The effect of antenatal magnesium sulfate on left ventricular afterload and myocardial function measured using deformation and rotational mechanics imaging

ARTICLE *in* JOURNAL OF PERINATOLOGY: OFFICIAL JOURNAL OF THE CALIFORNIA PERINATAL ASSOCIATION · AUGUST 2015

Impact Factor: 2.07 · DOI: 10.1038/jp.2015.104 · Source: PubMed

5 AUTHORS, INCLUDING:

Adam James

Rotunda Hospital

12 PUBLICATIONS **19** CITATIONS

SEE PROFILE

Afif EL-Khuffash

Royal College of Surgeons in Ireland

55 PUBLICATIONS **503** CITATIONS

SEE PROFILE

Journal of Perinatology (2015), 1–6

www.nature.com/jp

ORIGINAL ARTICLE

The effect of antenatal magnesium sulfate on left ventricular afterload and myocardial function measured using deformation and rotational mechanics imaging

AT James[1], JD Corcoran[1,2], B Hayes[1], O Franklin[3] and A EL-Khuffash[1,2]

OBJECTIVE: Assess the effect of antenatal magnesium sulfate ($MgSO_4$) on left ventricular function measured using deformation and rotational mechanics imaging.

STUDY DESIGN: Infants who received $MgSO_4$ were matched for gestation, birth weight and mode of delivery with controls. Echocardiography was carried out on days 1 and 2 to measure left ventricle longitudinal strain (LV LS), twist, untwist rate, ejection fraction (EF), and systemic vascular resistance (SVR).

RESULTS: Thirty-eight infants with a median gestation and birth weight of 27.1 weeks and 923 g were included. On day 1, the $MgSO_4$ group ($n = 19$) had a lower SVR and higher LV LS, EF, twist and untwist rate than the Control group ($n = 19$) (all $P < 0.05$). There were no differences between the groups on day 2.

CONCLUSION: Antenatal $MgSO_4$ administration is associated with a lower SVR and higher myocardial function on day 1 in preterm infants < 29 weeks gestation.

Journal of Perinatology advance online publication, 20 August 2015; doi:10.1038/jp.2015.104

INTRODUCTION

The use of antenatal magnesium sulfate ($MgSO_4$) before premature birth for neuroprotection is now well established with most centers offering this therapeutic intervention.[1] Recently, lower magnesium levels in preterm infants during the neonatal period were associated with adverse neurodevelopmental outcomes.[2] However, the impact of antenatal $MgSO_4$ administration on the haemodynamic status of preterm infants during the first 48 h of age is poorly understood. Recent studies have demonstrated inconsistent results of the effect of $MgSO_4$ on cerebral blood flow using Doppler flow measurements.[3,4] Similarly, the early myocardial effects of $MgSO_4$ have not been extensively studied. A recent randomized controlled trial on the effect of $MgSO_4$ on the cardiovascular system in the first 24 h of age demonstrated no consistent cardiovascular effects.[5] Further studies are required to assess the impact of $MgSO_4$ on left myocardial performance, systemic blood flow, LV loading conditions and systemic vascular resistance (SVR) in the first few hours of life.

Recently, our group have demonstrated the feasibility and reproducibility of left ventricular (LV) longitudinal strain (LS) measured using speckle-tracking echocardiography, and LV rotational mechanics (LV apical and basal rotation, LV twist and LV untwist rate) in extremely preterm infants.[6,7] LV LS measured using speckle-tracking echocardiography has the advantage of detecting early myocardial dysfunction in different diseases.[8,9] Similarly, LV rotational mechanics can be assessed using speckle-tracking echocardiography to measure LV twist (the wringing motion of the LV during systole) and LV untwist rate (the recoil of the LV during early diastole thereby generating a suction force for LV filling). The application of those novel echocardiography parameters and their relationship to loading conditions and SVR in preterm infants warrants further study.

In this study, we hypothesize that preterm infants exposed to antenatal $MgSO_4$ for the purposes of neuroprotection have a lower LV afterload and SVR, and a higher myocardial performance measured using speckle-tracking echocardiography. The primary aim of the study was to assess the effect of $MgSO_4$ administration on LV functional parameters, systemic blood flow and loading conditions when compared with infants who did not receive $MgSO_4$.

METHODS

This was a cohort study nested within a larger cohort study designed to define longitudinal myocardial functional parameters in preterm infants < 29 weeks gestation.[10] This patient cohort of 105 infants was assimilated between January 2013 and December 2014 from the Rotunda Hospital, Dublin, Ireland (a tertiary neonatal intensive care unit with 9000 deliveries per annum). Infants who did not receive antenatal $MgSO_4$ (Control group) were matched for gestation (±2 days), birth weight (±100 g) and mode of delivery with infants who were in receipt of $MgSO_4$ before delivery ($MgSO_4$ group). The investigator performing the matching (AK) was blinded to all other infants' characteristics and outcome measures. All infants were inborn in the Rotunda Hospital. Written parental informed consent was obtained from all participants and ethical approval was obtained from the Hospital Ethics Committee.

In the Rotunda Hospital, mothers with pregnancies < 32 weeks gestation who are likely to deliver within 12–24 h are given a 4 g loading dose of $MgSO_4$ over a 20-min period for fetal neuroprotection. No subsequent infusion of $MgSO_4$ is given. Mothers also receive a course of antenatal steroids before delivery where possible (two doses of

[1]Department of Neonatology, The Rotunda Hospital, Dublin, Ireland; [2]Department of Paediatrics, The Royal College of Surgeons in Ireland, Dublin, Ireland and [3]Department of Paediatric Cardiology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland. Correspondence: Dr A EL-Khuffash, Consultant Neonatologist, The Rotunda Hospital, Parnell Street, Dublin 1, Ireland.
E-mail: afif@physicians.ie
Received 23 April 2015; revised 21 July 2015; accepted 22 July 2015

beclomethasone 12 mg, 12 h apart). The main reason for not receiving $MgSO_4$ is the lack of time available between presentation and delivery, or an unexpected preterm delivery. All preterm infants in this study received surfactant and caffeine before the first echocardiography scan.

Clinical demographics

Antenatal, birth and neonatal characteristics were obtained from the database. In addition, clinical cardio-respiratory characteristics during the two echocardiography assessments were collected and included: systolic and diastolic blood pressure, heart rate, mean airway pressure, oxygen requirements, oxygen saturation, invasive ventilation and pH. The following clinical outcomes were also obtained: intraventricular hemorrhage assessed on day 7 of age and classified according to Papile Classification;[11] pulmonary hemorrhage; necrotizing enterocolitis with radiological evidence of pneumatosis; chronic lung disease (CLD) defined as the need for oxygen at 36 weeks corrected gestation; death before discharge.

Echocardiography assessment

Echocardiography was performed on day 1 of life at a median [interquartile range] of 11 h [9–13] (day 1) and at day 2 of life at a median of 40 h [37–46] (day 2) using the Vivid I or Vivid S6 echocardiography system and 10–12 MHz multi-frequency probes (GE Medical, Milwaukee, WI, USA). All studies were conducted using a standardized functional protocol adapted from recently published guidelines.[12] The scans were all stored as raw data in an archiving system (EchoPac, General Electric, version 112 revision 1.3) for later offline analysis. All offline analysis was carried out by a single investigator (ATJ) who was blinded to the $MgSO_4$ status of the infants.

We obtained the following conventional echocardiography markers. The methods for obtaining those parameters, their feasibility and reproducibility, and their reference ranges for this population are described in detail elsewhere:[6,7,10,13] patent ductus arteriosus (PDA) diameter; ejection fraction (EF) measured by Simpson's biplane method; left ventricular output (LVO). For all echocardiography parameters, an average measurement was obtained from three consecutive cardiac cycles. LV wall stress ($g\,cm^{-2}$) was calculated as: $(1.35 \times (\text{mean arterial pressure}) \times (\text{LVESD}))/(4 \times (\text{LVPWT}) \times (1+\text{LVPWT/LVESD}))$, where 1.35 is the conversion factor from millimeters of mercury to grams per square centimeter, LVESD is the LV cavity end-systolic diameter and LVPWT is the LV posterior wall thickness at end systole. Mean arterial pressure was used because it has been shown to provide a reasonable estimate of LV end-systolic pressure in children.[14,15] SVR was calculated by using the following formula: (mean systemic BP – mean tricuspid valve inflow pressure gradient)/LVO.[16]

LV LS. Images were recorded in three planes from the apical four, two and three chamber views at a frame rate of around 110 frames per second to achieve a frame rate to heart rate ratio of 0.7–0.9 as this has been demonstrated to achieve optimal reproducibility.[17] Offline analysis was performed using the EchoPAC system (GE) by tracing the endocardial border to create a region of interest encompassing the entire myocardial wall. Tracking was automatically performed, and the analysis was accepted after visual inspection and when the software indicated adequate tracking. Strain was then calculated for each plane and averaged to provide global LV LS. We previously demonstrated high reproducibility of this technique in preterm infants with an intraclass correlation coefficient of 0.92 (95% CI 0.78–0.97) for intra-observer, and an intraclass correlation coefficient of 0.93 (95% CI 0.66–0.98) for inter-observer reproducibility (all $P < 0.001$).[7]

Left ventricular rotational mechanics. LV base (level of mitral valve) and apex (image distal to papillary muscle) in short axis were obtained from the LV short-axis parasternal view at a similar frame rate to heart rate ratio described above. Data were analyzed using the software described above. The region of interest was obtained manually by tracing around the endocardial border of the LV wall as described above. The software tracks the rotation of the apex and base throughout the cardiac cycle. Peak systole was defined as the time of aortic valve closure. Peak rotation of the apex and base, peak LV twist in systole, and LV untwisting rate in early diastole were determined. The peak rotation was defined as the maximal amount of rotation, positive or negative, during systole. Similarly, the peak twisting was defined as the maximal amount of twist between these time points. Untwisting rate per unit time was measured in the opposite direction during early diastole. We previously reported intra- and inter-observer reproducibility of those parameters with intraclass correlation coefficient values ranging between 0.70 and 0.96.[6]

Right ventricular fractional area change. This describes the change in the RV cavity area from diastole to systole in the four chamber view and provides the dominant contribution to RV EF.[18] There is a strong correlation between right ventricular fractional area change (RV FAC) and RV EF determined by MRI.[19] RV FAC appears to be uninfluenced by significant intra-atrial shunts[20] and therefore may reflect blood returning from the upper and lower circulation. This measurement is obtained by averaging FAC from the apical four-chamber and three-chamber views. The RV three-chamber view is acquired by rotating the transducer anticlockwise from the standard apical four-chamber view until the LV is no longer visible followed by anterior tilting of the probe. Recently, the feasibility, reproducibility and reference values of RV FAC in preterm infants have been established.[10,18]

Statistical analysis

The cohort was divided into two groups based on whether or not they received antenatal $MgSO_4$. Continuous data were tested for normality using the Shapiro–Wilk test and a histogram representation and presented as mean (s.d.) if normally distributed or median [interquartile range] if skewed. Normally distributed data were compared using the Student's *t*-test and skewed data were compared using the Mann–Whitney *U*-test. Categorical variables were presented using count (percent) and compared using Chi-square or Fisher-Exact tests as appropriate. Logistic regression was used to assess the independent effects of $MgSO_4$ and antenatal steroids on CLD. Linear regression was used to assess the independent effect of $MgSO_4$ and antenatal steroids on the echocardiography functional parameters. A *P*-value < 0.05 was considered significant. SPSS (IBM version 22) was used to conduct the statistical analysis.

RESULTS

Nineteen infants < 29 weeks gestation did not receive antenatal $MgSO_4$ over a 2-year period out of a total of 105 infants (18%). Those infants were matched from the same cohort with 19 infants who were in receipt of $MgSO_4$. All infants in the $MgSO_4$ group received the drug within 4 h of delivery. There was no difference in gestation, birth weight, gender, mode of delivery or other antenatal characteristics between the two groups (Table 1). There was a trend toward more antenatal steroid use in the $MgSO_4$ group ($P = 0.05$, Table 1). Infants in the $MgSO_4$ group had a higher rate of CLD compared with the Control group (Table 1). There was no difference between the groups in any of the other parameters. None of the infants developed early onset sepsis.

On day 1, infants in the $MgSO_4$ group had a lower systolic blood pressure (43 (5) vs 50 (11), $P = 0.03$) and a slightly higher pH (7.35 (0.04) vs 7.31 (0.06), $P = 0.01$) when compared with the Control group. There was no difference in any of the other clinical cardio-respiratory characteristics between the groups (Table 2). On day 1, infants in the $MgSO_4$ group had a significantly lower SVR and a significantly higher EF, LV LS, basal rotation, twist, LV untwisting rate and RV FAC. There was a trend toward a lower LV wall stress in the $MgSO_4$ group ($P = 0.06$) (Table 2, Figure 1). All infants had a PDA with no difference in PDA diameter between the groups. On day 2, there were no differences in any of the clinical or echocardiography parameters between the two groups with the exception of a clinically irrelevant difference in oxygen saturations. Seventeen infants in each group had a PDA with no difference in the diameter between the groups (Table 2).

On logistic regression, the association between $MgSO_4$ and CLD became a trend when controlling for antenatal steroids ($P = 0.06$). On linear regression, the association between $MgSO_4$ and EF, LV LS, basal rotation, twist and RV FAC remained significant

when controlling for antenatal steroids (Table 3). Antenatal steroids did not have an independent effect on any of the outcome parameters of interest.

Table 1. Infant characteristics and clinical outcomes

	Control	*$MgSO_4$*	P
Gestation (weeks)	27.4 [25.5–28.0]	27.8 [26.1–28.5]	0.5
Birth weight (g)	980 [921–1143]	880 [810–1220]	0.7
Male	12 (63)	12 (63)	1.0
Cesarean section	10 (53)	10 (53)	1.0
Maternal weight (kg)	62 [57–74]	62 [58–75]	1.0
Maternal body mass index (kg/m^2)	22.8 [20.8–25.9]	22.1 [20.7–28.6]	1.0
Absent end diastolic flow in umbilical artery	0	1 (5)	1.0
Preterm prolonged rupture of membranes	6 (32)	6 (32)	1.0
Antepartum hemorrhage	4 (21)	3 (16)	1.0
Chorioamnionitis	0	1 (5)	1.0
Pre-eclampsia	0	0	NA
Small for gestational age	1 (5)	1 (5)	1.0
5 Min Apgar score	8 [6–9]	9 [8–9]	0.3
Cord pH	7.33 [7.28–7.38]	7.36 [7.35–7.38]	0.2
Full course of antenatal steroids	7 (37)	14 (74)	0.05
Grades III and IV IVH	5 (26)	1 (5)	0.2
Inotropes use (1st week of age)	3 (16)	4 (21)	1.0
Pulmonary hemorrhage	4 (21)	0	0.1
Necrotizing enterocolitis	4 (21)	1 (5)	0.3
Chronic lung disease (in survivors)	5 (31)	13 (68)	0.04
Death before discharge	3 (16)	0	0.2

Abbreviation: IVH, intraventricular hemorrhage. Data are presented as medians [interquartile range] or count (percent). All the cesarean sections in both groups were performed under spinal anesthesia.

DISCUSSION

In this matched cohort study, we demonstrated that exposure to antenatal $MgSO_4$ in preterm infants < 29 weeks gestation is associated with a lower systolic BP and SVR on day 1 of age when compared with infants who did not receive $MgSO_4$. Consequently, those infants had better LV function illustrated by higher LV longitudinal strain, twist and untwist rate, and higher systemic blood flow illustrated by higher LV EF and RV fractional area change, although LVO was not different between the groups. Most of those associations remained significant when controlling for antenatal steroid administration, which was understandably more prevalent in the $MgSO_4$ group. There was no difference in any of the parameters between $MgSO_4$-exposed infants and controls on day 2 of age.

Magnesium is a common cation found in the body with up to 30% of total body concentrations present in intracellular muscle compartments. It has important roles in several processes including gating of calcium channels and trans-cellular membrane ion flux, regulation of vasomotor tone, muscle contraction, cardiac excitability and neurotransmitter release. At a cellular level, magnesium interacts with calcium to regulate its intracellular concentrations. Through its role as a non-competitive inhibitor of inositol 1,4,5-triphosphate (IP_3)-gated calcium channels, magnesium acts as an intracellular calcium antagonist.[21] In the cardiovascular system, magnesium acts as a potent vasodilator through calcium antagonism outlined above leading to a decrease in peripheral vascular resistance and a concomitant increase in cardiac output. Clinically, magnesium administration to mothers with pre-eclampsia results in a significant reduction in SVR and an increase in cardiac output (measured using bioimpedance) with an effect occurring 4 h after administration.[22] It may also possess myocardial stabilizing properties and an improvement of contractile response of stunned myocardium following acute myocardial infarction in adults.[23]

The effect of $MgSO_4$ on the haemodynamic status of preterm infants remains an area of active research. The properties of magnesium described above could explain the potential

Table 2. Difference in cardiorespiratory characteristics and echocardiography parameters between infants with and without $MgSO_4$ on days 1 and 2

	Day 1			*Day 2*		
	Control	*$MgSO_4$*	P	*Control*	*$MgSO_4$*	P
Cardiorespiratory characteristics						
FiO_2	21 [21–47]	21 [21–25]	0.39	21 [21–60]	21 [21–29]	0.73
Mean airway pressure (cm H_2O)	9 (3)	8 (2)	0.18	9 (3)	8 (2)	0.18
Oxygen saturations (%)	95 (3)	95 (2)	0.83	97 (3)	95 (2)	0.02
Invasive ventilation	9 (47)	10 (53)	1.0	8 (42)	7 (37)	1.0
Heart rate	155 (13)	154 (17)	0.75	166 (10)	168 (14)	0.67
Systolic BP (mm Hg)	50 (11)	43 (5)	0.03	53 (9)	52 (8)	0.87
Diastolic BP (mm Hg)	29 (9)	27 (5)	0.59	29 (6)	32 (7)	0.20
pH	7.31 (0.06)	7.35 (0.04)	0.01	7.32 (0.06)	7.31 (0.06)	0.70
Echocardiography parameters						
PDA diameter (mm)	2.4 (0.6)	2.4 (0.4)	0.76	2.7 (0.6)	2.5 (0.9)	0.50
Ejection fraction (%)	55 (8)	60 (6)	0.03	61 (9)	61 (8)	0.87
Left ventricular output ($ml\,kg^{-1}\,min^{-1}$)	138 (70)	155 (50)	0.41	200 (83)	213 (81)	0.63
SVR ($mm\,Hg\,ml^{-1}\,kg^{-1}\,min^{-1}$)	293 [211–479]	238 [170–282]	0.03	203 [151–287]	173 [134–296]	0.72
Wall stress ($g\,cm^{-2}$)	23 (9)	18 (7)	0.06	23 (11)	22 (9)	0.97
LV longitudinal strain (%)	−12.7 (5.3)	−17.4 (3.6)	0.04	−19.6 (2.2)	−20.1 (8.1)	0.84
LV basal rotation (°)	5.6 (7.5)	−1.1 (4.7)	0.03	0.5 (8.1)	−1.0 (8.8)	0.74
LV apical rotation (°)	9.9 (7.4)	9.6 (3.5)	0.9	11.4 (2.5)	10.2 (2.9)	0.42
LV twist (°)	4.1 (2.7)	8.8 (3.2)	0.01	8.5 (1.4)	7.9 (5.1)	0.76
LV untwist rate ($°\,s^{-1}$)	−55 (27)	−110 (59)	0.02	−105 (21)	−73 (55)	0.13
RV FAC (%)	29 [24–39]	39 [30–45]	< 0.01	39 [36–46]	44 [40–50]	0.1

Abbreviations: BP, blood pressure; FAC, fractional area change; FiO_2, fractional inspired oxygen; LV, left ventricle; PDA, patent ductus arteriosus; RV, right ventricle; SVR, systemic vascular resistance. Data are presented as means (s.d.), medians [interquartile ranges] or count (%).

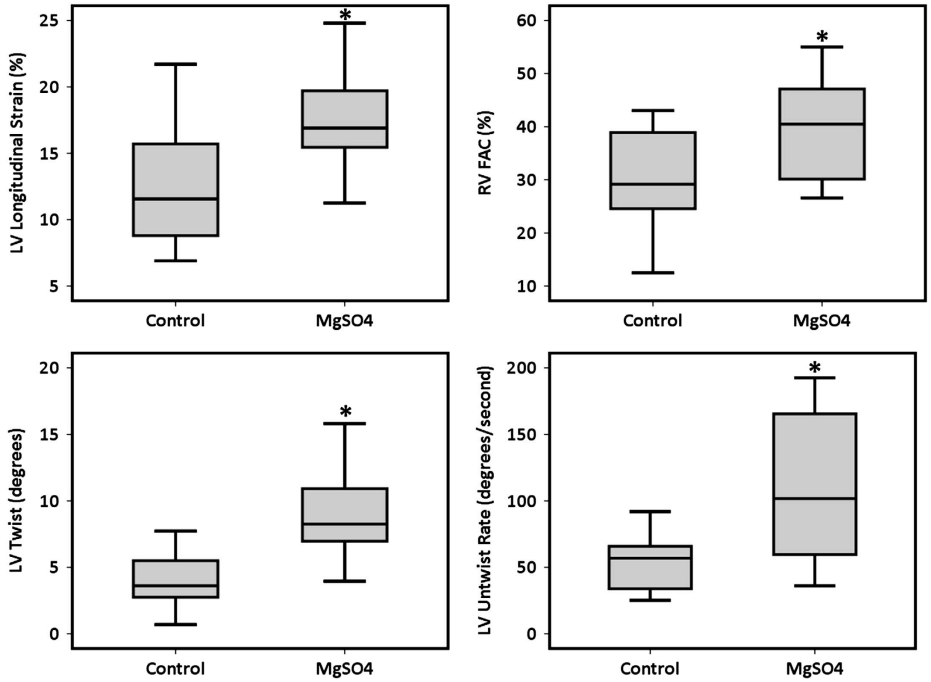

Figure 1. Difference in function parameters between controls and infants in receipt of $MgSO_4$. LV, left ventricle; RV FAC, right ventricle fractional area change. *P-value < 0.05 compared with Control group.

Table 3. Independent effect of $MgSO_4$ and antenatal steroids on outcome parameters using logistic and linear regression

	$MgSO_4$		*Antenatal steroids*	
Outcome	β *Coefficient*	P	β *Coefficient*	P
Chronic lung disease	1.4	0.06	0.3	0.67
Ejection fraction	5.5	0.04	−0.5	0.87
SVR	−82.7	0.06	−46.2	0.29
LV longitudinal strain	4.6	0.04	−0.7	0.75
Basal rotation	−6.7	0.02	5.1	0.07
LV twist	4.5	0.02	−1.9	0.26
LV untwist rate	−57.8	0.06	−13.8	0.63
RV FAC	0.1	0.03	0.03	0.24

Abbreviations: FAC, fractional area change; LV, left ventricle; RV, right ventricle; SVR, systemic vascular resistance. Logistic regression was used for chronic lung disease and linear regression for the remainder of the outcomes. We included $MgSO_4$ use and antenatal steroids as predictor-independent variables and the outcome/functional parameters as dependent variables. The *P*-value in each column represents the significance of the independent effect of the two predictor variables on each outcome tested; β coefficients are unstandardized.

mechanism of its action on the haemodynamic system in preterm infants. This study is the first to assess the impact of antenatal $MgSO_4$ administration on novel echocardiography parameters in the preterm neonatal setting. LV LS measured using speckle-tracking techniques may be a more sensitive marker of myocardial performance than conventional measures (such as shortening fraction). Animal studies have demonstrated that strain measurements are highly dependent on afterload.[24] We recently demonstrated that LV LS in preterm infants is negatively influenced by increasing afterload in the post-PDA ligation model.[7,8] Similarly in this study, we illustrated that $MgSO_4$ administration results in lower blood pressure and SVR (and possibly lower LV wall stress) that leads to a higher LV LS. The lower blood pressure in this cohort did not translate to an increased use of inotropes. The BP-lowering effect of $MgSO_4$ in this setting was previously demonstrated by others.[25]

The use of LV rotational mechanics in preterm infants is gaining interest and this is an example of their application in a clinical setting to further delineate the haemodynamic effects of a therapeutic intervention.[6] LV twist describes the wringing motion of the LV during systole, and is the net result of the contrasting rotation of the apex (in a positive anticlockwise direction) and the base (in a negative clockwise direction) along the long axis of the left ventricle. LV untwist contributes directly to early diastolic filling and is influenced by muscle fiber compliance and elastic recoil properties. These rotational parameters can add important information on myocardial performance.[26] Increased afterload appears to decrease LV twist and untwist rate in experimental animal models (mongrel dogs) and human adults.[27] This is supported by our data demonstrating higher basal rotation, twist and untwist values in infants in receipt of $MgSO_4$ and exposed to lower LV afterload.

The effect of $MgSO_4$ on systemic blood flow remains unclear. In a randomized controlled trial of antenatal $MgSO_4$ administration. Paradisis *et al.*[5] could not demonstrate consistent effects of $MgSO_4$ on systemic blood flow measured using right ventricular output and superior vena cava flow. Although the study demonstrated that a higher proportion of infant in the $MgSO_4$ group had a superior vena cava flow $< 41\ ml\ kg^{-1}\ min^{-1}$ between 10 and 12 h of age, mean superior vena cava flow was not different between the groups. The apparent lack of effect of $MgSO_4$ on systemic blood flow may have stemmed from the poor reproducibility of those methods in determining blood flow.[28,29] This study did not report magnesium levels in the two groups. In our cohort, we demonstrated higher EF (indicating higher cardiac output and pulmonary circulation) and a higher RV FAC (indicating higher RV EF and systemic blood flow) in infants receiving $MgSO_4$. Those methods are reliable and reproducible in preterm infants.[10,18] This may indicate that a lower SVR and higher myocardial performance translated to an increase in systemic

blood flow in those infants. However, further studies are needed to confirm this association. The administration of $MgSO_4$ does not appear to have an influence on PDA diameter or closure rates in the first 2 days of age in our study population.

The clinical relevance of those findings is yet to be determined. In our cohort, with the exception of CLD (which may have been due to the increased survival in that group), there was no significant difference in any of the other outcome parameters between the two groups. It is noteworthy however, that only one infant in the $MgSO_4$ group developed a severe intraventricular hemorrhage (and no deaths) compared with five cases of severe intraventricular hemorrhage in the controls (and three deaths). Previous studies have demonstrated that a stable cardiac output in the first few days of life is protective against severe intraventricular hemorrhage.[30]

The lack of difference in the function parameters between the two groups on day 2 may indicate that the effect of $MgSO_4$ administration is short lived. However, it is noteworthy that on day 2, infant in the Control group achieve function values comparable to those in the $MgSO_4$ group. SVR falls in both groups on day 2 (but to a greater extent in the Control group) and therefore, the improvement of function in the Control group on day 2 may be related to a lowering of SVR.

This study has important limitations. We did not measure infant magnesium levels over the study period and as such, we were unable to examine the associations between the function parameters and magnesium levels. This potential association should be assessed in a larger cohort of infants in future studies. Although, the two groups with the exception of antenatal steroids were well matched, there may have been unknown confounders that have resulted in the difference in the outcome parameters. SVR calculations using echocardiography become problematic in the context of a PDA as what the LV senses will be influenced by the pulmonary vascular resistance. As we had no infants born to mothers with pre-eclampsia, and only one infant born to a mother with chorioamnionitis, the effect of those conditions on the haemodynamic parameters could not be assessed. In addition, maternal weight and body mass index could have potentially affected magnesium distribution in both the mother and the infant. However, as those two parameters were very similar across the two groups, it was not possible to examine their independent effect on magnesium levels or the echocardiography parameters. Finally, the sample size was relatively small and any differences between the groups may have been a result of a type 1 error.

CONCLUSION

The antenatal administration of $MgSO_4$ to preterm infants results in important haemodynamic effects during the first day of age characterized by a lower blood pressure and SVR and a higher myocardial functional parameters. The application of novel echocardiography parameters in preterm infants can help delineate differences in myocardial performance of preterm infants exposed to different therapeutic interventions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This research has received funding from the EU FP7/2007-2013 under grant agreement no. 260777 (the HIP Trial) and from Friends of the Rotunda Research Grant (reference: FoR/EQUIPMENT/101572).

REFERENCES

1 Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* 2009; (1): CD004661.
2 Doll E, Wilkes J, Cook LJ, Korgenski EK, Faix RG, Yoder BA *et al.* Neonatal magnesium levels correlate with motor outcomes in premature infants: a long-term retrospective cohort study. *Front Pediatr* 2014; **2**: 120.
3 Imamoglu EY, Gursoy T, Karatekin G, Ovali F. Effects of antenatal magnesium sulfate treatment on cerebral blood flow velocities in preterm neonates. *J Perinatol* 2014; **34**(3): 192–196.
4 Shokry M, Elsedfy GO, Bassiouny MM, Anmin M, Abozid H. Effects of antenatal magnesium sulfate therapy on cerebral and systemic hemodynamics in preterm newborns. *Acta Obstet Gynecol Scand* 2010; **89**(6): 801–806.
5 Paradisis M, Osborn DA, Evans N, Kluckow M. Randomized controlled trial of magnesium sulfate in women at risk of preterm delivery-neonatal cardiovascular effects. *J Perinatol* 2012; **32**(9): 665–670.
6 James A, Corcoran JD, Mertens L, Franklin O, El-Khuffash A. Left ventricular rotational mechanics in preterm infants less than 29 weeks' gestation over the first week after birth. *J Am Soc Echocardiogr* 2015; **28**(7): 808–817.
7 El-Khuffash AF, Jain A, Dragulescu A, McNamara PJ, Mertens L. Acute changes in myocardial systolic function in preterm infants undergoing patent ductus arteriosus ligation: a tissue Doppler and myocardial deformation study. *J Am Soc Echocardiogr* 2012; **25**(10): 1058–1067.
8 El-Khuffash AF, Jain A, Weisz D, Mertens L, McNamara PJ. Assessment and treatment of post patent ductus arteriosus ligation syndrome. *J Pediatr* 2014; **165** (1): 46–52.
9 Sehgal A, Wong F, Menahem S. Speckle tracking derived strain in infants with severe perinatal asphyxia: a comparative case control study. *Cardiovasc Ultrasound* 2013; **11**: 34.
10 James AT, Corcoran JD, Jain A, McNamara PJ, Mertens L, Franklin O *et al.* Assessment of myocardial performance in preterm infants less than 29 weeks gestation during the transitional period. *Early Hum Dev* 2014; **90**(12): 829–835.
11 Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978; **92**(4): 529–534.
12 Mertens L, Seri I, Marek J, Arlettaz R, Barker P, McNamara P *et al.* Targeted neonatal echocardiography in the neonatal intensive care unit: practice guidelines and recommendations for training writing group of the American Society of Echocardiography (ASE) in collaboration with the European Association of Echocardiography (EAE) and the Association for European Pediatric Cardiologists (AEPC). *J Am Soc Echocardiogr* 2011; **24**(10): 1057–1078.
13 de Waal K, Lakkundi A, Othman F. Speckle tracking echocardiography in very preterm infants: feasibility and reference values. *Early Hum Dev* 2014; **90**(6): 275–279.
14 Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK *et al.* Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr* 2010; **23**(5): 465–495.
15 Rowland DG, Gutgesell HP. Use of mean arterial pressure for noninvasive determination of left ventricular end-systolic wall stress in infants and children. *Am J Cardiol* 1994; **74**(1): 98–99.
16 Noori S, Friedlich P, Seri I, Wong P. Changes in myocardial function and hemodynamics after ligation of the ductus arteriosus in preterm infants. *J Pediatr* 2007; **150**(6): 597–602.
17 Levy PT, Holland MR, Sekarski TJ, Hamvas A, Singh GK. Feasibility and reproducibility of systolic right ventricular strain measurement by speckle-tracking echocardiography in premature infants. *J Am Soc Echocardiogr* 2013; **26**(10): 1201–1213.
18 Levy PT, Dioneda B, Holland MR, Sekarski TJ, Lee CK, Mathur A *et al.* Right ventricular function in preterm and term neonates: reference values for right ventricle areas and fractional area of change. *J Am Soc Echocardiogr* 2015; **28**: 559–569.
19 Anavekar NS, Gerson D, Skali H, Kwong RY, Yucel EK, Solomon SD. Two-dimensional assessment of right ventricular function: an echocardiographic-MRI correlative study. *Echocardiography* 2007; **24**(5): 452–456.
20 Kowalik E, Kowalski M, Hoffman P. Is right ventricular myocardial deformation affected by degree of interatrial shunt in adults? *Eur J Echocardiogr* 2011; **12**(5): 400–405.
21 Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth* 1999; **83**(2): 302–320.
22 Scardo JA, Hogg BB, Newman RB. Favorable hemodynamic effects of magnesium sulfate in preeclampsia. *Am J Obstet Gynecol* 1995; **173**(4): 1249–1253.

23 Dyckner T. Serum magnesium in acute myocardial infarction. Relation to arrhythmias. *Acta Med Scand* 1980; **207**(1–2): 59–66.
24 Ferferieva V, Van den Bergh A, Claus P, Jasaityte R, Veulemans P, Pellens M *et al.* The relative value of strain and strain rate for defining intrinsic myocardial function. *Am J Physiol Heart Circ Physiol* 2012; **302**(1): H188–H195.
25 Rantonen T, Kaapa P, Gronlund J, Ekblad U, Helenius H, Kero P *et al.* Maternal magnesium sulfate treatment is associated with reduced brain-blood flow perfusion in preterm infants. *Crit Care Med* 2001; **29**(7): 1460–1465.
26 Buckberg G, Hoffman JI, Nanda NC, Coghlan C, Saleh S, Athanasuleas C. Ventricular torsion and untwisting: further insights into mechanics and timing interdependence: a viewpoint. *Echocardiography* 2011; **28**(7): 782–804.
27 Burns AT, La GA, Prior DL, Macisaac AI. Left ventricular torsion parameters are affected by acute changes in load. *Echocardiography* 2010; **27**(4): 407–414.
28 Lee A, Liestol K, Nestaas E, Brunvand L, Lindemann R, Fugelseth D. Superior vena cava flow: feasibility and reliability of the off-line analyses. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**(2): F121–F125.
29 Ficial B, Finnemore AE, Cox DJ, Broadhouse KM, Price AN, Durighel G *et al.* Validation study of the accuracy of echocardiographic measurements of systemic blood flow volume in newborn infants. *J Am Soc Echocardiogr* 2013; **26**(12): 1365–1371.
30 Noori S, McCoy M, Anderson MP, Ramji F, Seri I. Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. *J Pediatr* 2014; **164**(2): 264–270.