***Research Article***

***Antenatal magnesium sulfate and preeclampsia differentially affect neonatal cerebral oxygenation***

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Short Title: Magnesium sulfate, preeclampsia, and neonatal cerebral hemodynamics

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**Online supplemental material: Methods**

**Sample size calculation**

Based on previous studies on cerebral near-infrared spectroscopy, a total of 22 infants (11 infants exposed to MgSO4 and 11 controls) would be sufficient to be able to demonstrate a clinically relevant difference in our primary outcome variable cFTOE of 0.1 with a standard deviation of 0.07, a power of 90%, and a significance level of 5%.[1, 2] PE was estimated to be the indication for about one fifth of MgSO4 use at our tertiary care unit. To be able to secondarily analyze the influence of PE on cFTOE, we therefore needed to include at least 60 MgSO4-exposed infants and an equally large control group.

**References**

[1] Keating P, Verhagen E, van Hoften J, ter Horst H, Bos AF: Effect of indomethacin infused over 30 minutes on cerebral fractional tissue oxygen extraction in preterm newborns with a patent ductus arteriosus. Neonatology 2010;98:232-237.

[2] Andropoulos DB, Stayer SA, Diaz LK, Ramamoorthy C: Neurological monitoring for congenital heart surgery. Anesth Analg 2004;99:1365-75.

**Online supplemental material: Results**

**Supplemental Figure 1.** Inclusion flow-chart. CBF, cerebral blood flow; IVH, intraventricular hemorrhage; NICU, neonatal intensive care; NIRS, near-infrared spectroscopy; PEH, preexisting hypertension; PIH, pregnancy-induced hypertension; UMCG, University Medical Center Groningen.

**Infants <32 weeks gestational age**

NICU UMCG

June 2016 – June 2018

n = 271

**Excluded**

No simultaneous cerebral NIRS and CBF measurements (n=74)

Cardiac or chromosomal abnormalities (n=12)

IVH ≥ grade 3 before measurements (n=18)

PIH or PEH (n=9)

Maternal sildenafil (n=4), ketanserin (n=1), indomethacin (n=5)

**Included in analyses**

June 2016 – June 2018

n = 148

**Supplemental Table 1.** Mean values ±SD (number of measurements) for cerebral FTOE, resistance index, peak-systolic blood flow velocity, and %time of impaired cerebral autoregulation within the first 5 days after birth for (a) infants with and without antenatal MgSO4-exposure and (b) infants born following PE and non-PE pregnancy.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **(a)** | **Antenatal MgSO4** | | | | **No antenatal MgSO4** | | | |
| **Day** | **RI** | **PSV (cm/s)** | **cFTOE** | **% time impaired CAR** | **RI** | **PSV (cm/s)** | **cFTOE** | **% time impaired CAR** |
| **1** | 0.70 ±0.08  (26) | 19.60 ±14.42 (26) | 0.15 ±0.08  (70) | 10.46 ±10.26  (15) | 0.67 ±0.07  (21) | 20.0 ±9.43  (21) | 0.16 ±0.09  (64) | 7.28 ±8.67  (12) |
| **2** | 0.71 ±0.08  (31) | 24.54 ±12.43 (30) | 0.14 ±0.09  (73) | 11.31 ±12.17  (22) | 0.71 ±0.09  (32) | 21.31 ±12.74  (31) | 0.17 ±0.13  (69) | 12.72 ±19.80 (17) |
| **3** | 0.72 ±0.08  (21) | 20.13 ±7.73  (19) | 0.15 ±0.10  (74) | 7.10 ±6.93  (22) | 0.72 ±0.09  (14) | 24.34 ±14.29  (14) | 0.17 ±0.10  (69) | 4.96 ±7.36  (23) |
| **4** | 0.76 ±0.08  (14) | 28.04 ±8.90  (14) | 0.16 ±0.09  (73) | 6.62 ±9.08  (22) | 0.70 ±0.07  (14) | 22.34 ±11.76  (13) | 0.20 ±0.09  (68) | 8.58 ±8.14  (20) |
| **5** | 0.73 ±0.06  (10) | 24.96 ±14.83  (10) | 0.18 ±0.10  (68) | 6.74 ±7.78  (23) | 0.71 ±0.07  (9) | 25.55 ±8.40  (10) | 0.19 ±0.10  (65) | 6.74 ±7.44  (19) |
| **(b)** | **PE** | | | | **No PE** | | | |
| **Day** | **RI** | **PSV (cm/s)** | **cFTOE** | **% time impaired CAR** | **RI** | **PSV (cm/s)** | **cFTOE** | **% time impaired CAR** |
| **1** | 0.70 ±0.11  (7) | 13.63 ±4.66  (7) | 0.13 ±0.09  (25) | 8.55 ±9.28  (4) | 0.69 ±0.06  (40) | 20.83 ±12.95 (40) | 0.16 ±0.08  (109) | 9.13 ±9.79  (23) |
| **2** | 0.67 ±0.08  (12) | 18.49 ±7.38  (11) | 0.12 ±0.10  (27) | 13.46 ±16.74  (5) | 0.72 ±0.08  (51) | 23.93 ±13.31 (50) | 0.17 ±0.12  (115) | 11.70 ±15.83  (34) |
| **3** | 0.72 ±0.10  (9) | 19.60 ±6.07  (9) | 0.12 ±0.10  (28) | 12.23 ±8.10  (6) | 0.72 ±0.08  (26) | 22.78 ±12.36 (24) | 0.17 ±0.09  (115) | 5.05 ±6.60  (39) |
| **4** | 0.75 ±0.07  (7) | 25.37 ±7.70  (7) | 0.14 ±0.10  (25) | 12.57 ±14.76  (6) | 0.72 ±0.08  (21) | 25.27 ±11.59 (20) | 0.19 ±0.09  (116) | 6.72 ±7.10  (36) |
| **5** | 0.69 ±0.09  (2) | 18.25 ±2.47  (2) | 0.15 ±0.10  (23) | 8.50 ±6.61  (7) | 0.73 ±0.06  (17) | 26.09 ±12.54 (16) | 0.19 ±0.09  (110) | 6.53 ±7.76  (35) |

CAR, cerebral autoregulation; cFTOE, cerebral fractional tissue oxygen extraction; MgSO4, magnesium sulfate; PE, preeclampsia; PSV, peak-systolic velocity; RI, resistance index.

**Supplemental Table 2.** Mean values ±SD (number of measurements) for the cerebral oxygen saturation, arterial oxygen saturation, mean arterial blood pressure, and heart rate within the first 5 days after birth for (a) infants with and without antenatal MgSO4-exposure and (b) infants born following PE and non-PE pregnancy.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **(a)** | **Antenatal MgSO4** | | | | **No antenatal MgSO4** | | | |
| **Day** | **rcSO2 (%)** | **SaO2 (%)** | **MABP (mmHg)** | **HR (beats/min)** | **rcSO2 (%)** | **SaO2 (%)** | **MABP (mmHg)** | **HR (beats/min)** |
| **1** | 79 ±8 (70) | 94 ±4 (70) | 34 ±4 (15) | 148 ±11 (67) | 79 ±9 (64) | 94 ±4 (65) | 35 ±4 (12) | 149 ±12 (63) |
| **2** | 81 ±9 (73) | 94 ±3 (73) | 36 ±5 (23) | 150 ±9 (71) | 80 ±8 (69) | 94 ±3 (70) | 37 ±8 (18) | 149 ±11 (68) |
| **3** | 80 ±9 (74) | 94 ±4 (74) | 38 ±6 (23) | 153 ±9 (72) | 79 ±9 (69) | 95 ±3 (69) | 36 ±5 (23) | 151 ±11 (68) |
| **4** | 79 ±9 (73) | 94 ±3 (73) | 38 ±6 (22) | 153 ±9 (69) | 77 ±8 (68) | 95 ±3 (68) | 38 ±8 (20) | 150 ±12 (67)\* |
| **5** | 78 ±9 (68) | 94 ±3 (68) | 39 ±10 (23) | 154 ±11 (66) | 78 ±8 (65) | 96 ±3 (65)\* | 38 ±8 (20) | 152 ±11 (65) |
| **(b)** | **PE** | | | | **No PE** | | | |
| **Day** | **rcSO2 (%)** | **SaO2 (%)** | **MABP (mmHg)** | **HR (beats/min)** | **rcSO2 (%)** | **SaO2 (%)** | **MABP (mmHg)** | **HR (beats/min)** |
| **1** | 80 ±9 (25) | 93 ±4 (26) | 32 ±5 (4) | 147 ±8 (26) | 79 ±8 (109) | 94 ±4 (109) | 35 ±4 (23) | 149 ±12 (104) |
| **2** | 81 ±10 (27) | 93 ±3 (27) | 38 ±7 (5) | 150 ±8 (27) | 80 ±8 (115) | 94 ±3 (116)\*\* | 37 ±6 (36) | 149 ±11 (112) |
| **3** | 82 ±9 (28) | 93 ±3 (28) | 40 ±9 (7) | 152 ±10 (28) | 79 ±9 (115) | 95 ±3 (115)\*\* | 36 ±5 (39) | 151 ±11 (112) |
| **4** | 80 ±10 (25) | 93 ±3 (25) | 39 ±10 (6) | 154 ±8 (24) | 78 ±8 (116) | 95 ±3 (116)\*\* | 38 ±7 (36) | 151 ±11 (112) |
| **5** | 80 ±10 (23) | 95 ±3 (23) | 36 ±9 (7) | 158 ±10 (23) | 77 ±8 (110) | 95 ±3 (110) | 39 ±10 (36) | 152 ±11 (108)\*\* |

\* and \*\* indicate a difference compared to the exposure group at *p* < 0.1 and *p* < 0.05, respectively, as assessed using a Student’s t-test or Mann-Whitney U test. HR, heart rate; MABP, mean arterial blood pressure; MgSO4, magnesium sulfate; PE, preeclampsia; rcSO2, regional cerebral tissue oxygen saturation;SaO2, arterial oxygen saturation.

**Supplemental Table 3.** Correlation coefficients (number of analyzed infants) between postnatal cerebral rcSO2 and blood flow parameters within the first 5 days after birth for (a) infants with and without antenatal MgSO4-exposure and (b) infants born following PE and non-PE pregnancy.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **(a)** | | **Antenatal MgSO4** | | | **No antenatal MgSO4** | | |
|  | | **RI** | **PSV** | **EDV** | **RI** | **PSV** | **EDV** |
| **rcSO2 day** | **1** | 0.140 (23) | -0.242 (23) | -0.316 (23) | -0.047 (20) | -0.541 (20)\*\* | -0.515 (20)\*\* |
| **2** | -0.073 (31) | -0.038 (30) | 0.028 (30) | -0.102 (32) | -0.006 (31) | 0.146 (31) |
| **3** | -0.222 (20) | -0.123 (18) | 0.071 (18) | -0.209 (14) | 0.301 (14) | 0.341 (14) |
| **4** | -0.087 (14) | -0.284 (14) | 0.002 (14) | -0.259 (12) | -0.620 (11)\*\* | -0.345 (11) |
| **5** | -0.172 (10) | -0.236 (10) | -0.091 (10) | 0.183 (9) | -0.731 (8)\*\* | -0.310 (8) |
| **(b)** | | **PE** | | | **No PE** | | |
|  | | **RI** | **PSV** | **EDV** | **RI** | **PSV** | **EDV** |
| **rcSO2 day** | **1** | 0.275 (5) | -0.600 (5) | -0.500 (5) | 0.021 (38) | -0.308 (38)\* | -0.324 (38)\*\* |
| **2** | -0.102 (12) | -0.761 (11)\*\* | -0.500 (11) | -0.030 (51) | 0.115 (50) | 0.153 (50) |
| **3** | -0.317 (9) | 0.033 (9) | 0.167 (9) | -0.135 (25) | 0.049 (23) | 0.086 (23) |
| **4** | -0.136 (6) | -0.212 (6) | -0.143 (6) | -0.068 (20) | -0.421 (19)\* | -0.285 (19) |
| **5** | NC (2) | NC (2) | NC (2) | 0.144 (17) | -0.305 (16) | -0.027 (16) |

\* and \*\* depict differences at *p*<0.1 and *p*<0.05, respectively. EDV, end-diastolic velocity; rcSO2, regional cerebral tissue oxygen saturation; MgSO4, magnesium sulfate; NC, not computable; PE, preeclampsia; PSV, peak-systolic velocity; RI, resistance index.