12 (66.7)	19 (90.5)	35 (92.1)	34 (94.4)	63 (94.0)	71 (83.5)	85 (93.4)	111 (94.1)	430 (90.7)
CP or suspect CP = yes	6 (33.3)	2 (9.5)	3 (7.9)	2 (5.6)	4 (6.0)	14 (16.5)	6 (6.6)	7 (5.9)	44 (9.3)
Total	**18**	**21**	**38**	**36**	**67**	**85**	**91**	**118**	**474**

p-value was used. Table 2 gives an overview of the included predictors in the final model. The variables retained after this stepwise method were tested for correlations via the chi-square test in crosstabs to prevent overfitting of the model. Multicollinearity was subsequently assessed by means of Variance Inflation Factor (VIF) to check for a linear relationship between the predictors. The resulting model with the lowest goodness of fit value was considered to contain the most important predictors for (suspect) CP. The composite outcome (suspect CP or CP) in this dataset is low (9.3%), hence odds ratio's (OR) can be interpreted as relative risk (RR) (28).

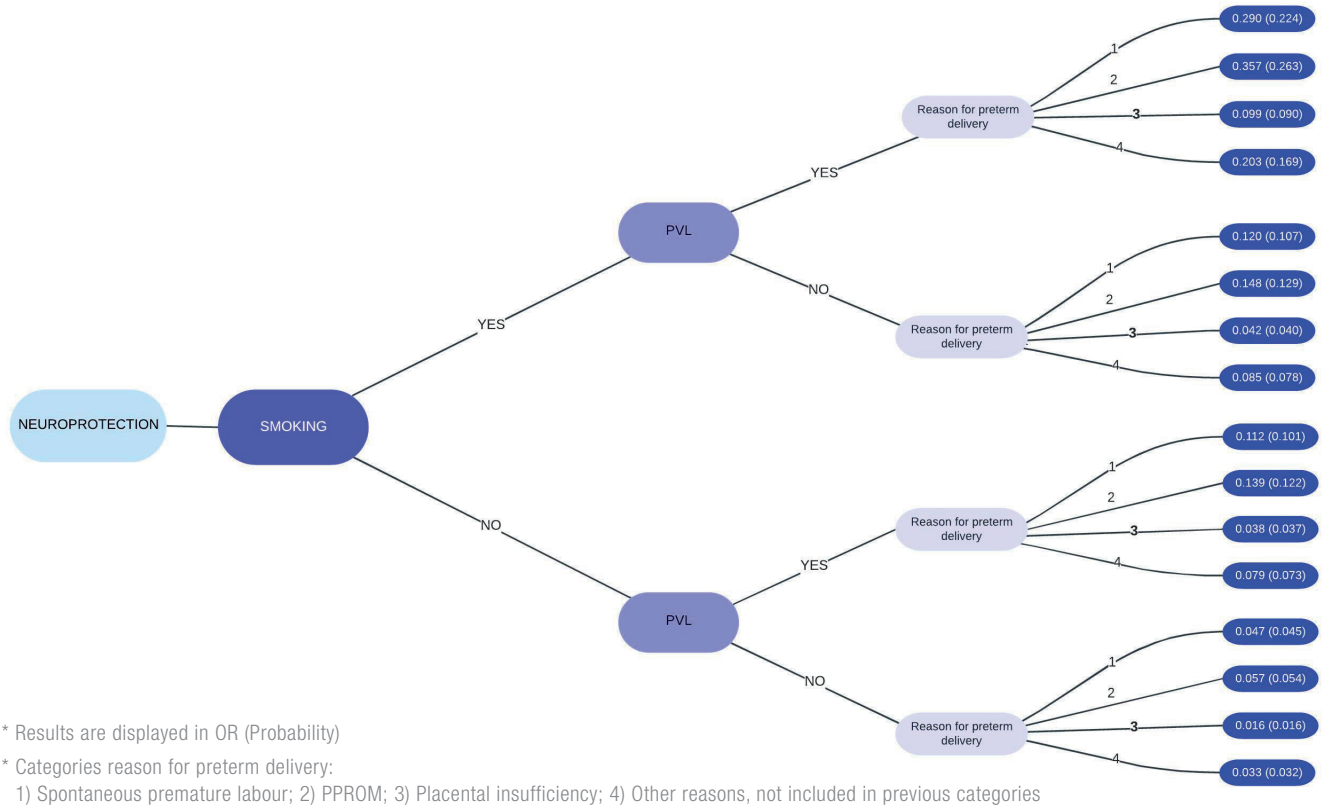
Of the initial dataset (1363 neonates born between 2012 and 2018), 848 neonates were born before 32 weeks' gestation. Of the 708 neonates discharged from the NICU (16.5 % neonatal mortality), only 474 presented for follow-up in the Centre for Developmental Disorders. There was no missing outcome data. Five missing values were found for the variable smoking, no missing values were observed in the other variables. Antenatal MgSO4 was given in 293 (61.8%) of cases. In the dataset, more males than females where under follow-up (resp. 55.3% versus 44.7%). There were 30.6% multiple births. Different reasons for preterm delivery were noted in the dataset: spontaneous premature labour (SPL), premature preterm rupture of membranes (PPROM), placental insufficiency and other not further specified reasons (respectively 34.6%, 33.3%, 26.2% and 5.9%). The composite outcome (suspect CP or CP) was present in 44 (9.3%) neonates. The incidence of (suspect) CP according to gestational age is presented in Table 3.

Antenatal neuroprotection was associated with a 62% lower risk of (suspect) CP (OR: 0.38 (95%CI: 0.19, 0.75); p = 0.005) adjusted for smoking, PVL and reason for preterm delivery.

Periventricular leukomalacia and smoking were associated with a higher risk of (suspect) CP (respectively (OR: 2.41 (95%CI: 1.20, 4.82); p = 0.013) and (OR: 2.57 (95%CI: 1.21, 5.44); p = 0.014)) irrespective of the other factors: administration of neuroprotection, aetiology of preterm delivery, PVL and smoking.

When gestational age was examined in relation to CP in an individual GEE model, a correlation was observed (p = 0.022 (95%CI: 0.718, 0.974)). However, when a GEE model with multiple variables was constructed, gestational age was no longer significantly correlated with CP (p = 0.295 (95%CI 0.764, 1.085)).

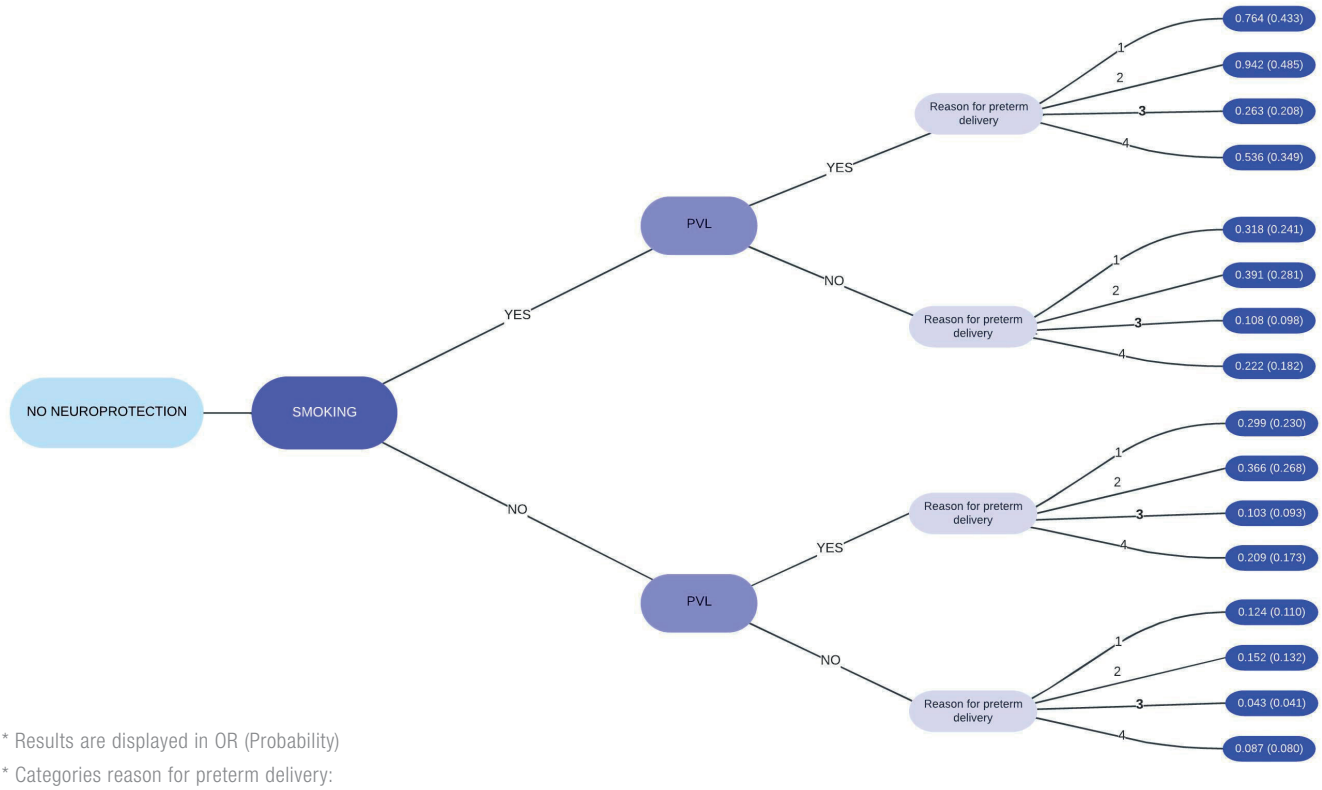
Figure 1: Tree diagram with odds and probability of (Suspect) CP with the significant factors when neuroprotection is given.



* Results are displayed in OR (Probability)

* Categories reason for preterm delivery:
1) Spontaneous premature labour; 2) PPROM; 3) Placental insufficiency; 4) Other reasons, not included in previous categories

Figure 2: Tree diagram with odds and probability of (Suspect) CP with the significant factors when neuroprotection is not given.



* Results are displayed in OR (Probability)

* Categories reason for preterm delivery:
1) Spontaneous premature labour; 2) PPROM; 3) Placental insufficiency; 4) Other reasons, not included in previous categories

Adjusted for smoking, PVL and neuroprotection, there is no obvious association between the reason of preterm delivery and (suspect) CP (placental insufficiency versus SPL (OR: 0.34 (95%CI: 0.11, 1.08); p = 0.068), PPROM versus SPL (OR: 1, 23 (95%CI: 0.60, 2.52); p = 0.567) and other causes of preterm delivery versus SPL (OR: 0.70 (95%CI: 0.17, 2.99); p = 0.633)).

Table 4 was composed to present the model in a practical way. It shows all possible combinations of the four predictors with their corresponding odds on the composite outcome. A tree diagram was also created to represent the model more practically (Figure 1 and 2).

Table 4: Possible combinations with probability and odds.

Neuro-protection	PVL	Smoking	Reason	N	CP (%)	Probability[1]	Odds[2]
0	0	0	1	40	0 (0)	0,110	0.124
0	0	0	2	47	4 (8.5)	0.132	0.152
0	0	0	3	14	1 (7.1)	0.041	0.043
0	0	0	4	13	3 (23.1)	0.080	0.087
1	0	0	1	63	7 (11.1)	0.045	0.047
1	0	0	2	58	4 (6.9)	0.054	0.057
1	0	0	3	73	1 (1.4)	0.016	0.016
1	0	0	4	6	0 (0)	0.032	0.033
0	1	0	1	12	2 (16.7)	0.230	0.299
0	1	0	2	14	7 (50)	0.268	0.366
0	1	0	3	3	0 (0)	0.093	0.103
0	1	0	4	4	0 (0)	0.173	0.209
0	0	1	1	11	6 (54.5)	0.241	0.318
0	0	1	2	8	1 (12.5)	0.281	0.391
0	0	1	3	5	1 (20)	0.098	0.108
0	0	1	4	4	0 (0)	0.182	0.222
1	0	1	1	6	0 (0)	0.107	0.120
1	0	1	2	11	0 (0)	0.129	0.148
1	0	1	3	7	0 (0)	0.040	0.042
1	0	1	4	0	0 (0)	0.078	0.085
0	1	1	1	1	0 (0)	0.433	0.764
0	1	1	2	2	2 (100)	0.485	0.942
0	1	1	3	2	1 (50)	0.208	0.263
0	1	1	4	1	0 (0)	0.349	0.536
1	1	0	1	26	2 (7.7)	0.101	0.112
1	1	0	2	14	1 (7.1)	0.122	0.139
1	1	0	3	17	0 (0)	0.037	0.038
1	1	0	4	0	0 (0)	0.073	0.079
1	1	1	1	3	0 (0)	0.224	0.290
1	1	1	2	2	1 (50)	0.263	0.357
1	1	1	3	2	0 (0)	0.090	0.099
1	1	1	4	0	0 (0)	0.169	0.203
.	.	Missing	.	5	0 (0)		

Discussion

The aim of this study was to identify predictive factors that could be used for counselling at the time of discharge from the NICU. Four factors were identified: neuroprotection with MgSO4, PVL, smoking and reason for preterm delivery. One of the categories within the variable reason for preterm delivery, namely placental insufficiency, is associated with PVL and smoking. When this variable was added in the combined GEE model, it gave a better fit, even though none of the categories in the variable were significantly correlated with CP. Furthermore, preeclampsia is included in the category placental insufficiency. Women suffering from preeclampsia also receive MgSO4, this is another reason why the variable reason for preterm delivery affects the goodness of fit of the model. The variable gestational age was not significantly correlated with CP in this study, contrary to evidence found in the literature. Gestational age is regarded as one of the most important risk factors for CP in literature. While a significant association was observed between gestational age and the composite outcome in the univariate analysis, this significant association disappeared in the multivariate analysis. A possible explanation for this phenomenon is that the variables PVL and reason for preterm delivery, which are correlated to the variable gestational age, are included in the final model. Therefore, the incorporation of gestational age as a predictor was not of added value.

Using these factors, a mean odds of developing CP can be calculated (Table 4). We present an example to illustrate the practical application of the prediction model. Consider a neonate whose mother received neuroprotection and smoked during pregnancy. The neonate did not develop PVL and was born preterm due to PPROM. In this case, the average odds of (suspected) CP would be 0.148. Table 4 represents all possible combinations with their respective odds of (suspected) CP. From this table, it is confirmed that the average odds of (suspected) CP are the lowest when neuroprotection is provided, the neonate does not develop PVL, the mother does not smoke, and the reason for preterm delivery is placental insufficiency (odds = 0.016). Conversely, the average odds of (suspected) CP are the highest when no neuroprotection is given, the neonate develops PVL, the mother smokes, and the reason for preterm delivery is PPROM (odds = 0.942).

Strengths and limitations

Data collection was conducted both retrospectively and prospectively, resulting in a higher quality study compared to conventional retrospective studies. A superior data collection can be obtained by solely using prospective studies.

The findings in this study correlated with the results found in literature. Furthermore, from a clinical perspective, these results can also be expected.

Only neonates with a known outcome were included in this study. Thus, neonates who were not further followed at the Centre for Developmental Disorders, regardless of the reason why, were not included. This could have resulted in an overestimation of the incidence of CP in the study population. The risk of selection bias should therefore be taken into account.

As mentioned earlier, CP is a heterogeneous group of disorders. Based on the identified factors, counselling can be provided regarding the presence or absence of CP. However, no statement can be made regarding the severity of the disorder.

In the RCTs and meta-analyses, different doses of MgSO4 are infused. Further investigations could focus on two topics. First, the ideal dose of MgSO4 as a neuroprotective agent. Secondly, the long-term effects of the administration of MgSO4 on the development of the children.

Conclusion

In this study, several predictive factors for (suspect) CP are identified in the specific population of extremely to very preterm neonates who are discharged from the NICU. Neuroprotection with MgSO4 is found to be a protective factor. Factors that are negatively associated with CP are PVL, smoking during pregnancy and reason for preterm delivery. Despite extensive research on this topic, this study contributes to raising awareness of potential contributing factors, thereby fostering discussion and encouraging further investigation. Additionally, the findings of this study corroborate existing hypotheses concerning the prevention of CP. This study demonstrates an association between

maternal smoking and the development of (suspected) cerebral palsy (CP). The influence of additional maternal health factors on the development of (suspected) CP warrants further investigation.

Conflicts of interest: All authors declare that they have no conflicts of interest.

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APPENDIX: SEARCH STRATEGY

A. PubMed

A search was conducted using the MeSH terms 'premature birth', 'parturition', 'neurodevelopmental disorders', 'cerebral palsy', 'infant mortality', 'neuroprotection', and 'magnesium sulfate'. An 'All fields' search was also performed to identify articles where these terms appeared only in the abstract or full text, rather than the title. On October 29, 2019, 152 articles were found. A second search on September 25, 2020, yielded 171 articles.

The search query was:

("premature birth"[MeSH] OR ("premature"[All Fields] AND "birth"[All Fields]) OR "premature birth"[All Fields] OR ("premature"[All Fields] AND ("parturition"[Mesh] OR "parturition"[All Fields] OR "birth"[All Fields]))) AND ("Neurodevelopmental Disorders"[Mesh] OR "Cerebral Palsy"[Mesh] OR "infant mortality"[Mesh] OR "Neurodevelopmental Disorders"[All Fields] OR "cerebral palsy"[All Fields] OR "infant mortality"[All Fields] OR ("cerebral"[All Fields] AND "palsy"[All Fields])) AND ("neuroprotection"[Mesh Terms] OR "neuroprotection"[All Fields] OR "magnesium sulfate"[Mesh] OR "magnesium sulfate"[All Fields])

B. Embase

A search was conducted using the PICO model with Emtree terms 'prematurity', 'premature labor', 'magnesium sulfate', 'neuroprotection', 'brain protection', 'cerebral palsy', 'infant mortality', and 'motor dysfunction'. On October 29, 2019, 700 articles were found. A second search on September 25, 2020, yielded 733 articles.

The search query was:

('prematurity'/exp OR 'prematurity' OR 'premature labor'/exp OR 'premature labor') AND ('magnesium sulfate'/exp OR 'magnesium sulfate' OR 'neuroprotection'/exp OR 'neuroprotection' OR 'brain protection'/exp OR 'brain protection') AND ('cerebral palsy'/exp OR 'cerebral palsy' OR 'infant mortality'/exp OR 'infant mortality' OR 'motor dysfunction'/exp OR 'motor dysfunction')

Inclusion and Exclusion Criteria

Using the above search strategy, a total of 904 articles were found. Randomized controlled trials (RCTs), meta-analyses, and reviews were included. Only studies with full text available were retained. Duplicates (n = 216) were removed using the EndNote software. Studies were initially screened based on the title and abstract, followed by full-text screening. Selection was based on the PICO model. Studies not involving the appropriate study population were excluded. Studies using a different neuroprotective agent (e.g., erythropoietin) or using MgSO4 for other purposes (e.g., tocolysis) were excluded. Studies that did not investigate CP outcomes were excluded.

This master's thesis aims to correlate findings from the PRETURN dataset with those from the literature. Only studies with the highest evidence levels, such as meta-analyses and RCTs, were used for comparison. Observational studies were not included. Articles were excluded if they were not in English, French, or Dutch. Due to evolving knowledge on MgSO4 as a neuroprotective agent, only studies published after 2000 were considered. Four additional articles were identified using the snowball method, resulting in a final selection of 14 articles (see PRISMA (Figure 1)).

PRISMA flowchart