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NEURO-DEVELOPMENTAL FOLLOW-UP OF NEONATES TREATED WITH MAGNESIUM SULFATE FOR PERSISTENT PULMONARY HYPERTENSION

THESE

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par
Silvia GALLI

Médecin diplômée de la Confédération Suisse

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Neuro-developmental follow-up of neonates treated with magnesium sulfate for persistent pulmonary hypertension

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Directrice de l'Ecole doctorale

Rapport de synthèse

DEVENIR NEURO-DEVELOPPEMENTAL DE NOUVEAU-NES TRAITES PAR DU SULFATE DE MAGNESIUM POUR UNE HYPERTENSION PULMONAIRE PERSISTANTE

L'hypertension pulmonaire persistante du nouveau-né (HTPP) est un trouble de l'adaptation post-natale de la circulation pulmonaire caractérisé par une défaillance de la diminution normale des résistances vasculaires pulmonaires, accompagné d'un shunt droite-gauche, résultant en une hypoxémie profonde. C'est une pathologie sévère nécessitant des soins intensifs avec un risque augmenté de handicaps neurologiques chez les survivants.

Le traitement de l'HTPP du nouveau-né inclut une ventilation mécanique ainsi que différents agents pharmacologiques pour dilater les vaisseaux pulmonaires, dont le sulfate de magnésium ($MgSO_4$) à hautes doses par voie intraveineuse et le monoxyde d'azote par voie inhalée (iNO). Le $MgSO_4$ est une alternative thérapeutique de l'HTPP du nouveau-né avec peu d'effets secondaires et une mortalité basse. Il a aussi été démontré que le $MgSO_4$ est un traitement de l'HTPP du nouveau-né autant efficace que le iNO et moins coûteux.

Des études sur le suivi neuro-développemental de nouveau-nés avec HTPP traités selon différentes méthodes ont été publiées reportant des taux élevés de handicaps majeurs et mineurs. Plus récemment, des études de suivi après traitement par iNO ont montré des taux plus bas qu'avec des traitements antérieurs. Le devenir neuro-développemental à long terme d'enfants traités avec du $MgSO_4$ n'a pas été documenté.

Le but de cette étude est de décrire le développement des enfants qui ont présenté une HTPP traitée seulement avec du $MgSO_4$, de reporter l'incidence de handicaps majeurs et mineurs, et de les comparer à un groupe contrôle d'enfants sains du même âge ainsi qu'aux données de la littérature.

La population consiste en 33 nouveau-nés traités pour une HTPP avec seulement du $MgSO_4$ (groupe étude) et 32 nouveau-nés à terme sains (groupe contrôle). Un suivi neuro-développemental standardisé et approfondi a été effectué aux âges clés de 18 mois et 5 ans.

Les taux de handicaps majeurs à 18 mois et 5 ans dans le groupe étude étaient de 6% et 11,4% respectivement, et de 0% aux deux âges dans le groupe contrôle. Les taux de handicaps mineurs aux mêmes âges étaient de 3% et 26,9% pour le groupe étude, et de 0% et 26,1% pour le groupe contrôle. Les quotients développementaux moyens à 18 mois étaient de 106,6 (DS 1,6) dans le groupe étude et de 118,3 (DS 1,0) dans le groupe contrôle ($P < 0,001$). L'index général intellectuel en âge préscolaire était de 112.6 (DS 3.7), respectivement de 119.3 (DS 3.1), sans différence significative entre les deux groupes.

A 18 mois, les taux de handicaps majeurs et mineurs dans les groupes études et contrôle étaient de 6% et 3%. Dans la littérature, des taux entre 0% et 33% ont été décrits. A cet âge, il y avait une différence significative pour tous les scores du test de Griffiths, même en tenant compte du status socio-économique de la famille. Ceci suggère un léger retard du développement global et non une altération spécifique. Ces différences n'étaient plus significatives en âge préscolaire, suggérant un rattrapage développemental. Le taux de handicaps majeurs en âge préscolaire pour le groupe étude était de 11.5%, sans aucune infirmité motrice cérébrale. Ces résultats correspondent à ceux d'études de suivi après d'autres traitements jusqu'à l'âge de 24 mois avec des taux variant de 0% à 15%. Le taux de handicaps mineurs était de 26.9% dans le groupe étude et de 26.1% dans le groupe contrôle, sans différence significative entre les deux groupes. L'incidence de handicaps mineurs dans le groupe étude était plutôt élevée en comparaison aux données de la littérature (6 à 22% à 6 ans). Une explication possible est que nous avons considéré des problèmes de langage et de comportement comme handicaps mineurs. Ceci suggère une différence méthodologique et non une plus mauvaise issue dans nos deux groupes. Les évaluations cognitives des enfants des deux groupes se trouvaient dans la norme, ce qui est aussi le cas dans la littérature.

En conclusion, cette étude longitudinale non randomisée d'enfants traités avec du $MgSO_4$ seul pour une HTPP sévère ne montre pas de conséquences sur le devenir neuro-développemental à long terme. Cette étude le démontre pour la première fois. Malgré le fait que iNO soit le traitement actuellement recommandé pour l'HTPP du nopuveau-né, le $MgSO_4$ reste largement utilisé, en particulier dans des pays en voie de développement. L'absence de complications neuro-développementales majeures à long terme permet de considérer l'administration du $MgSO_4$ pour le traitement de l'HTPP du nouveau-né en cas de non réponse ou d'inaccessibilité au iNO.

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Neuro-developmental follow-up of neonates treated with magnesium sulfate for persistent pulmonary hypertension

S. Galli, M. Bickle Graz, M. Forcada-Guex, V. Muehlethaler, L. Jaunin and J.-F. Tolsa *
Developmental Unit, Pediatric Department, Centre Hospitalier Universitaire Vaudois and University of Lausanne, 1011 Lausanne, Switzerland

Abstract. Persistent pulmonary hypertension of the newborn (PPHN) is a life threatening condition associated with an increased risk of neurological impairment. Magnesium sulfate ($MgSO_4$) is an alternative and low cost treatment for PPHN. Despite more appropriate and available therapies $MgSO_4$ is still widely used, especially in developing countries, but long-term follow-up is unknown. In a retrospective controlled study we evaluated whether $MgSO_4$ therapy for PPHN was associated with increased neuro-developmental impairments at follow-up, as compared to a control group. Population consisted of 33 infants treated for PPHN with $MgSO_4$ only (study group) and 32 healthy term infants (control group). Extensive neuro-developmental follow-up examination was performed at 18 months and 5 years of age. Rate of major impairments and minor impairments were evaluated and compared to the literature.
The rates of major impairments in the study group at 18 months and 5 years were 6% and 11.4%, respectively, and 0% at both ages in the control group. The rates of minor impairments at the same ages were 3% and 26.9% for the study group, and 0% and 26.1% for the control group. Mean developmental quotients at 18 months were 106.6 (SD 1.6) in the study group and 118.3 (SD 1.0) in the control group ($p < 0.001$). General intellectual index at preschool age was not significantly different between the two groups. Treatment with $MgSO_4$ does not increase the rate of disability, as compared to other treatments for PPHN.

Keywords: Persistent pulmonary hypertension of the newborn, magnesium sulfate, neuro-developmental follow-up

1. Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a pulmonary vascular disorder characterized by a failure of the normal postnatal fall in pulmonary vascular resistance which leads to persisting right to left shunts across the fetal channels and resultant hypoxemia [28]. Newborn infants with PPHN are at risk for severe hypoxemia and its complications, including death, chronic lung disease, and abnormal neurocognitive outcome. This condition occurs in nearly-term, term, and mostly post-term newborns. Based on a recent survey, PPHN incidence is 1.9 per 1000 live births with a wide variation observed among centers (0.43–6.82 per 1000 live births) [53].

Different risk factors and etiologies have been associated with PPHN such as perinatal asphyxia, aspiration of clear, bloody or meconial amniotic fluid, severe infections and hyaline membrane disease. Major malformations like diaphragmatic hernia and pulmonary hypoplasia are also associated with PPHN.

Associated morbidities and mortality are very variable and depend mainly on underlying etiologies and the type of treatments. The mortality rate is estimated at 11% ranging between 4% and 33% [53].

Different treatments have been proposed and reviewed [29,54]. Besides mechanical ventilation, vasodilator agents are administered intravenously (Tolazoline, Prostacyclin, Magnesium sulfate) or via inhala-

*Corresponding author: Dr. J.-F. Tolsa, Division of Neonatology, Pediatric Department, University Hospital CHUV, 1011 Lausanne, Switzerland. Tel.: +41 21 314 36 92; Fax: +41 21 314 34 77; E-mail: Jean-Francois.Tolsa@chuv.ch.

tion like nitric oxide (iNO) or prostacyclin. Extracorporeal membrane oxygenation (ECMO) is still recommended in case of failure of these therapies. Before the era of iNO, high doses of magnesium sulfate ($MgSO_4$) have been proposed in preterm and term newborns [1, 50,56]. $MgSO_4$ has been shown to be effective, with few side effects and low mortality [50]. Despite the fact that iNO is now recognized as the first line treatment for PPHN [11], $MgSO_4$ therapy is still widely used, especially in developing countries where iNO is not available [8,14,15,41]. Recently, $MgSO_4$ has also been shown to be as safe in treating moderate PPHN as iNO, and cheaper [42]. Neuro-developmental follow-up studies of infants with PPHN following different kinds of treatments (hyperventilation, vasodilators and ECMO) have been published during the last 20 years reporting a high rate of minor and major handicaps [5, 10,24,31,46,55]. More recently, follow-up studies of newborn infants treated with iNO showed that the occurrence of minor and major handicaps was lower than with previous treatments [17,34,49]. Besides its use for the treatment of PPHN, $MgSO_4$ has also been evaluated for its neuroprotective effects during fetal or neonatal hypoxic-ischemic injury. Both protective and deleterious effects have been reported in animal studies [22, 45] as well as in human studies [26,33].

Newborn infants suffering from PPHN are in a condition of hypoxia-ischemia, which may have effects on the brain and be influenced by high doses of $MgSO_4$. However long-term effects on neurodevelopment of $MgSO_4$ as a treatment for severe PPHN have not been reported so far [25].

The purpose of this study is to report the incidence of major and minor handicaps and to describe the development of children who presented with PPHN treated only with $MgSO_4$, as compared to a control group of healthy children of the same age and to the data of the literature.

2. Methods

2.1. Population

Population consisted in two groups of patients. A "study" group of infants who had presented PPHN treated with $MgSO_4$ and a "control" group of healthy newborns born during the same period. Written and oral information were given to parents about our follow-up program, which has been approved by the ethics committee for clinical research of the University of Lausanne.

2.2. Study group

Eighty-five newborns admitted to our Neonatal Intensive Care Unit with severe persistent pulmonary hypertension were treated with $MgSO_4$ between January 1, 1992 and December 31, 1998 as described previously [50]. This treatment was offered as a compassionate therapy to the parents while no other better treatment was available in our unit at that time. Briefly, a loading dose of 200 mg/kg $MgSO_4$ was given intravenously over 20 minutes, followed by a continuous infusion of 20–150 mg/kg/hour to obtain a total magnesium blood concentration between 3.5 and 5.5 mmol/l. Cardiac output was supported with dopamine and/or dobutamine infusion. Duration of magnesium therapy was between 3 to 5 days. No side effects were observed. The diagnosis of PPHN was considered in the presence of a persistent hypoxemia (post-ductal partial arterial pressure in oxygen (PaO_2) < 50 mmHg or <6.67 KPa) under respiratory support with a fraction of inspired oxygen (FiO_2) of 1.0 and maximal conventional ventilation. PPHN was also considered under similar respiratory support in the presence of persistent hypoxemia out of proportion to the degree of lung disease on the chest radiograph and/or an important lability of oxygenation with great variations in PaO_2 without changes in ventilator settings. PPHN was confirmed by echocardiography in all patients and cardiac heart disease was ruled out.

Among the 85 infants, 33 were excluded, 21 because they were on other therapies before initiating treatment with $MgSO_4$ (9 intravenous tolazoline and/or hyperventilation, 12 iNO), and 12 because of the presence of major malformations including diaphragmatic hernia and lung hypoplasia associated with various clinical syndromes. Among the 52 newborns treated with $MgSO_4$ only, 4 died in the neonatal period (7.7%) and 1 after discharge from sudden infant death. Forty-seven newborns were finally included in our neuro-developmental follow-up program.

Among the 47 survivors, 14 were lost to follow-up, 33 (70.2%) were examined at our neuro-developmental clinic at 18 months and 26 (55.3%) were controlled a second time at preschool age (3.5 to 5 years).

2.3. Control group

Thirty-six infants, all full-term newborns (gestational age $\geqslant$37 weeks), born in the maternity of the University Hospital in Lausanne, were enrolled in our follow-up program from January 1 to December 31, 1998.

Infants from mothers with multiple pregnancies, difficulties during pregnancy or delivery, somatic abnormalities, or from parents with psychiatric problems were excluded. Thirty-two children (88.9%) were examined at 18 months and 23 (63.9%) at preschool age.

2.4. Neonatal data

Neonatal history, as well as demographic and social data, were retrospectively collected for each patient. Clinical data included birth characteristics, neonatal pathologies associated with the development of PPHN, and treatment including ventilatory settings during the neonatal hospitalization. The lowest PaO_2, the Oxygenation Index (OI) and the Alveolo-arterial Oxygen Difference (A-aDO_2) were registered as severity indices before the introduction of $MgSO_4$. Pathologies associated with the development of PPHN were respiratory distress syndromes following meconium aspiration, pneumothoraces, infection, asphyxia, and hyaline membrane disease.

Socio-economic status (SES) was calculated by a six-point scale of parental occupation, a score of 1 representing an academic position and a score of 6, unskilled work [30].

2.5. Follow-up procedure

Children were examined by pediatricians at 18 months and at pre-school age by pediatricians and psychologists not involved in the initial neonatal care.

Follow-up examination at 18 months consisted of a detailed neurological examination according to Amiel-Tison [3] and of an assessment of psychomotor development using the Griffiths scales [23]. The evaluation of vision and hearing was also performed [48]. If necessary, children were referred to an ophthalmologist and/or for audiometric assessment.

Follow-up examination at pre-school age included a comprehensive standardized neurological examination adapted from Touwen [52]. The evaluation of vision and hearing was performed as at 18 months.

Cognitive abilities were evaluated with the McCarthy Scale of Children's Abilities [38] administered by a psychologist who also evaluated clinically the language and behavioral characteristics according to the Diagnostic and Statistical Manual Disorders (DSM IV) [2].

2.6. Outcome parameters

At 18 months, outcome parameters included major impairments, minor impairments and psychomotor development. Major impairments consisted in developmental delay with a developmental quotient below 70, cerebral palsy (CP), neuro-sensory hearing loss (auditory threshold above 60 dB), severe visual impairment and epilepsy. Minor impairments included non-CP neurological abnormalities and sensorial disorders such as minor hearing loss, squint and refractive errors. Psychomotor development was evaluated by the 5 Griffiths sub-scores, Locomotor, Personal-Social, Hearing and Speech, Eye-Hand Coordination and Performance, and the global Development Score (DQ). Each score was standardized for an expected value of 100 with a Standard Deviation (SD) of 15.

At preschool age, outcome parameters included major impairments, minor impairments and cognitive abilities. Major impairments were defined as at 18 months, with intelligence quotient below 70. Minor impairments included neuro-motor signs, minor hearing loss, squint, refractive errors, language and behavior disorders. For each child, a General Intellectual Index (GII) with scores in the five subscales of the McCarthy Scale of Children's Abilities was calculated. GII was standardized for an expected value of 100 (SD of 16) and the subscale scores (Index) for an expected value of 50 (SD of 10).

2.7. Statistics

All the informations were registered and analyzed using the Statistical Package for Social Science software (SPSS, version 10.0). Univariate analysis of variance (ANOVA) and the Chi-square test with Yates correction, or the Fischer's test (for small numbers) were performed for comparisons between groups. Multivariate analysis of variance (MANOVA) was chosen when one independent variable was to be controlled. The threshold for statistical significance was considered when p value was below 0.05.

3. Results

Birth characteristics of the 65 patients (33 treated with $MgSO_4$, 32 control) who were followed are summarized in Table 1.

There were no statistical differences in the neonatal characteristics between the study and the control groups

Table 1
Birth characteristics

Birth characteristics	Study group ($n = 33$)	Control group ($n = 32$)	p value
Males (%)	20 (60,6)	18 (56,3)	NS
Gestational age (weeks)	37.1 (2.3)	39.8 (1.1)	NS
Birth weight (grams)	2905 (570)	3303 (466)	NS
Inborn	10 (30)	32 (100)	<0.001
Apgar at 1 minute	7.1 (2.1)	8.8 (1.4)	<0.001
Apgar at 5 minutes	7.9 (1.9)	9.3 (0.8)	<0.001
SES index (Largo)	3.2 (1.2)	2.3 (1.1)	0.004

Values represent means (standard deviations in parenthesis), except for males expressed in actual numbers.

except for the APGAR scores at 1 and 5 minutes which were significantly lower in the study group ($p < 0.001$). The SES was significantly higher in the study group ($p = 0.004$), corresponding to a lower socio-economic status.

3.1. Neonatal course in the study group

Pathologies associated with the development of PPHN consisted for the 33 children followed-up in 12 (36%) aspiration syndromes, 9 (27%) pneumothoraces, 12 (36%) sepsis/pneumonia, 7 (21%) neonatal asphyxia, and 4 (12%) hyaline membrane disease. Before the introduction of $MgSO_4$, all patients were under maximal conventional ventilation with a mean airway pressure of 16.7 (SD 3.0) cm H_2O and an FiO_2 of 1.0. The patients were severely ill with a lowest mean PaO_2 of 41.5 (SD 11.5) mmHg, an OI of 45.2 (SD 21.2) and an a-A DO_2 of 626.5 (SD 14.8) mmHg. All newborns were treated with a potentially ototoxic agent, 31 (94%) with furosemide and 33 (100%) with gentamicin. Mean duration of $MgSO_4$ therapy was 3.4 (SD 1.4) days. Conventional ventilation was necessary during a mean of 7.8 (SD 4.2) days and total oxygen supplementation during a mean of 17.9 (SD 30.1) days. They were all discharged from hospital free of any treatment after a mean hospital stay of 31 (SD 26) days.

The neonatal course of the 14 infants lost to follow-up did not differ from that of the 33 children followed-up except for the mean airway pressure which was significantly higher for the followed group, respectively 16.7 (3.0) and 13.9 (2.5) cm H_2O, $p < 0.03$.

3.2. Outcome at 18 months

Thirty-three children were examined at 18 months of age in the study group and 32 in the control group. The age of the infants at the follow-up evaluation was 19.7 months (SD 2.1; range 17.5–25.0) for the study group and 18.4 months (SD 0.5; range 18.0–19.5) for the control group.

Most of the infants in the study group and all controls were neurologically normal at 18 months. In the study group, major impairments were detected in 2 infants and minor impairments in 1 infant. Among the children with major impairments, one presented a severe visual impairment due to a bilateral optical atrophy, which was considered to be unrelated to neonatal history, and the other one presented a severe sensorineural hearing loss in the context of a Streptococcus B sepsis complicated by multiple pneumothoraces and PPHN. The child with minor impairment had a squint.

The mean DQ of infants without major impairment was of 106.6 (SE 1.6) in the study group ($n = 31$) and of 118.3 (SE 1.0) in the control group ($n = 32$). The difference between the 2 groups was statistically significant (F: 38.82; $p < 0.001$) and remained significant even when the SES was controlled (F: 33.01; $p < 0.001$). A normal distribution was observed for the two groups with a shift on the left for the study group (Fig. 1). This shift is congruent with the difference observed for the means.

The components of the 5 subscales of the Griffiths scale were analyzed separately for the study and the control groups. The means of the subscales and standard deviations are illustrated in Fig. 2. All the scores were significantly lower for the study group, even when the SES was controlled.

3.3. Outcomes at preschool age

Preschool age evaluation was performed between 3,5 and 5 years in 26 children in the study group and 23 in the control group. Seven children from the study group were lost for this second follow-up visit. According to their parents and/or pediatrician they were all developing normally.

The age of the children at the preschool follow-up evaluation was 51.1 months (SD 9.2) for the study group and 45.2 months (SD 0.9) for the control group.

Most children of both groups were neurologically normal at preschool age. The incidence of major impairments at preschool age was of 11.5%. A third child of the study group presented a major impairment. This child developed at the age of 3.5 years epilepsy and mental retardation (GII<50) of probable genetic etiology. During the neonatal period he never had seizures and cerebral ultrasound were normal. No child in the control group developed a major impairment.

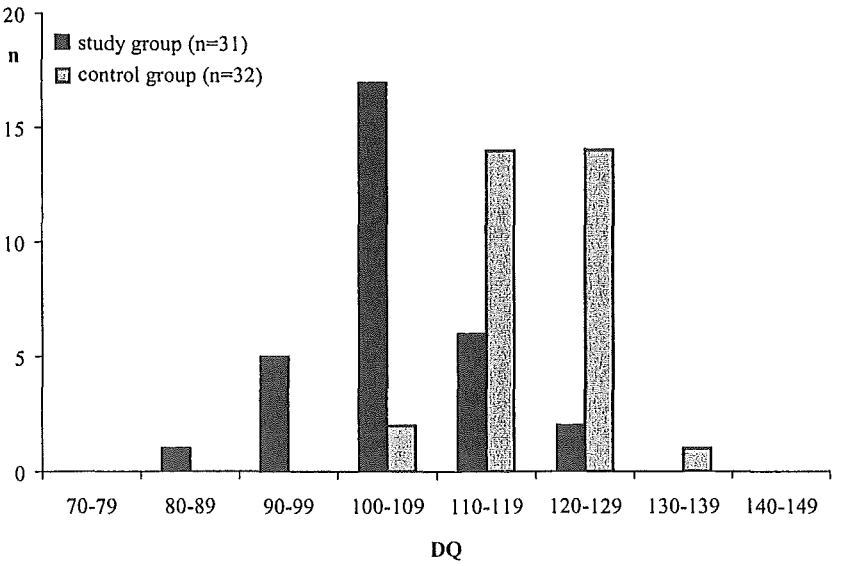
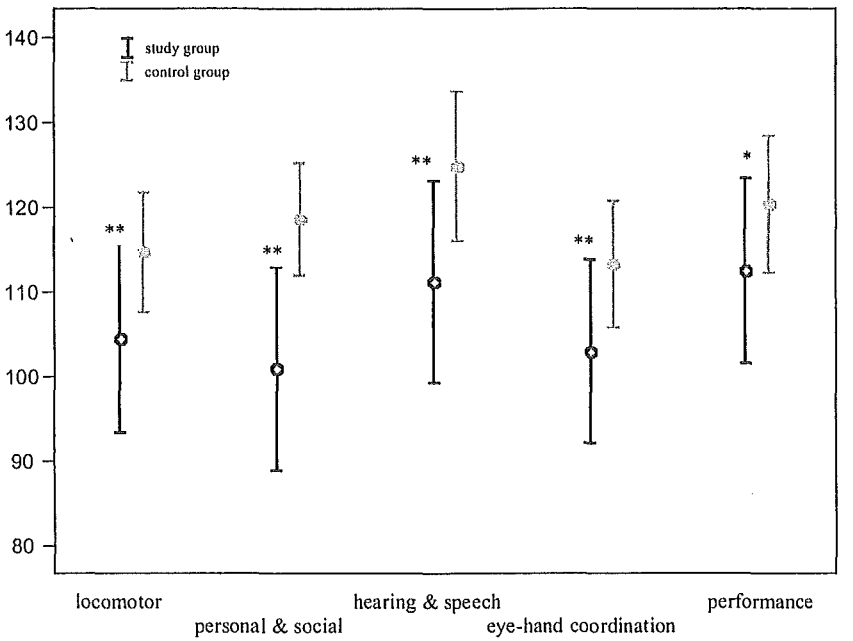


Fig. 1. Developmental Quotient (DQ) at 18 months (children without major impairment).



Bars represent means ± 1 SD
MANOVA, SES controlled: ** $p < 0.001$, * $p < 0.01$

Fig. 2. Griffith's subscales at 18 months.

An increase in minor impairments was observed between 18 months and preschool age in both groups. Minor impairments were observed in 7 children (26.9%) in the study group and in 7 children (30.4%) in the control group.

Concerning the cognitive competences, the means for the GII for the study and the control groups (infants with major impairments excluded) were of 112.6 (SD 3.7) and 119.3 (SD 3.1), respectively. These scores were not statistically different whether the SES was

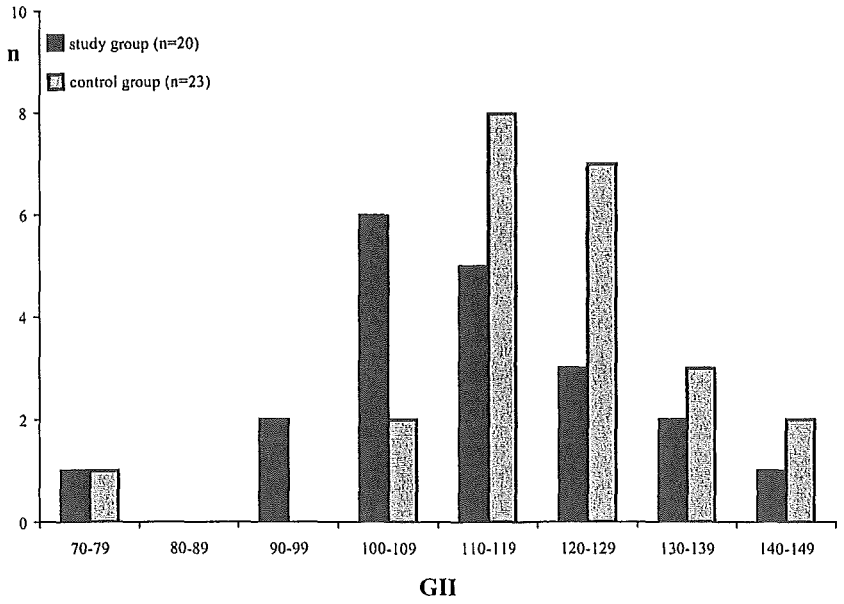


Fig. 3. General Intellectual Index (GII) at preschool age (children without major impairment).

controlled (F: 0.101) or not (F: 2.029).

Figure 3 illustrates the distribution of the scores for the General Intellectual Index in the two groups. A normal distribution was observed for the two groups with a shift on the left for the study group. However the overlap of the two groups increased between 18 months and preschool age and statistical differences were no longer observed.

The 5 subscales of the McCarthy scale of children's abilities were analyzed separately for the study and the control groups and are illustrated in Fig. 4. When the SES is not controlled, the scores for the quantitative index (F: 4.16; $p < 0.05$) and the memory index (F: 5.44; $p < 0.05$) are significantly different between the two groups. This is no longer the case when the SES is taken into account in a MANOVA analysis.

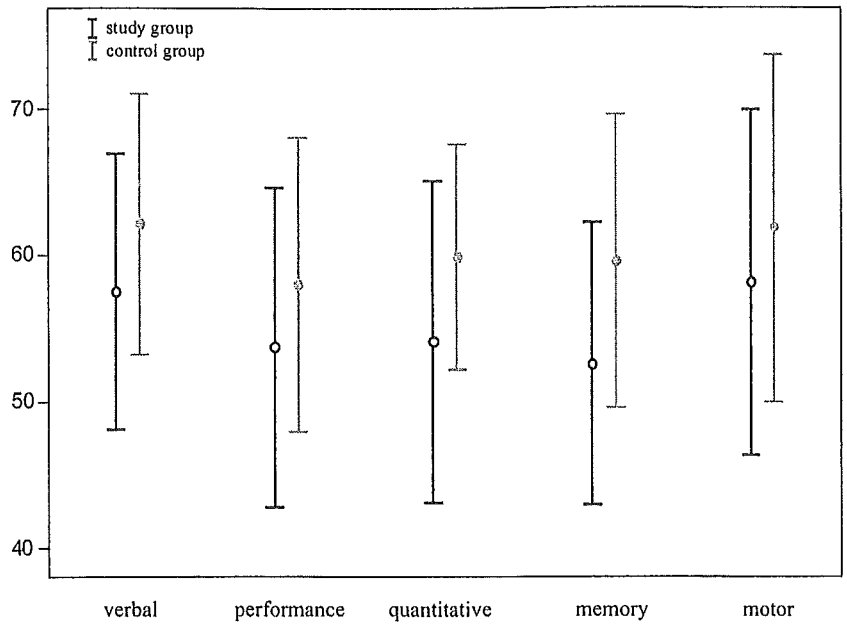
4. Discussion

Magnesium sulfate is an alternative and low cost treatment for PPHN. Despite more appropriate and available therapies such as iNO or prostacyclin, high doses of $MgSO_4$ are still widely used, especially in developing countries [8,14,15,41]. At high serum concentrations, magnesium is a muscle relaxant and vasodilatory agent. Animal studies have shown that magnesium can prevent and reduce hypoxia-induced pulmonary hypertension [12,37]. Substantial evidence suggests that magnesium may modulate vasoactivity by affecting the influx of extracellular Ca^{2+}. Inhibition of voltage-dependent Ca^{2+} channels by magnesium may be one of the mechanisms by which the pulmonary vasculature relaxes during intravenous treatment with magnesium [51]. It may also act through effects on the metabolism of prostaglandins, suppression of the release of catecholamines, activation of adenyl cyclase, and reduction of the responsiveness of smooth muscles to vasopressors [54].

Neuro-developmental outcome of infants treated for PPHN with various therapies have been extensively reported [4,6,19,31,34,36,44,49] but long-term outcome of infants treated with high doses of magnesium is not documented [25]. Moreover, the effects of high doses of magnesium on fetuses in case of maternal therapy for pre-eclampsia [13,35,39,40] or in newborns to prevent adverse outcomes of severe birth asphyxia [16,26, 32] are controversial. We therefore aim to describe the long term follow up of infants treated with high doses of magnesium as a sole therapy for severe PPHN compared to a control group and the literature.

Our population of newborns treated with high doses of $MgSO_4$ consisted in 52 neonates among which 4 died in the neonatal period (mortality rate 7.7%). This mortality rate is comparable to recent data with other treatments [27,49].

At 18 months, 2 children (6 %) had major impairments and 1 (3%) a minor impairment. Widely divergent incidences of impairments are reported in the literature. They vary between 0% [6] and 33% [31],



Bars represent means ± 1 SD
MANOVA, SES controlled: * $p < 0.05$

Fig. 4. McCarthy subscales at preschool age.

reflecting the difficulty in comparing outcome data of follow-up studies with methodological differences.

Mean DQ scores of the study and the control groups observed at 18 months were all distributed in the normal range. There was a significant difference between the two groups on all the scores of the Griffith's test, even when the socio-economic status of the family was controlled. This suggests a minor global developmental delay and not a specific developmental alteration. These differences are difficult to explain and were no longer significant at preschool age, suggesting a developmental catch-up. We postulate that the minor developmental delay observed at 18 months might be in relation to prolonged neonatal hospitalization. An intermediate developmental evaluation at 6 months would have been useful to confirm this hypothesis.

Our results are in agreement with studies reporting follow-up after other treatments until the age of 24 months using the Bayley test which includes a mental and a psychomotor scale [6,7,19,24,44].

Our rate of major impairments at preschool age is 11.5%, with no cerebral palsy. Follow-up studies of children treated with various therapies for PPHN report different rates of major impairment at preschool age: after hyperventilation 0% [4], after hyperventilation and tolazoline 7.5% [47], after tolazoline alone 14.3% to 14.8% [10,36], and finally after ECMO the rates lie between 4 and 15% [9,20,21,46]. For inhaled NO, the actually recommended treatment, the reported rate of major impairment is 6.7% at 3 years [27]. Our results lie in the same range as these different studies.

One particular outcome reported in the literature is the rate of hearing loss. It has been shown that sensori-neural hearing loss among children with severe neonatal respiratory failure is related to the ototoxic drugs used for supportive therapy (diuretics, aminoglycosides and neuromuscular blockers), and not to the severity of the disease or the treatment of the respiratory failure [43]. In our population, although all the children were treated with aminoglycosides and/or furosemide, we observed only 1 patient with hearing loss (3.8%). Neuromuscular blockers were not used since high serum concentrations of magnesium already induce some neuromuscular blockade [18].

At preschool age, 7 (26.9%) children presented minor impairments in the study group, and 6 (26.1%) in the control group. There was no significant difference between the two groups. We also considered language and behavior disorders like hyperactivity as minor impairments, which are not considered as such in most follow-up studies.

Our incidence of minor impairments is quite high in comparison with published data. In previous reports

the incidence varied from 6.7% to 22% between 1 to 6 years [4,21,27,36]. A possible explanation for our higher rate is that we also considered language and behavior disorders as minor impairments. The rate of minor impairments was high in the control group as well. This suggests a methodological difference between our and the previous studies, and not a poorer outcome in our two groups.

Cognition in pre-school age, assessed by the McCarthy Scales, was in the normal range both for the study and the control group, with no statistical difference. Cognitive outcome in the literature, using different tests, reported scores in the normal range as well [4, 10,20,27,36,46,47].

In conclusion, this longitudinal non-randomized study of children treated with magnesium alone for severe PPHN shows no detrimental effect of this treatment on long-term neuro-developmental outcome. It is the first time to our knowledge that this is demonstrated. Severity of outcome in our population was related to the severity of disease and associated conditions, as well as to genetic conditions. Despite the fact that iNO is the actual recommended treatment for PPHN, $MgSO_4$ is still widely used, especially in developing countries as recent literature suggests. The absence of detrimental neuro-developmental effects deems it safe to administer when there is no other choice.

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References

[1] Y.K. Abu-Osba, O. Galal, K. Manasra and A. Rejjal, Treatment of severe persistent pulmonary hypertension of the newborn with magnesium sulphate, *Arch Dis Child* **67** (1992), 31–35.

[2] American Psychiatric Association. DSM-IV Manuel diagnostique et statistique des troubles mentaux. Masson, 1994.

[3] C. Amiel-Tison, A method for neurologic evaluation within the first year of life, *Curr Probl Pediatr* **7** (1976), 1–50.

[4] R.A. Ballard and C.H. Leonard, Developmental follow-up of infants with persistent pulmonary hypertension of the newborn, *Clin Perinatol* **11** (1984), 737–744.

[5] A.J. Bennett, N.J. Shaw, J.E. Gregg and N.V. Subhedar, Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide, *Acta Paediatr* **90** (2001), 573–576.

[6] J.C. Bernbaum, P.H. Sheridan, M.H. Gewitz, W.W. Fox and G.J. Peckham, Long-term follow-up of newborns with persistent pulmonary hypertension, *Crit Care Med* **12** (1984), 579–583.

[7] E.M. Bifano and A. Pfannenstiel, Duration of Hyperventilation and Outcome in Infants With Persistent Pulmonary Hypertension, *Pediatrics* **81** (1988), 657–661.

[8] S. Chandran, M. Haqueb, H.T. Wickramasinghec and Z. Wint, Use of Magnesium Sulphate in Severe Persistent Pulmonary Hypertension of the Newborn, *J Trop Pediatr* **50** (2004), 219–223.

[9] P.Y. Cheung, M.M. Haluschak, N.N. Finer and C.M.T. Robertson, Sensorineural hearing loss in survivors of neonatal extracorporeal membrane oxygenation, *Early Hum Dev* **44** (1996), 225–233.

[10] R.S. Cohen, D.K. Stevenson, N. Malachowski, R.L. Ariagno, J.D. Johnson and P. Sunshine, Late morbidity among survivors of respiratory failure treated with tolazoline, *Pediatrics* **97** (1980), 644–647.

[11] Committee on Fetus and Newborn, Use of Inhaled Nitric Oxide, *Pediatrics* **106** (2000), 344–345.

[12] G.J.A. Cropp, Reduction of hypoxic pulmonary constriction by magnesium chloride, *J Appl Physiol* **24**(1968), 755–760.

[13] C.A. Crowther, J.E. Hiller, L.W. Doyle and R.R. Haslam, Effect of Magnesium Sulfate Given for Neuroprotection Before Preterm Birth: A Randomized Controlled Trial, *JAMA* **290** (2003), 2669–2676.

[14] S.H. Daffa and W.A. Milaat, Role of magnesium sulphate in treatment of severe persistent pulmonary hypertension of the neoborn, *Saudi Med J* **23** (2002), 1266–1269.

[15] S.R. Daga, D.V. Gosavi, B. Verma and V.K. Ahuja, Magnesium sulphate for management of pulmonary hypertension in non-ventilated newborns, *J Trop Pediatr* **46** (2000), 52–53.

[16] H.H. de Haan, A.J. Gunn, C.E. Williams, M.A. Heymann and P.D. Gluckman, Magnesium sulfate therapy during asphyxia in near-term fetal lambs does not compromise the fetus but does not reduce cerebral injury, *Am J Obst Gynecol* **176** (1997), 18–27.

[17] Jr. M. Ellington, D. O'Reilly, E.N. Allred, M.C. McCormick, D.L. Wessel and S. Kourembanas, Child Health Status, Neurodevelopmental Outcome, and Parental Satisfaction in a Randomized, Controlled Trial of Nitric Oxide for Persistent Pulmonary Hypertension of the Newborn, *Pediatrics* **107** (2001), 1351–1356.

[18] W.J. Fawcett, D.J. Haxby and D.A. Male, Magnesium: Physiology and pharmacology, *Br J Anaesth* **83** (1999), 302–320.

[19] B. Ferrera, D.E. Johnson, C. Pi-Nian and T.R. Thompson, Efficacy and neurologic outcome of profound hypocapneic alkalosis for the treatment of persistent pulmonary hypertension in infancy, *Pediatrics* **105** (1984), 457–461.

[20] P. Glass, A.E. Wagner, P.H. Papero, S.R. Rajasingham, L.A. Civitello, M.S. Kjaer, C.E. Coffman and B.L. Short, Neurodevelopmental status at age five years of neonates treated with extracorporeal membrane oxygenation, *Pediatrics* **127** (1995), 447–457.

[21] L.J. Graziani, M. Gringlas, S. Baumgart. Cerebrovascular complications and neurodevelopmental sequelae of neonatal ECMO, *Clin Perinatol* **24** (1997), 655–675.

[22] K. Greenwood, P. Cox, H. Mehmet, J. Penrice, P.N. Amess, E.B. Cady, J.S. Wyatt and A.D. Edwards, Magnesium Sulfate Treatment after Transient Hypoxia-Ischemia in the Newborn

Piglet Does Not Protect against Cerebral Damage, *Ped Res* **48** (2000), 346–350.
[23] R. Griffifths, *The Abilities of Babies*. University of London Press ed. 1970.
[24] K.D. Hendricks-Munoz and J.P. Walton, Hearing Loss in Infants With Persistent Fetal Circulation, *Pediatrics* **81** (1988), 650–656.
[25] J.J.R.G. Ho, Magnesium sulfate for persistent pulmonary hypertension of the newborn. Cochrane Database Syst Rev 2007, John Wiley & Sons, Ltd.
[26] H. Ichiba, T. Yokoi, H. Tamai, T. Ueda, T. Kim and T. Yamano, Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate, *Pediatr Int* **48** (2006), 70–75.
[27] H. Ichiba, S. Matsunami, F. Itoh, T. Ueda, Y. Ohsasa and T. Yamano, Three-year follow up of term and near-term infants treated with inhaled nitric oxide, *Ped Int* **45** (2003), 290–293.
[28] J.P. Kinsella and S.H. Abman, Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn, *Pediatrics* **126** (1995), 853–864.
[29] G.G. Konduri, New approaches for persistent pulmonary hypertension of newborn, *Clin Perinatol* **31** (2004), 591–611.
[30] R.H. Largo, D. Pfister, L.Molinari, S. Kundu, A. Lipp and G. Duc, Significance of prenatal, perinatal, and postnatal factors in the development of AGA preterm infants at five to seven years, *Dev Med Child Neurol* **31** (1989), 440–456.
[31] A.M. Leavitt and J.F. Watchko, Neurodevelopmental outcome following persistent pulmonary hypertension of the neonate, *J Perinatol* **7** (1987), 288–291.
[32] M. Levene, M. Blennow, A. Whitelaw, E. Hanko, V. Fellman and R. Hartley, Acute effects of two different doses of magnesium sulphate in infants with birth asphyxia, *Arch Dis Child – Fetal Neonatal Ed* **73** (1995), F174–F177.
[33] A. Leviton, N. Paneth, M. Susser, Má. Reuss, E.N. Allred and K. Kuban, Maternal Receipt of Magnesium Sulfate Does Not Seem to Reduce the Risk of Neonatal White Matter Damage, *Pediatrics* **99** (1997), e2.
[34] P.H. Lipkin, D. Davidson, L. Spivak, R. Straube, J. Rhines and C.T. Chang, Neurodevelopmental and medical outcomes of persistent pulmonary hypertension in term newborns treated with nitric oxide, *Pediatrics* **140** (2002), 306–310.
[35] S. Marret, L. Marpeau, V. Zupan-Simunek, D. Eurin, C. Leveque, M.F. Hellot and J. Bénichou, PREMAG trial group, Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial*, *Br J Obstet Gynaecol* **114** (2007), 310–318.
[36] M.J. Marron, M.A. Crisafi, J.M.Jr. Driscoll, J.T. Wung, Y.T. Driscoll, T.H. Fay and L.S. James, Hearing and Neurodevelopmental Outcome in Survivors of Persistent Pulmonary Hypertension of the Newborn, *Pediatrics* **90** (1992), 392–396.
[37] R. Mathew, B.T. Altura and B.M. Altura, Strain differences in pulmonary hypertensive response to monocrotaline alkaloid and the beneficial effect of oral magnesium treatment, *Magnesium* **8** (1989), 110–116.
[38] D. McCarthy, *Manual for the McCarthy Scales of Children's Abilities*, Psychological Corporation, New York, NY, 1972.
[39] R. Mittendorf, J. Dambrosia, P.G. Pryde, K.S. Lee, J.G. Gianopoulos, R.E. Besinger and P.G. Tomich, Association between the use of antenatal magnesium sulfate in preterm labor and adverse health outcomes in infants, *Am J Obstet Gynecol* **186** (2002), 1111–1118.
[40] R. Mittendorf and P.G. Pryde, A review of the role for magnesium sulphate in preterm labour, *Br J Obstet Gynaecol* **112** (2005), 84–88.
[41] P.M. Nair and M.F. Bataclan, Persistent pulmonary hypertension of the newborn, *Saudi Med J* **25** (2004), 693–699.
[42] F. Raimondi, F. Migliaro, L. Capasso, G. Ausanio, M. Bisceglia, P. Giliberti, F. Messina, G. Salvia and R. Paludetto, Intravenous Magnesium sulphate vs. Inhaled Nitric Oxyde for Moderate, Persistent Pulmonary Hypertension of the Newborn. A Multicentre, Retrospective Study, *J Trop Ped 2007 (Epub ahead of print)*
[43] C.M.T. Robertson, M.T. Juzer, A. Peliowski, C.E. Philip and P.Y. Cheung, Ototoxic drugs and sensorineural hearing loss following severe neonatal respiratory failure, *Acta Paediatrica* **95** (2006), 214–223.
[44] A.A. Rosenberg, J.M. Kennaugh, S.G. Moreland, L.M. Fashaw, K.A. Hale, F.M. Torielli, S.H. Abman and J.P. Kinsella, Longitudinal follow-up of a cohort of newborn infants treated with inhaled nitric oxide for persistent pulmonary hypertension, *Pediatrics* **131** (1997), 70–75.
[45] H. Sameshima and T. Ikenoue, Long-term magnesium sulfate treatment as protection against hypoxic-ischemic brain injury in seven-day-old rats, *Am J Obstet Gynecol* **184** (2001), 185–190.
[46] R.E. Schumacher, T.W. Palmer, D.W. Roloff, P.A. LaClaire and R.H. Bartlett, Follow-up of Infants Treated With Extracorporeal Membrane Oxygenation for Newborn Respiratory Failure, *Pediatrics* **87** (1991), 451–457.
[47] E.J. Sell, J.A. Gaines, C. Gluckman and E. Williams, Persistent fetal circulation. Neurodevelopmental outcome, *Arch Ped Adol Med* **139** (1985), 25–28.
[48] M. Sheridan, *Manual for the Stycar vision test*, National Foundation for Educational Research, 1960.
[49] The Neonatal Inhaled Nitric Oxide Study Group*, Inhaled nitric oxide in term and near-term infants, Neurodevelopmental follow-up of The Neonatal Inhaled Nitric Oxide Study Group (NINOS), *Pediatrics* **136** (2000), 611–617.
[50] J.F. Tolsa, J. Cotting, N. Sekarski, M. Payot, J.L. Micheli and A. Calame, Magnesium sulphate as an alternative and safe treatment for severe persistent pulmonary hypertension of the newborn, *Arch Dis Child – Fetal Neonatal Ed.* **72** (1995), F184–F187.
[51] J.F. Tolsa, Y. Gao and J.U. Raj, Developmental change in magnesium sulfate-induced relaxation of rabbit smooth muscle arteries, *J Appl Physio* **87** (1999), 1589–1594.
[52] B. Touwen, The examination of the child with minor neurological dysfunction, Clinics in developmental medicine, Heinemann, London 71, 1979.
[53] M.C. Walsh-Sukys, J.E. Tyson, L.L. Wright, C.R. Bauer, S.B. Korones, D.K. Stevenson, J. Verter, B.J. Stoll, J.A. Lemmons, L.A. Papile, S.Shankaran, E.F. Donovan, W.Oh, R.A. Ehrenkranz and A.A. Fanaroff, Persistent Pulmonary Hypertension of the Newborn in the Era Before Nitric Oxide: Practice Variation and Outcomes, *Pediatrics* **105** (2000), 14–20.
[54] B. Weinberger, K. Weiss, D.E. Heck, D.L. Laskin and J.D. Laskin, Pharmacologic therapy of persistent pulmonary hypertension of the newborn, *Pharmacol Therap* **89** (2001), 67–79.
[55] S.R. Wildin, S.H. Landry and J.B. Zwischenberger, Prospective, Controlled Study of Developmental Outcome in Survivors of Extracorporeal Membrane Oxygenation: The First 24 Months, *Pediatrics* **93** (1994), 404–408.
[56] T.J. Wu, R.J. Teng and K.I. Tsou, Persistent Pulmonary Hypertension of the Newborn Treated With Magnesium Sulfate in Premature Neonates, *Pediatrics* **96** (1995), 472–474.