Effect of maternal tocolysis on the incidence of severe periventricular/intraventricular haemorrhage in very low birthweight infants

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Abstract

***Aim*—To examine the relation between grade III–IV periventricular/intraventricular haemorrhage (PVH/IVH) and antenatal exposure to tocolytic treatment in very low birthweight (VLBW) premature infants.**

***Study design*—The study population consisted of 2794 infants from the Israel National VLBW Infant Database, of gestational age 24–32 weeks, who had a cranial ultrasound examination during the first 28 days of life. Infants of mothers with pregnancy induced hypertension or those exposed to more than one tocolytic drug were excluded. Of the 2794 infants, 2013 (72%) had not been exposed to tocolysis and 781 (28%) had been exposed to a single tocolytic agent. To evaluate the effect of tocolysis and confounding variables on grade III–IV PVH/IVH, the χ^2 test, univariate analysis, and a logistic regression model were used.**

***Results*—Of the 781 infants (28%) exposed to tocolysis, 341 (12.2%) were exposed to magnesium sulphate, 263 (9.4%) to ritodrine, and 177 (6.3%) to indomethacin. The overall incidence of grade III–IV PVH/IVH was 13.4%. In the multivariate logistic regression analysis, the following factors were related significantly and independently to grade III–IV PVH/IVH: no prenatal steroid treatment, low gestational age, one minute Apgar score 0–3, respiratory distress syndrome, patent ductus arteriosus, mechanical ventilation, and pneumothorax. Infants exposed to ritodrine tocolysis (but not to the other tocolytic drugs) were at significantly lower risk of grade III–IV PVH/IVH after adjustment for other variables (odds ratio = 0.3; 95% confidence interval 0.2 to 0.6).**

***Conclusion*—This study suggests that antenatal exposure of VLBW infants to ritodrine tocolysis, in contrast with tocolysis induced by magnesium sulphate or indomethacin, was associated with a lower incidence of grade III–IV PVH/IVH.**

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Keywords: periventricular haemorrhage; intraventricular haemorrhage; very low birthweight; tocolytics

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Periventricular/intraventricular haemorrhage (PVH/IVH) is very commonly associated with neurological morbidity and mortality in very low birthweight (VLBW) premature infants, and therefore its prevention is of prime importance.[1] A considerable number of VLBW infants are exposed in utero to tocolytic drugs. Agents currently in use include magnesium sulphate, β-mimetics, prostaglandin synthetase inhibitors, and calcium channel blockers.[2 3] All of these potentially have adverse effects on the fetus and the neonate.[2]

It has been reported that antenatal exposure to β-mimetics, magnesium sulphate, or prostaglandin synthetase inhibitors may be associated with an increased incidence of PVH/IVH among premature infants.[4–7] However, other studies have suggested that tocolysis may have no effect, or even a protective effect, on PVH/IVH.[8–13] It is thus evident that the effect of tocolytic drugs on the incidence of neonatal PVH/IVH remains controversial. The goal of our study was to determine the relation between various tocolytic drugs used in Israel and the incidence of grade III–IV PVH/IVH in VLBW infants. Data collected for the Israel National VLBW infant database were used for this analysis.

Methods

This study is based on analysis of data extracted from the Israel Neonatal Network data collected on VLBW newborn infants (birth weight ⩽ 1500 g) born in Israel from January 1995 to December 1998 inclusive. All 28 neonatal departments in Israel are included in data collection, which comprises the Israel National VLBW Infant Database. A structured form is filled in for each infant. The data collected include parental information, maternal pregnancy history, and antenatal care, details of the delivery, the infant's status at delivery, diagnoses, procedures and complications during hospital stay, and outcome at discharge. All departments use an operating manual and standard definitions.

During this four year period, 5555 VLBW infants were registered in the database, accounting for 98% of all VLBW infant births in Israel. From this population, 2761 infants were excluded for the following reasons: 204 infants died in the delivery room, 870 were less than 24 weeks or more than 32 weeks of gestation, 858 infants were born to mothers with pregnancy induced hypertension, 389 did not have a cranial ultrasound examination, and 440 infants received a combination of tocolytic drugs. Thus the final study population comprised 2794 infants, of whom 2013 (72%) had not been exposed to tocolytic treatment. Of the

Table 1 Univariate analysis of incidence of grade III–IV PVH/IVH according to risk factors

Variable	No of infants	IVH		p Value
		No	%	
Total	2794	374	13.4	
Tocolysis				
No therapy	2013	303	15.1	
Magnesium sulphate	341	34	10.0	<0.01
Ritodrine	263	14	5.3	
Indomethacin	177	23	13.0	
Antenatal steroid therapy				
Full	1161	76	6.6	
Partial	489	68	13.9	<0.01
None	1133	228	20.1	
Multiple birth				
Yes	1159	127	10.0	<0.01
No	1635	247	15.1	
PROM (>6 hours)				
Yes	932	102	10.0	0.01
No	1856	270	14.6	
Amnionitis				
Yes	329	53	16.1	0.13
No	2461	321	13.0	
Delivery				
Vaginal	1097	187	17.1	<0.01
Caesarean section	1697	187	11.0	
Gestational age (weeks)				
24–25	293	106	36.2	
26–27	614	123	20.0	<0.01
28–29	871	126	12.2	
≥30	1016	39	3.8	
Birth weight (g)				
>750	290	83	28.6	
750–999	703	136	19.4	<0.01
1000–1249	890	92	10.1	
≥1250	971	63	6.5	
SGA				
Yes	315	40	12.7	0.70
No	2479	334	13.5	
One minute Apgar score				
0–3	506	127	25.1	
4–7	1159	167	14.4	<0.01
≥8	1070	64	6.0	
Five minute Apgar score				
0–3	59	20	33.9	
4–7	556	119	20.4	<0.01
≥8	2071	211	10.2	
RDS				
Yes	1799	344	19.1	<0.01
No	995	30	3.0	
PDA				
Yes	797	170	21.3	<0.01
No	1996	204	10.2	
Mechanical ventilation				
Yes	1997	365	18.3	<0.01
No	797	9	1.1	
Pneumothorax				
Yes	235	72	30.6	<0.01
No	2559	302	11.8	
Sepsis				
Yes	979	147	15.0	0.06
No	1815	227	12.5	

PVH, Periventricular haemorrhage; IVH, intraventricular haemorrhage; PROM, premature rupture of the membranes; SGA; small for gestational age; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus.

Table 2 Multivariate analysis of risk factors for grade III–IV PVH/IVH

Confounding variables	No of infants	Odds ratio (95% CI)
Tocolysis		
No therapy	2013	1.0
Magnesium sulphate	341	0.8 (0.5 to 1.2)
Ritodrine	263	0.3 (0.2 to 0.6)
Indomethacin	177	1.0 (0.6 to 1.6)
Antenatal steroid therapy		
Full	1161	1.0
Partial	489	1.6 (1.1 to 2.4)
None	1133	2.1 (1.5 to 2.9)
Multiple birth		
Yes	1159	0.9 (0.7 to 1.2)
No	1635	1.0
PROM (>6 hours)		
Yes	932	0.9 (0.6 to 1.1)
No	1856	1.0
Amnionitis		
Yes	329	1.0 (0.7 to 1.5)
No	2461	1.0
Delivery		
Vaginal	1097	1.3 (1.0 to 1.7)
Caesarean section	1697	1.0
Gestational age (weeks)		
24 to 25	293	5.3 (3.0 to 9.8)
26 to 27	614	3.0 (1.9 to 5.0)
28 to 29	871	2.2 (1.4 to 3.4)
≥30	1016	1.0
Birth weight (g)		
<750	290	0.9 (0.5 to 1.5)
750 to 999	703	1.0 (0.6 to 1.6)
1000 to 1249	890	0.9 (0.6 to 1.3)
≥1250	971	1.0
One minute Apgar score		
0 to 3	506	2.0 (1.3 to 3.0)
4 to 7	1159	1.4 (1.0 to 2.0)
≥8	1070	1.0
Five minute Apgar score		
0 to 3	59	1.5 (0.8 to 2.8)
4 to 7	556	1.0 (0.7 to 1.3)
≥8	2071	1.0
RDS		
Yes	1799	2.3 (1.5 to 3.6)
No	995	1.0
PDA		
Yes	797	1.3 (1.0 to 1.6)
No	1996	1.0
Mechanical ventilation		
Yes	1997	4.1 (2.1 to 9.2)
No	797	1.0
Pneumothorax		
Yes	235	1.8 (1.3 to 2.5)
No	2559	1.0
Sepsis		
Yes	979	0.8 (0.6 to 1.1)
No	1815	1.0

PVH, Periventricular haemorrhage; IVH, intraventricular haemorrhage; PROM, premature rupture of the membranes; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus.

remaining 781 infants, 341 (12.2%) were exposed to magnesium sulphate treatment only, 263 (9.4%) to the β-mimetic ritodrine only, and 177 (6.3%) to indomethacin only.

The presence of the dependent variable grade III–IV PVH/IVH was diagnosed by cranial ultrasonography performed within the first 28 days of life and graded according to the classification of Papile *et al*.[14] The following variables that could affect the incidence of PVH/IVH were included in the analysis: tocolytic treatment, antenatal steroid treatment, multiple gestation, premature rupture of membranes (PROM), amnionitis, mode of delivery, gestational age, birth weight, small for gestational age (SGA), Apgar scores, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), mechanical ventilation, pneumothorax, and sepsis.

Gestational age (in completed weeks) was defined as the attending neonatologist's best estimate of gestational age based on obstetric history, prenatal ultrasound, and postnatal physical examination. SGA was defined according to the intrauterine growth charts of Usher and Mclean.[15] Antenatal steroid treatment was defined as "incomplete" if delivery occurred less than 24 hours after the first dose or more than one week after the last dose, and "complete" if delivery occurred more than 24 hours and less than seven days after a complete course of treatment. Tocolytic treatment was defined as treatment with a tocolytic drug for at least 12 hours before delivery. The tocolytic drugs predominantly used in Israel during this

Table 3 Percentage of grade III–IV PVH/IVH by tocolytic treatment, stratified by gestational age, birth weight, and antenatal steroid treatment

	No tocolysis		*Magnesium*		*Ritodrine*		*Indomethacin*		*Total*	
	No	*% IVH*	*No*	*% IVH*	*No*	*% IVH*	*No*	*% IVH*	*No*	*% IVH*
Gestational age (weeks)										
24–25	193	41.5	45	31.1	31	12.9	24	33.3	293	36.2
26–27	441	22.7	71	16.9	63	11.1	39	10.3	614	20.0
28–29	604	15.6	111	4.5	88	3.4	68	5.9	872	12.2
⩾30	775	2.6	114	3.7	81	0.0	46	15.2	1017	3.8
Birth weight (g)										
<750	212	30.7	29	27.6	30	6.7	19	42.1	290	28.6
750–999	500	21.2	87	17.2	63	12.7	53	13.2	704	19.3
1000–1249	585	14.0	113	4.4	80	3.8	52	3.9	880	11.1
⩾1250	716	7.0	112	5.4	90	1.1	53	11.3	972	6.5
Steroid treatment										
Full	652	6.6	216	7.4	172	2.3	121	10.7	1163	6.5
Partial	306	15.0	98	12.2	61	9.8	24	16.7	489	13.9
None	1049	20.2	27	22.2	28	14.3	29	20.7	1133	20.1

The number of infants and percentage of grade III–IV PVH/IVH in the specific category are shown.
PVH, Periventricular haemorrhage; IVH, intraventricular haemorrhage.

period were the β-mimetic ritodrine, magnesium sulphate, and indomethacin. PROM was defined as membrane rupture more than six hours before the onset of regular spontaneous uterine contractions. Diagnosis of amnionitis was based on high maternal temperature (>37.8°C orally or > 38°C rectally) recorded twice in one hour, during the rupture of membranes or during the first six hours after delivery, provided no other cause for the fever was found. Sepsis was diagnosed in the presence of positive blood cultures. In cases of staphylococcus coagulase negative sepsis, the presence of clinical signs of infection was required. The diagnosis of RDS was recorded in the presence of a chest radiograph consistent with RDS, together with supplemental oxygen or mechanical ventilation treatment. PDA was diagnosed if a heart murmur compatible with PDA was detected and left to right ductal shunting was shown by Doppler examination. In addition, two or more of the following were required: bounding peripheral pulses, hyperdynamic precordium, radiographic evidence of cardiomegaly or pulmonary oedema, and inability to decrease ventilator settings in the first 48 hours after birth.

STATISTICAL ANALYSIS

To evaluate the effect of the potential risk factors on the incidence of grade III–IV PVH/IVH, a χ^2 test for contingency tables was used. On completion of the univariate analyses, any variable for which the univariate test had a p value < 0.25 was considered for inclusion in the multivariate model.[16] The logistic regression model was used to assess the net effect of each independent variable on the risk of developing grade III–IV PVH-IVH. The SAS statistical program was used for analysis of the data.

Results

The incidence of grade III–IV PVH/IVH was 13.4% in the whole study group, 15.1% in the no-tocolysis group, 10% in the magnesium sulphate tocolysis group, 5.3% in the ritodrine group, and 13.0% in the indomethacin group. In the univariate analysis (table 1), tocolytic treatment, lack of maternal antenatal steroid treatment, multiple births, PROM, vaginal delivery, low gestational age, low birth weight, Apgar scores of 0–3 at one and five minutes after delivery, RDS, PDA, mechanical ventilation, and pneumothorax were also significantly related to grade III–IV PVH/IVH.

In the multivariate logistic regression analysis (table 2), the following factors were significantly and independently related to grade III–IV PVH/IVH: lack of antenatal steroid treatment, gestational age, one minute Apgar score 0–3, RDS, PDA, mechanical ventilation, and pneumothorax. Infants exposed to ritodrine tocolysis were at significantly lower risk of grade III–IV PVH/IVH after adjustment for the other variables (odds ratio (OR) = 0.3; 95% confidence interval (CI) = 0.2 to 0.6). This effect was not noted in infants exposed to magnesium sulphate (OR = 0.8; 95% CI = 0.5 to 1.2) or indomethacin (OR = 1.0; 95% CI = 0.6 to 1.6) tocolysis. The Hosmer and Lemeshow goodness of fit test showed a p value of 0.84.

Table 3 shows the percentage of grade III–IV PVH/IVH by type of tocolytic treatment, stratified by gestational age, birth weight, and antenatal steroid treatment. The percentage of severe IVH in infants whose mothers received ritodrine tocolysis was lower than that among infants whose mothers were treated with other agents or among those not receiving any tocolytic treatment. This trend was observed in all gestational age, birth weight, and antenatal steroid treatment groups.

Discussion

The results of this study suggest that maternal tocolytic treatment with ritodrine was associated with lower incidence of grade III–IV PVH/IVH, whereas magnesium sulphate and indomethacin tocolysis did not appear to have any influence on the incidence of grade III–IV IVH in VLBW infants.

The current literature on the effect of tocolytic treatment on the incidence of neonatal PVH/IVH comprises mostly retrospective and small sample studies, and the results are controversial. The retrospective study of Groome *et al*[4] showed that β-mimetic tocolytic treatment may be associated with more than a twofold increase in the incidence of neonatal PVH/IVH. However, Özcan *et al*[8] found that

ritodrine did not have a significant effect on the incidence of neonatal PVH/IVH, and Ment *et al*[13] even reported a decreased incidence of neonatal PVH/IVH with maternal β-mimetic tocolytic treatment.

Primary fetal side effects of β-mimetic tocolysis are reduction in arterial blood pressure and tachycardia.[2 3] β-Mimetic tocolytic treatment is, however, well tolerated by most fetuses, and side effects are strongly dose dependent.[4]

Several possible mechanisms for the effect of ritodrine in reducing the incidence of grade III–IV PVH/IVH may be considered. β-Mimetic tocolytic drugs have been used for treatment of acute intrapartum fetal distress by reducing uterine contractions.[17] As fetal distress is a risk factor for PVH/IVH,[1] this effect may reduce the incidence of haemorrhage. β-Mimetic drugs administered to mothers may promote neonatal lung maturation, resorption of alveolar fluid, and decreased lung water content.[18–21] Laros *et al*[22] found that maximal inspiratory pressure was lower in infants with RDS who were exposed to β-mimetic tocolysis. Ritodrine may thus theoretically decrease the risk of PVH/IVH by improving respiratory status and reduce mechanical ventilation requirements. However, we were unable to grade the severity of RDS from the data collected.

Sudden blood pressure elevation in sick VLBW infants with impaired autoregulation of cerebral perfusion may result in germinal matrix capillary rupture and subsequent PVH/IVH.[1] It may be speculated that the systemic vasodilator effect of β-mimetic tocolysis[2 3] could reduce grade III–IV PVH/IVH by preventing blood pressure elevation in VLBW infants during perinatal asphyxia. Another possible effect is that sympathomimetic agents may have a role in controlling the tone or permeability of vascular walls within the central nervous system.[23] However, at present these effects are speculative, and the relation between β-mimetic tocolysis and reduction of PVH/IVH needs to be further explored.

Magnesium sulphate has several neuroprotective effects including vasoconstriction inhibition, reduction of free radical formation, and prevention of calcium influx into cells during hypoxia, thus preventing nerve cell death.[24] Kuban *et al*[12] suggested a protective effect of maternal magnesium administration on neonatal PVH/IVH. However, Stigson *et al*[7] suggested that magnesium tocolysis may increase the incidence of neonatal grade I IVH, and the study of Iannucci *et al*[5] indirectly implied that magnesium tocolysis may be associated with increased incidence of PVH/IVH. The study of Salafia *et al*[25] found an increased incidence of early PVH/IVH (< 72 hours) among infants whose mothers were exposed to less than 48 hours of antenatal steroids and received magnesium. Our study confirms the results of Leviton *et al*[11] who found no effect of magnesium sulphate administered before delivery on neonatal PVH/IVH. Recently Rantonen *et al*[26] found grade III–IV PVH/IVH in 15% of infants exposed to maternal ritodrine treatment, in 9% of infants whose mothers received tocolytic magnesium, and in none of those exposed to magnesium for pre-eclampsia. These differences were not significant.

Norton *et al*[6] found that indomethacin tocolysis increased the risk of neonatal PVH/IVH. The study of Iannucci *et al*[5] suggested that indomethacin tocolysis may contribute to the occurrence of PVH/IVH. Post partum administration of indomethacin, however, lowered the incidence and severity of neonatal PVH/IVH.[9 10] The inhibition of prostaglandin synthesis by indomethacin may protect the brain by decreasing baseline cerebral blood flow, microvasculature permeability, which occurs in response to hypoxic-ischaemic insults, and free radical formation.[27] This theoretically may reduce the incidence of PVH/IVH. Our study, however, did not show a significant association between indomethacin tocolysis and the incidence of grade III–IV PVH/IVH.

Ment *et al*[28] found that antenatal steroid treatment reduces grade III–IV PVH/IVH. Recently the EPICure study[29] found that major cerebral scan abnormalities were less common in infants born before 25 completed weeks of gestation and whose mothers had received steroids for more than 24 hours before delivery. Although cerebral scan abnormalities were more common if the mother had received tocolytic agents, no details on the tocolytic treatment were given in this study, and this analysis did not include intracranial abnormalities in infants who died before discharge.

The protective role of antenatal steroid treatment on the incidence of grade III–IV PVH/IVH is confirmed by our study. It should be emphasised, however, that only 42% of the infants in our study were exposed to a full course of antenatal steroids and 17.5% to a partial course. Total exposure to antenatal steroid treatment increased over the study period from 45% in 1995 to over 62% in 1998. The relatively high proportion of infants not exposed to steroid treatment may also be associated with regional variations or late presentation by some mothers.

Low gestational age and asphyxia, as reflected by the Apgar scores, had an adverse effect on the incidence of grade III–IV IVH. However, in our logistic regression analysis the type of delivery did not affect the incidence of severe haemorrhage. The elimination of low birth weight from the final logistic model was due to the strong association between birth weight and gestational age.

Our study has several drawbacks and the results should be interpreted with some caution. The study was based on data obtained from the Israel National VLBW database and the tocolytic treatment was not randomised. Given the large number of centres participating in this study, the care of the mother and infant was not standardised, and the dose and duration of the tocolytic treatment and various management protocols are not accounted for. The database does, however, include almost every VLBW infant born in Israel during the study period, and completion of the data form is based on the use of standard definitions.

Although we defined grade III–IV PVH/IVH as described by Papile *et al*,[14] we are aware that echo density in the white matter adjacent to the ventricular wall is often not a haemorrhage.[30] Therefore grade III–IV PVH/IVH should perhaps more properly be viewed as haemocephalus, with or without accompanying periventricular white matter damage. We also do not have data on the age at the time of diagnosis of PVH/IVH. We thus could not distinguish between early onset PVH/IVH, which may be caused by obstetrical factors, such as route of delivery and the use of tocolytic agents, and late onset PVH/IVH, which may be the result of non-obstetrical factors, such as mechanical ventilation and pneumothorax.

Our population based study and large sample size do, however, suggest a possible protective effect of ritodrine tocolysis on the incidence of severe PVH/IVH among VLBW infants. Further controlled studies are justified to clarify the very important clinical issue of the relation between commonly used tocolytic agents and neonatal PVH/IVH.

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The Israel Neonatal Network participating centres in the Israel National VLBW infant database are: Assaf Harofeh Medical Center, Rishon Le Zion; Barzilay Medical Center, Ashkelon; Bikur Holim Hospital, Jerusalem; Bnei Zion Medical Centre, Haifa; Carmel Medical Center, Haifa; English (Scottish) Hospital, Nazareth; French Hospital, Nazareth; Hadassah University Hospital Ein-Karem, Jerusalem; Hadassah University Hospital Har Hazofim, Jerusalem; Haemek Medical Center, Afula; Hillel Yafe Medical Center, Hadera; Italian Hospital, Nazareth; Kaplan Hospital, Rehovot; Laniado Hospital, Netanya; Maayanei Hayeshua Hospital, Bnei-Brak; Meir Medical Center, Kefar Saba; Misgav Ladach Hospital, Jerusalem; Naharia Hospital, Naharia; Poria Hospital, Tiberias; Rambam Medical Center, Haifa; Rivka Ziv Hospital, Zefat; Schneider Children's Medical Center of Israel and Rabin Medical Center (Belinson Campus), Petach-Tikva; Shaare-Zedek Hospital, Jerusalem; Sheba Medical Center, Tel-Hashomer; Soroka Medical Center, Beer-Sheva; Sourasky Medical Center, Tel-Aviv; Wolfson Medical Center, Holon; Yoseftal Hospital, Eilat

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