A follow up on the feasibility after national implementation of magnesium sulfate for neuroprotection prior to preterm birth

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Abstract
Introduction: The risk for brain injury manifested as cerebral palsy is higher in very preterm born children than in term. Prenatal administration of magnesium sulfate (MgSO4) has been shown to be neuroprotective and reduces the proportion of very preterm born children later diagnosed with cerebral palsy. A Swedish national clinical practice guideline was implemented in March 2020, stipulating the administration of a single intravenous dose of 6 g MgSO4 1–24 h prior to delivery before gestational age 32+0, aiming for 90% treatment coverage. The aim of this study was to evaluate the feasibility of this new clinical practice guideline in the first year of its implementation.

Material and methods: Data on MgSO4 treatment were collected by reviewing the medical charts of women who gave birth to live born children in gestational age 22+0–31+6 during the period of March 1, 2020 to February 28, 2021, at five Swedish university hospitals. Women with pre-eclampsia, eclampsia, or high elevated liver enzymes low platelets (HELLP) were excluded.

Results: A total of 388 women were eligible and 79% received treatment with MgSO4. Of the 21% not receiving treatment, 9% did not receive treatment due to lack of knowledge about the clinical practice guideline, 9% were not possible to treat and 3% had missing data. The proportion treated increased from 72% to 87% from the first

Abbreviations: CP, cerebral palsy; GA, gestational age; HELLP, high elevated liver enzymes low platelets; KVÅ, treatments and actions in medical care code; MgSO4, magnesium sulfate; SNQ, Swedish Neonatal Quality Register; SPR, Swedish Pregnancy Register.

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1 | INTRODUCTION

Cerebral palsy (CP) is a non-progressive lifelong impairment of movement and posture usually caused by brain injury in the perinatal period. Associated conditions include epilepsy and intellectual disability as well as impairment of speech, hearing, and vision.\(^1\) The severity of the disorder spans from slight motor difficulties to severe impairments of motor function, hindering movement and verbal communication.\(^2\)

Although approximately half of the children with CP are born at term, the disorder is much more common in children born preterm. The Surveillance of CP in European network presented a CP prevalence for extremely preterm children, that is, born at gestational age (GA) <28 weeks of 48/1000 live births and among very preterm (born at GA 28–32) of 42/1000, as compared to 4/1000 for late preterm (GA 33–36)\(^3\) and 1/1000 for children born at term.\(^4\)

The etiology for CP differs markedly depending on GA at birth. In term births, the majority suffer a brain injury occurring before onset of labor, whereas the injury at extremely or very preterm birth predominately occurs perinatally, around the time of birth or closely after.\(^5\) The administration of magnesium sulfate (MgSO\(_4\)) to women at risk of imminent preterm birth before GA 32 has been shown to have neuroprotective effects, decreasing the risk of brain injury leading to CP.\(^6\) MgSO\(_4\) has been widely used in clinical practice for decades for tocolysis and prevention and treatment of eclampsia, and its safety is well studied.\(^7\)

The use of MgSO\(_4\) as neuroprotection for the fetus at risk of preterm birth before GA 32 is recommended by the World Health Organization\(^8\) and has been implemented as a clinical routine in the US, Australia and England since several years. Finland implemented MgSO\(_4\) for fetal neuroprotection already in 2012,\(^9\) whereas the other Nordic countries have been more hesitant to introduce the neuroprophylaxis.

In Sweden a national clinical practice guideline has been delayed, partly due to a debate on which dose to use since the literature is inconsistent, with doses varying between studies from a 4g single bolus dose to 6g bolus dose followed by a 2g/h infusion.\(^10\)–\(^15\) A Cochrane meta-analysis concluded that the use of a maintenance dose did not show any additional effect on the CP prevalence\(^16\) and it is not proven that a maintenance infusion is necessary. Some studies have also implicated concern regarding high doses, especially given as prolonged infusions, in extremely preterm births (before GA 28).\(^17\)

Another aspect of clinical guidelines including maintenance infusions is the risk of a lack in staff compliance, both due to the extra work burden of needing a separate intravenous line, the added time for preparing the infusion compared to a bolus dose and also the need for surveillance of the mother during treatment.\(^18\) Hence, based on existing experimental and clinical research,\(^19\)–\(^20\) an expert consensus on administering a single bolus dose of 6 g MgSO\(_4\) to women at imminent risk of preterm birth prior to GA 32+0 was reached in Sweden. A clinical practice guideline was thereafter created by the Swedish Society for Obstetrics and Gynecology perinatal working group together with the Swedish Neonatal Society and implemented nationwide during February 2020. As implementing new guidelines in clinical practice can be challenging as well as important,\(^21\) a follow-up on the feasibility and compliance to the new routine was the aim of this study. The proportion of women getting treatment is a good indicator of the quality of care and a target of 90% receiving treatment has been set based on the treatment target for antenatal steroids created priorly by the Swedish Neonatal Quality Register (SNQ) steering group.\(^22\)

2 | MATERIAL AND METHODS

This study was designed as a retrospective medical chart review. The clinical practice guideline recommends administering a single, slow bolus dose injection of 6 g MgSO\(_4\) iv for 20–30min, when preterm birth is expected or planned within 1–24h. If the treatment is given less than 1h prior to delivery it is stated in the guideline.
that the effect is believed to be less, but it is not harmful and hence administration is encouraged. No extra monitoring of the mother is needed while the bolus dose is given. If birth is delayed, the guideline dictates a second dose when 24 h have passed since the first dose, in case preterm birth still is imminent; however, not repeated more than once. This treatment should not be given to women already receiving intravenous MgSO$_4$ for another indication such as pre-eclampsia. In addition to diagnose coding with the 10th International Classification of Diseases (ICD-10), treatments and actions are in Sweden recorded with classification of actions in medical care (KVÅ), enabling quality register follow-up. The clinical guideline dictates using the KVÅ-code for intravenous administration of MgSO$_4$, and from November 2020 a specific ICD-code became available and replaced the preliminary KVÅ-code. Both these codes in this article are referred to as classification codes. The two quality registers; the Swedish Pregnancy Register (SPR) and the SNQ, collects data about pregnancy and the neonatal period. Currently only SPR registers the use of antenatal MgSO$_4$.

The guideline was sent to all obstetrical clinics in Sweden and presented at two national meetings for specialists in obstetrics in Sweden during 2018 and 2019. Additionally, the guideline was presented at a national meeting for all heads of obstetrical clinics in Sweden and published in the national magazine for specialists in obstetrics and gynecology. The implementation of the guideline started in February 2020 and all clinics were encouraged to use the new guideline by March 2020. Questions were directed to the perinatal working group, which also supported all clinics in the implementation through personal communication.

The follow-up was performed through data collection from medical charts including all preterm live births at GA 22+0 to 31+6, between March 1, 2020 to February 28, 2021 at five Swedish university hospitals, all having a member represented in the perinatal working group as well as being researchers in this study. The hospitals included were the University Hospital of Umeå, Uppsala University Hospital, Karolinska University Hospital (Södertörn and Huddinge), Sahlgrenska University Hospital (Gothenburg) and Skåne University Hospital (Lund and Malmö). Exclusion criteria were pre-eclampsia, eclampsia, high elevated liver enzymes low platelets (HELLP) and neonatal palliative care. The neonatal care for extremely preterm children (born at <28 GA) in Sweden is centralized to university hospitals. Local data collection was performed or overviewed and controlled by members of the research group.

Data were collected as one inclusion per parturient, regardless of single or multiple pregnancies, due to the treatment being given to the mother. An iatrogenic preterm delivery was defined as induction of labor or cesarean delivery without preceding spontaneous labor.

2.1 | Statistical analyses

Data were anonymized and all data were checked manually for consistency and validity. The number of patients retrieved was controlled against data from the SNQ register. Time from start of injection with MgSO$_4$ to birth was calculated in Microsoft® Excel® as well as some of the descriptive data and further analysis was performed in IBM® SPSS® Statistics (28.0.1.1). In cases of multiple births, the time to the first birth was calculated. Distribution was calculated in mean and median with respective dispersion measures. Comparison of the average between groups was made with the independent samples median test due to a large difference between mean and median. The proportion of women receiving treatment and the use of classification codes was compared between groups with cross tabulation and Pearson chi-square test. Level of significance was set at $p < 0.05$.

2.2 | Ethics statement

The Regional Ethical Review Board in Gothenburg approved the study (registration no. Dnr 2022-02472-01 on June 30, 2022, and Dnr 202204904-02 on September 25, 2022) and informed consent was not required. The data were coded and have been registered in accordance with the General Data Protection Regulation (GDPR) and approved by the Data Protection Officer at Sahlgrenska University Hospital. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

3 | RESULTS

A total of 479 women giving birth in gestational week 22±0 to 31+6 between March 1, 2020 and February 28, 2021, at the five included university hospitals were identified through medical charts, matching the number of women registered in SNQ with the same criteria for inclusion (also 479). By search for live births, stillbirth was automatically excluded at identification. A total of 90 women were then excluded due to pre-eclampsia, eclampsia or HELLP and one woman due to a child subjected to palliative care, leaving 388 included women with a mean gestational age of 27±5. Data on inclusion and subgroups are presented in Table 1.

MgSO$_4$ was administered to 305 (78.6%) of the women of whom 246 (80.7%) received treatment within the established timeframe of 1–24 h predelivery (Figure 1). Treatment was given less than 1 h before delivery in 44 women (14.4%). In 29 women (7.5%) the first dose was administered before the specified 24 h time frame before birth (range: 26–236 h), of whom 12 (3.1%) delivered without receiving a second dose. The remaining 17 women received a second dose before delivery, out of whom two women delivered >24 h after the second dose was administered. Average time from start of injection with MgSO$_4$ to delivery was 8.66 h (range: 0.02–236.6 h) SD 22.3, median 3.4 (Figure 1).

When comparing the proportion of women receiving treatment over time, there was a positive trend whereby 71.6% received treatment in the first 3 months compared to 87.1% in the last 3 months of the study period ($p = 0.06$).
TABLE 1 Antenatal MgSO₄ as neuroprotection for the child at preterm birth before GA 32+0, 1 year from implementing a national clinical practice guideline in Sweden.

<table>
<thead>
<tr>
<th>Variable group</th>
<th>Variable</th>
<th>Frequency of treatment administration</th>
<th>Time from administration start to delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (% of total)</td>
<td>Treatment with MgSO₄ N (% within variable)</td>
</tr>
<tr>
<td>MgSO₄ treatment</td>
<td>Yes/No</td>
<td>387 (99.7%)</td>
<td>305 (78.6%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>GA group</td>
<td>Extremely preterm (GA &lt;28)</td>
<td>202 (52.1%)</td>
<td>155 (77.1%)</td>
</tr>
<tr>
<td></td>
<td>Very preterm (GA 28–31)</td>
<td>186 (47.9%)</td>
<td>150 (80.6%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Reason for preterm delivery</td>
<td>Spontaneous</td>
<td>272 (70.1%)</td>
<td>216 (79.7%)</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic</td>
<td>116 (29.9%)</td>
<td>89 (76.7%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>Vaginal</td>
<td>155 (39.9%)</td>
<td>121 (78.1%)</td>
</tr>
<tr>
<td></td>
<td>Cesarean section</td>
<td>231 (59.8%)</td>
<td>184 (79.7%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>1 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Date of birth</td>
<td>2020-03-01–2020-05-31</td>
<td>109 (28.2%)</td>
<td>78 (71.6%)</td>
</tr>
<tr>
<td></td>
<td>2020-06-01–2020-08-31</td>
<td>91 (23.5%)</td>
<td>71 (78.0%)</td>
</tr>
<tr>
<td></td>
<td>2020-09-01–2020-11-30</td>
<td>94 (24.3%)</td>
<td>75 (79.8%)</td>
</tr>
<tr>
<td></td>
<td>2020-12-01–2021-02-28</td>
<td>93 (24.0%)</td>
<td>81 (87.1%)</td>
</tr>
</tbody>
</table>

* denotes p<0.05.

Abbreviations: GA, gestational age; MgSO₄, magnesium sulfate.

FIGURE 1 A histogram on the dispersion of time in hours from start of injection to delivery in women receiving treatment with antenatal magnesium sulfate (MgSO₄) during 1 year from implementation. Mean 8.69, SD 22.3 with 19 extreme outliers.
The correct classification code was used in 214 (69.0%) medical charts of the women who received treatment; however, it was not recorded in 97 cases (29.7%). In four cases (1.0%) the code was used even though treatment was not given. The proportion of women who received treatment and the use of classification codes is presented in Figure 2.

No significant difference was found in the proportion of women that received treatment between groups based on iatrogenic or spontaneous delivery, mode of delivery or gestational age group. The time from start of administration to delivery did not differ between gestational age groups. The median time from start of administration to delivery was significantly longer in vaginal deliveries (4.5 h) as compared to cesarean deliveries (2.8 h); \( p = 0.002 \).

Table 2 includes a list of reasons for not having administered treatment and information on whether treatment could have been given earlier with an enhanced clinical practice guideline. Among the 82 women (21.1%) not receiving treatment, the cause was fast progression of labor and/or serious illness of the mother or child in 35 (42.7%). In 34 women (8.7%) the treatment was not given due to lack of knowledge about the clinical practice guideline. An improved clinical practice guideline was assessed as not being able to change the outcome (administration) in 39 cases (10% of total) with reasons such as birth outside of hospital, need of intensive care of the mother or emergency cesarean section as a vital indication.
4 | DISCUSSION

Reviewing the Swedish implementation of a clinical practice guideline for antenatal MgSO_4 for fetal neuroprotection shows a high feasibility with the number of women treated being close to our national target of 90% at the end of the first year after the initiation. However, a future national follow-up will be problematic since the use of the correct classification code in the medical chart enabling register follow-up was both lower than the number treated and showed a declining trend over time.

In total, 79% of the women in our study received treatment, which is slightly higher than the 73% receiving treatment in a similar one-year follow-up in Australia. Another Australian study showed an increase in women treated from 63% to 86% over a 3-year follow-up within a quality intervention program. A French study reported 87% of children treated with antenatal MgSO_4 during a 5-year period after implementation of a clinical guideline. A third Australian study reported that 69% of children born 6–7 years after implementation of the medical guideline had received antenatal MgSO_4. The use of maintenance infusion has been reported as a barrier to initiating treatment and could explain why our study reached a higher proportion treated than comparable studies even though our time for follow-up after implementation was shorter.

Overall, the time frame from start of administration of MgSO_4 to delivery was short in our sample with a median of 3h and 22 min. Ow et al. reported a similar mean time; 3h and 58 min. No clinical study has yet clarified the optimal interval between MgSO_4 administration and delivery or for how long serum magnesium needs to be elevated in order to provide sufficient neuroprotection. However, Jonsdotter et al. showed that children born >8 h after administration had significantly lower levels of serum magnesium than children born 6–8 h after administration. Turitz et al. published data showing that MgSO_4 administered <12 h prior to delivery was associated with a reduced odds of CP compared with >12 h. Since cerebral injury in very preterm children probably occurs in the first days of life it might be beneficial to administer MgSO_4 close to the delivery. On the other hand, if MgSO_4 induces preconditioning in the brain that lasts for a few days as suggested by some experimental work the time between MgSO_4 and time of delivery may not be critical.

Our study showed a significantly longer time from administration to delivery for women giving birth vaginally as compared to those delivered by cesarean section, probably as a result of the indications for emergency cesarean sections in these gestational ages. When comparing groups based on reason for preterm delivery the women with spontaneous labor received treatment significantly closer to delivery compared to women with iatrogenic delivery. This could be due to the unpredictable nature of preterm labor, making it difficult to evaluate whether labor will subside or result in childbirth.

Most women in our study received one dose of 6g MgSO_4 and only 17 women received two doses (4%). In the study by Ow et al., where a maintenance infusion was used after the loading dose, the median dose was 11.5g and the longest infusion lasted for 4 days corresponding to approximately 192g of MgSO_4. Given the possible risk for negative adverse effects due to excessive doses there might be a considerable risk using maintenance infusions, speaking in favor of giving a single bolus dose.

In about half of the women who did not receive treatment this was due to unavoidable circumstances. However, in 13 women, no reason for not administering MgSO_4 was found. In a survey on barriers and enablers for antenatal MgSO_4 by Gatman et al., 21% of the hospitals reported patients not receiving treatment due to staff shortage. Not being able to evaluate the impact that staff shortage had on compliance to this guideline was a limitation of our study, especially since the implementation coincided with the Covid-19 pandemic that further strained already challenging working conditions. The 34 women who were deprived of treatment due to lack of knowledge about the routine plus the 13 women where no reason for not providing treatment was found, corresponds to 12% of the total, indicating that the treatment target of 90% should be achievable.

When comparing the cases who received treatment vs those who did not receive treatment, there were no significant differences in gestational age, reason for preterm delivery or mode of delivery. Neither was there any difference in time between administration and delivery between groups with different gestational ages. This could indicate that the care was equal, and treatment was given independently of the different prognosis due to gestational age and reason for preterm delivery. The fact that no woman declined treatment and that no treatment was aborted might indicate that the treatment was tolerable and that the women were well informed, which was also reported by Jonsdotter et al.

The classification code was registered in four women not receiving treatment. This might be due to treatment being prescribed but not given, or a misunderstanding by the doctor responsible for the medical chart. The number of women receiving treatment but not giving birth prior to 32+0 was not possible to identify due to the study design being retrospective, the low use of classification codes and limitations in what variables could be used when filtering for eligible women in the medical charts. Ow et al. reported 7% of the women receiving treatment with MgSO_4 not delivering prior to 32 weeks GA and it may be assumed that also in Sweden doses have been given where the pregnancy has continued beyond 32+0. Since the knowledge about the effects on children born at GA >32 receiving antenatal MgSO_4 is unknown, the failure to identify these are a further limitation.

Another limitation, which affects the generalizability of the study, is that we did not have a national, population-based cohort since we only included five out of six university hospitals accepting extremely preterm births and approximately half of hospitals admitting very preterm births. On the other hand, earlier studies that explored the same area all collected data from only one clinic making our study comparably more comprehensive. Additionally, our data were manually checked and then controlled against the national registers, which strengthens the quality of the data significantly.

The fact that the use of classification codes in medical charts were insufficient and decreasing warrants a special focus on this
aspect in future quality improvement work, as well as taking the low reliability on reported treatment in the SPR into account when designing future audits.

5 | CONCLUSION

Evaluating the feasibility of implementing a national clinical practice guideline regarding treatment with antenatal MgSO₄ shows that the proportion receiving treatment increased over time during the first year and almost reached our target of 90% in the last 3 months. Data on why treatment was not given indicated that our target is achievable. Since audit and feedback to the clinics are important factors for successful implementation of a clinical practice guideline and since compliance to clinical routines is a good indicator for the quality of care, continuous follow-up serves multiple purposes. A second study is planned in the future which will include all pre-term births prior to GA 32+0 in Sweden, and evaluate the prevalence of CP up to the age of 5 years among children by comparing data from 4 years before and 4 years after implementation of the clinical practice guideline.

AUTHOR CONTRIBUTIONS

YC, KP, MJ, SS, AH, JÅ, UÅ, MD and HH, conceived and designed the study. SH, AJ, YC, MJ, KP, SS, AH, MD collected all data. SH and YC analyzed the data and wrote the manuscript. All authors provided intellectual input and approved the manuscript. All authors provided intellectual input and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest. YC is currently an employee of AstraZeneca.

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