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Tocolytic indomethacin: effects on neonatal haemodynamics and cerebral autoregulation in the preterm newborn

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ABSTRACT

Background Indomethacin has vasoactive properties in cerebral and systemic vascular beds, and it improves cerebral autoregulatory ability. We speculated that tocolytic indomethacin will improve cerebral autoregulatory ability in the very preterm infant in early postnatal life.

Methods Eighteen stable preterm infants gestational age (GA) 25.3–29.6 weeks, birth weight (BW) 660–1430 grams), whose mothers had received 50–150 mg of tocolytic indomethacin within 24 h before birth, and 18 individually matched controls (GA 25.0–29.7 weeks, BW 700–1390 grams) were studied four times for 15 min in the first 24 h of life. Autoregulation was assessed by determining correlations between mean arterial blood pressure (MABP (mm Hg)) and near-infrared spectroscopy-monitored cerebral oxygenation ($rScO_2$).

Results MABPs were significantly higher in the indomethacin infants than in the control infants ($p=0.03$). A decreased ability to autoregulate was found in four of the indomethacin infants, and in six of the control infants, which is not significantly different.

Conclusions Prenatally administered indomethacin, given as a tocolytic in doses of 50–150 mg per day, improved transitional circulation in very preterm infants by significantly raising the MABP. It did not have an effect on the ability to autoregulate the cerebral circulation. In this study, no differences in short-term outcomes, like haemorrhagic or ischaemic cerebral lesions, were observed.

What is already known on this topic

- Tocolytic indomethacin has been associated with increased incidence of major periventricular haemorrhages and periventricular leucomalacia and increased incidence and severity of persistent ductus arteriosus in preterm infants.

What this study adds

- Tocolytic indomethacin given within 24 h before birth appears to have a beneficial effect on early neonatal circulation in very preterm infants, and does not appear to have adverse effects on cerebral oxygenation and blood flow.

BACKGROUND

Indomethacin has been in use as a tocolytic drug since the late 1970s.[1,2] It is an effective tocolytic with both direct and indirect effects on myometrial activity. Indomethacin readily crosses the placenta; foetal serum concentrations reach about half maternal levels in 2 h and equal maternal levels in about 6 h.[3] Serum half-life in the preterm newborn is 24 h or more, with an inverse relationship to gestational age.[3,4]

Indomethacin is also a potent vasoactive drug, causing vasoconstriction by direct and indirect action on vascular smooth muscle.[5,6] The drug has important effects on foetal and neonatal cerebral circulations, both in animal and human models.[7–9] Bolus injection of 0.1–0.3 mg/kg in the newborn was shown to result in cerebral arterial vasoconstriction and a decrease of cerebral blood flow, an effect dependent on the rate of infusion.[9–11] Results of several studies suggest an improvement of cerebral autoregulation after indomethacin,[8,12,13] while other studies have shown that effects on foetal cerebral blood flow are minor.[14] Tocolytic indomethacin has been associated with an increase of major periventricular haemorrhages (PIVH) in some studies[15,16]; but also with an increase of cystic periventricular leucomalacia (PVL),[16,17] the latter possibly through interference with inflammatory cascades associated with premature delivery. Interestingly, early postnatal administration to very preterm infants has been associated with a decrease of major PIVH[18,19] and a decrease of cerebral white matter damage,[20] possibly through an improvement of circulatory stability.

The aim of our study was to evaluate transitional haemodynamics and autoregulatory ability of the cerebral vascular bed in very preterm infants who had been exposed to tocolytic indomethacin. We speculated that tocolytic indomethacin would be associated with improvement of cerebral autoregulation in early postnatal life.

PATIENTS AND METHODS

Study group

Between 1 March 2009 and 31 October 2010, 132 preterm infants of gestational age under 30 weeks were admitted to the neonatal intensive care unit of Wilhelmina Children's Hospital. In 33 of these babies, the mother had been treated with indomethacin for imminent premature delivery; in 25, the mothers had received indomethacin (50–150 mg) within 24 h before giving birth. These

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infants were individually matched to infants with the same gestational age (within 1 week), birth weight (within 150 g), and gender. In addition, infants were matched for severity of initial clinical problems, that is, 5 min Apgar scores (within 2 points) and need for respiratory support (CPAP, mechanical ventilation). Circulatory parameters were not included in the matching procedure, as these could have reflected the effects of indomethacin. Finally, the participation of an infant depended on the availability of reliable data. Eventually, two groups of 18 infants were available for analysis.

Clinical data

Obstetric, intrapartum, and neonatal clinical data were collected from our patient database and from hospital records. Physiologic data were obtained through our neonatal monitoring program, that is, real-time collection of heart rate (HR), blood pressure, arterial saturation and cerebral saturation data.[21 22] Mean arterial blood pressure (MABP) was measured with indwelling catheters (umbilical, radial or tibial artery). Regional cerebral oxygen saturation ($rScO_2$) was determined using near-infrared spectroscopy (NIRS). All parameters were stored on a personal computer for later analysis (sample rate 1 Hz; capture software: Poly 5, Inspector Research Systems, Amsterdam, The Netherlands).

Brain ultrasound was performed as soon as possible after admission and repeated at least daily. PIVH was graded according to Papile,[23] PVL according to de Vries.[24] Doppler studies of the cerebral circulation were not routinely performed. The presence of a haemodynamically significant persistent ductus arteriosus was investigated routinely from day 2 and based on clinical indices and echocardiography (left atrial dilatation; internal ductal diameter >1.4 mm/kg; left pulmonary artery end diastolic flow >0.2 m/s). Cardiac output was not usually assessed. Respiratory distress syndrome was graded in 'no', 'moderate' (as seen on chest x-ray) and 'severe' (needing exogenous surfactant therapy). Blood pressure was considered too low (hypotension) when mean blood pressure in mm Hg dropped below the number of weeks gestation.

NIRS

The NIRS-determined $rScO_2$ was used as an estimator for changes in regional cerebral circulation. A 2-wavelength (730 and 810 nm) near-infrared spectrometer (INVOS 4100-5100, Somanetics Corp, Troy, Michigan, USA) was used. The transducer (small adult, SomaSensor SAFB-SM) with one light-emitting diode and two distant sensors (30 and 40 mm) was placed on the frontoparietal side of the infant's head. $rScO_2$ Is calculated from the differential signals obtained from these two sensors, expressed as the venous-weighted percentage of oxygenated haemoglobin (oxygenated haemoglobin/total haemoglobin (oxygenated haemoglobin+deoxygenated haemoglobin)).

Analysis of autoregulation

The correlation between $rScO_2$ and MABP was used to assess the autoregulation.[25] Four separate blocks of recordings, each lasting 15 min, were analysed. Whenever possible, blocks were obtained from each 3 h period between 6 h and 18 h of life. Within these periods, the timing was such that no diagnostic, therapeutic or nursing procedures were ongoing, thus avoiding disturbances of circulation and/or oxygenation. In addition, care was taken to exclude obvious artefacts.

MABP-$rScO_2$ correlations were determined in the very low-frequency range (1/60 Hz). A correlation coefficient of >0.5 was considered an indication of pressure passive cerebral circulation. Since it was expected that some infants would have no correlations >0.5, or for only 1 min or 2 min, while others would have correlations >0.5 for much longer periods, correlations >0.5 during 10% or more of the time in an infant were considered to indicate a clinically relevant decreased ability to autoregulate.

Signalbase was used for these calculations (Department of Medical Physics, University Medical Center Utrecht, The Netherlands).

Statistics

The PASW Statistics 17.0 package was used for statistical analysis (IBM corporation, Armond, New York, USA). Student t tests for independent samples, χ^2, or Mann–Whitney U tests were applied, wherever appropriate. A $p<0.05$ was considered significant.

RESULTS

Demographic and obstetric clinical data are presented in table 1, neonatal data in table 2. There was a significant difference between groups in the number of mothers who had received tocolytics other than indomethacin. Except for insignificant differences between the number of infants who were born by caesarean section, infants with prolonged premature rupture of membranes (PPROM) and amnionitis, and infants whose mothers had received antibiotics (more in the control group, table 1) and between the number of infants who were hypotensive in the first 24 h after birth and who received antihypotensive treatment (also more in the control group, table 2) there were no relevant differences between groups.

MABP, $rScO_2$, and HR results are presented in figure 1. MABPs were significantly higher in the indomethacin group than in the control group (36±6 vs 34±5 (mean±SD)) (p=0.03). There was an insignificant difference in $rScO_2$ between the indomethacin infants and the controls (64±10% vs 62±10% (mean±SD)). There was an insignificant difference in HR between the indomethacin infants and controls (146±11/min vs 148±8/min (mean±/SD)).

On average, pressure-passive cerebral circulation was seen during 10.5% of the time (range 0–100, median 2.5). No

Table 1 Demographic and obstetric data of study patients

	Indomethacin (n)	Controls (n)	
Gestational age (weeks)	27.2 (25^2–29^4)	27.4 (25^0–29^5)	
Birth weight (grams)	1025 (660–1430)	1010 (700–1390)	
Male/female	7/11	7/11	
One of twins	7	6	
Maternal steroids	18	18	
Maternal tocolytics (ex indomethacin)	18	9	p<0.005
Maternal pre-eclampsia	0	2	
Caesarean section (spinal/general anaesthesia)	3/1	5/3	
PPROM	4	6	
Amnionitis, clinical and microscopic	6	8	
Maternal antibiotics	6	10	

Gestational ages, birth weights: average (range).
PPROM, prolonged premature rupture of membranes.

Table 2 Neonatal outcome data of study patients

	Indomethacin (n)	Controls (n)
Apgar score at 1 min (median (range))	5 (2–8)	6 (3–9)
Apgar score at 5 min (median (range))	8 (6–9)	8 (6–10)
Severe RDS	7	7
Non-invasive respiratory support	11	10
Invasive respiratory support	7	8
Sedation (morphine)	7	9
Septicaemia in first 24 h	1	2
Hypotension in first 24 h	3	8
Vasopressors	1	5
PIVH, grade 2 or more	2	3
Cystic PVL	0	0
HSPDA	6	5
Decreased ability to autoregulate	4	6

HSPDA, haemodynamically significant patent ductus arteriosus diagnosed in the first 72 h of life; PIVH, periventricular haemorrhage; PVL, periventricular leucomalacia; RDS, respiratory distress syndrome.

pressure passivity was detected in nine indomethacin infants and in seven controls. A decreased ability to autoregulate (pressure passivity at least 10% of the time) was found in four indomethacin infants and in six controls (not significantly different).

DISCUSSION

In this study, we investigated early haemodynamic effects of antenatally administered indomethacin in very preterm newborn infants, particularly with respect to the ability to autoregulate the cerebral perfusion. Assuming that the degree of correlation between MABP and $rScO_2$ is an indicator of autoregulation, we did not find an improvement of the ability to autoregulate in infants whose mothers were given indomethacin shortly before delivery, as was suggested in fetal and neonatal lamb models.[8 12] MABPs were, however, significantly higher in the indomethacin infants than in the controls. This was corroborated by a trend to more need for treatment of low blood pressure in the controls.

Autoregulation of cerebral blood flow refers to the ability to keep the cerebral perfusion more or less constant over a specific range of blood pressures.[26] This ability has been reported to be limited or absent in certain clinical conditions, particularly in sick preterm infants.[27 28] The evaluation of autoregulation in the newborn infant is difficult, as there is no reliable technique to non-invasively measure cerebral perfusion. Several groups have used NIRS-determined oxygenation of the brain as a measure of cerebral perfusion.[28 29] In reality, NIRS enables evaluation of changes in cerebral perfusion through extrapolation of changes in oxygenated haemoglobin and deoxygenated haemoglobin, rather than providing a continuous quantification of blood flow.[22] Given that the presence of autoregulation is characterised by a relative absence of changes in cerebral perfusion during changes in blood pressure, the simultaneous recording of $rScO_2$ and MABP does enable a reasonable estimate of autoregulation.[25 28 30 31] Using NIRS, an inability to autoregulate has been seen under a variety of clinical conditions, particularly in the sickest infants.[28 30] One of these studies found pressure passivity during an average of 20% of the time.[28] In the present study, we used the correlation between MABP and $rScO_2$ over periods of 1 min to study autoregulation. This simple technique does not require sophisticated mathematics, and good agreement has been demonstrated between this correlation and more advanced analyses, such as coherence analysis.[31] We found pressure passivity during an average of 10% of the time, with about 40% of our patients showing no pressure passivity at all, and about 30% showing pressure passivity lasting at least 10% of the time.

Indomethacin is a potent vasoactive drug. Results of several studies have suggested an improvement of cerebral autoregulation after indomethacin[8 10 12] In this study, infants were included when their mothers had received 50–150 mg of indomethacin within 24 h before giving birth. In most cases, at least 50 mg of indomethacin was given within 12 h before delivery, presumably resulting in active serum concentrations in the baby at birth.[3] Since serum half-life in the preterm newborn is 24 h or more,[3 4] and rScO2 and MABP data were collected in the first 24 h of life, we assume that these data reflect the situation well before the drug was fully metabolised and excreted.

On the basis of correlations between MABP and $rScO_2$, we did not see any improvement of cerebral autoregulation in the babies who had been exposed to indomethacin in utero, as has been reported in fetal lamb studies.[8 12] We can only speculate why this would be the case. One possibility is that the relatively good clinical condition precluded an inability to autoregulate in most of our patients. Blood pressure variability was similar in both groups, but few patients actually had very low MABPs. This may be an important issue since, theoretically, lack of autoregulation is particularly seen in infants with lower blood pressures. Another possibility is that serum concentrations of indomethacin were insufficient to have a significant effect on autoregulation. We did not determine serum concentrations in

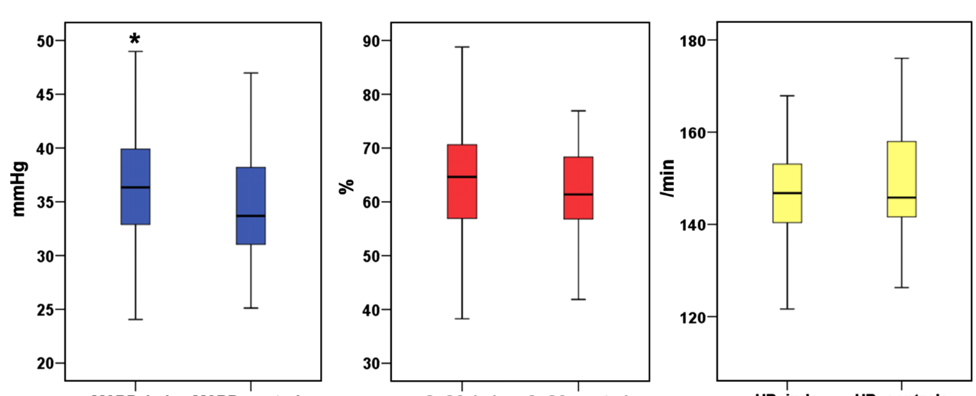

Figure 1 Box and whisker plots of mean arterial blood pressure (MABP), cerebral oxygenation ($rScO_2$), and heart rate (HR) results in indomethacin-exposed infants (indo) and in control infants (controls). *p=0.03.

the babies. Then, although the correlation between $rScO_2$ and MABP has been validated as a measure of autoregulation in the preterm baby, we cannot be sure that correlations over relatively short periods are suitable for the evaluation of autoregulation in relatively stable babies. Finally, the study group may have been too small to find a significant difference.

This study did, however, show higher MABPs in the exposed infants. The question is whether this finding should be attributed to antenatal exposure to indomethacin or to other factors. There were some differences between groups regarding several prenatal and early neonatal clinical characteristics. One noteworthy difference relates to the exposure of atosiban: all babies in the indomethacin group were also exposed to atosiban. Atosiban is an oxytocin antagonist that has been an effective tocolytic in case of premature labour.[32] However, since at least two studies have failed to demonstrate significant fetal circulatory effects of this medication, an effect on bloodpressure in the newborn is unlikely.[33 34] Another difference regards the number of infants who were antenatally exposed to other vasoactive medications. One infant was exposed to nifedipine and two were exposed to labetalol, all three controls. Blood pressures in these infants were, however, well within the range found for the entire group. Other differences between groups regard the slightly higher number of controls born after PPROM and amnionitis, and mothers who had received antibiotics. This is an important issue since neonatal infection is associated with a compromised circulation. None of the indomethacin infants born in the presence of amnionitis needed support of circulation, versus five of six of the controls. Clinically, however, control infants seemed to be in somewhat better condition at birth than indomethacin infants with 1 min Apgar scores, on average, one point higher. Finally, the total number of infants born by caesarean section was higher in the control group, due to more cases of maternal pre-eclampsia and placenta praevia. An effect of anaesthetic medication is, however, unlikely, as the majority of these babies were born after spinal anaesthesia. In summary, except possibly the presence of amnionitis, differences between groups do not provide an obvious explanation for the differences in MABP and the need for support of circulation.

If, in fact, exposure to indomethacin is the main explanation for higher MABPs, this finding seems to correspond to results of human and animal studies that demonstrated vasoconstriction after bolus injections of indomethacin.[5 6] Although that effect appears to be less pronounced when indomethacin is administered by slow infusion,[35] a small positive effect on blood pressure was recently also seen in a study of early postnatal indomethacin given over 1–2 h to prevent intraventricular haemorrhage, presumably as a result of an increase in cerebrovascular resistance.[36] Since we do not have any information about cardiac output or vascular resistance in our patients, we cannot be sure about the exact mechanism of our findings. We rather speculate that our findings relate to the effects of indomethacin on inflammatory cascades associated with premature birth, effects mediated through an inhibition of prostanoid and nitric oxide activity.[37–39] About one-third of our patients showed clinical and/or microscopic evidence of chorioamnionitis. Following this line of thought, we believe that indomethacin may have caused an improvement of the neonatal circulation by attenuating the negative effects of infection and inflammation in the exposed infants. This is corroborated by the fact that none of the infants exposed to indomethacin and born in the presence of amnionitis needed support of circulation, whereas the majority of control infants in similar circumstances did. The number of patients of our cohort was too small to substantiate this speculation.

In our group of exposed infants, we did not see an increased incidence of major PIVH or cystic PVL, as have been reported earlier,[15–17] possibly because of the small size of the group. Also, we did not see an increase in the number of PDAs that later needed treatment in the exposed infants, as has been reported.[40]

In conclusion, in this small retrospective cohort study of very preterm infants, we found that indomethacin, administered in doses of 50–150 mg per day as part of tocolytic management for imminent premature delivery, had a positive effect on postnatal MABP. There was no effect on cerebral autoregulation. Our results suggest that tocolytic indomethacin, when administered within 24 h before birth in doses from 50 to 150 mg, has a beneficial effect on early neonatal circulation in very preterm infants.

Contributors All authors participated in the design of the study, WB, JBD and PMAL in the collection of data, WB, FVB, LT and PMAL in the work-up of the data, and all authors in the draft of the paper.

Competing interests None.

Ethics approval The study was approved by the Medical Ethical Committee, University Medical Center, Utrecht NL.

Patient consent Obtained from the parents.

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