Randomised controlled trial of postnatal sodium supplementation in infants of 25–30 weeks gestational age: effects on cardiopulmonary adaptation

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Abstract

Background—It has previously been shown that, in preterm babies, routine sodium supplementation from 24 hours after birth is associated with increased risk of oxygen dependency and persistent expansion of the extracellular compartment.

Objective—To explore whether this is mediated by a delayed fall in pulmonary artery pressure (PAP). Postnatal changes in PAP, estimated as the ratio of time to peak velocity to right ventricular ejection time, corrected for heart rate (TPV:RVET(c)), were compared in preterm infants who received routine sodium supplements that were either early or delayed.

Methods—Infants were randomised, stratified according to sex and gestation, to receive a sodium intake of 4 mmol/kg/day starting either from 24 hours after birth or when a weight loss of 6% of birth weight was achieved. Echocardiographic assessment was made on the day of delivery (day 0), and on days 1, 2, 7, and 14. Babies with congenital heart disease were excluded.

Results—There was no difference between the two groups in TPV:RVET(c) measured sequentially after birth. On within group testing, when compared with values at birth, the ratio was higher by day 3 in the early supplemented group, suggesting a more rapid fall in PAP compared with the late supplemented group, in whom a significant fall did not occur until day 14.

Conclusions—The timing of sodium supplementation after preterm birth does not appear to affect the rate of fall in PAP as measured by the TPV:RVET(c) ratio. The previous observation linking routine sodium supplementation from 24 hours after birth with increased risk of continuing oxygen requirement therefore does not appear to be mediated by a delayed fall in PAP. Instead, the increased risk of continuing oxygen requirement is likely to be a direct consequence of persistent expansion of the extracellular compartment and increased pulmonary interstitial fluid, resulting from a sodium intake that exceeded sodium excretory capacity. This adds further weight to the view that clinical management, in this case the timing of routine sodium supplementation, should be individually tailored and delayed until the onset of postnatal extracellular volume contraction, marked clinically by weight loss.

Keywords: preterm; sodium and water balance; nutritional supplements; pulmonary artery pressure

Cardiopulmonary adaptation after birth, with a fall in pulmonary vascular resistance and pulmonary artery pressure (PAP) and rise in pulmonary blood flow, is a necessary prerequisite for successful transition to a gaseous environment. Doppler echocardiography is a non-invasive tool that can be used to follow postnatal cardiopulmonary adaptation.

There are several methods for estimating PAP, but the ratio of time to peak velocity (TPV) to right ventricular ejection time (RVET) has been a favoured approach despite well understood limitations. Sequential measurements can be made relatively easily. Changes in this ratio have been described in healthy preterm infants immediately after delivery and during the acute and recovery stages of hyaline membrane disease (HMD). Other methods, using either tricuspid regurgitation or ductal flow, are limited in that these features are not always present after the first few hours, or days, after delivery and so cannot be used to follow trends over an extended period.

Another feature of successful postnatal adaptation is a contraction of the extracellular fluid compartment. We have previously shown that early sodium supplementation delays the loss of extracellular fluid and has an adverse effect on oxygen dependency. The aim of this study was to explore whether these effects are mediated by a delayed fall in PAP. There are no published data on cardiopulmonary adaptation during different sodium supplementation regimens, although others have also described effects on sodium balance, extracellular fluid volume, and bronchopulmonary dysplasia.

Methods

These have been fully described previously. Briefly, infants born between 25 and 30 weeks gestation, admitted to the neonatal intensive care units at the Hammersmith and Queen Charlotte’s Hospitals, London, UK, were eligible for entry. Infants with major congenital
malformations, known chromosomal disorders, and those with known renal abnormalities were excluded. The trial was approved by the institutional research ethics committee. Written informed parental consent was obtained.

Infants were randomised to receive early or late sodium, stratified by sex and gestational age. If allocated to the early limb of the trial, the infant was prescribed no sodium for the first 24 hours after birth, and 4 mmol/kg/day thereafter; late group, received 4 mmol sodium/kg/day only when 6% of birth weight had been lost. Clinical staff caring for the infants were blind to which limb of the trial the baby was allocated. The appropriate amount of sodium was administered in parenteral nutrition fluid by pharmacy staff. For each infant, the CRIB (clinical risk index for babies) score,18 an index of disease severity, was calculated at 12 hours, and the mean a:A ratio for the first 24 hours after delivery.

DOPPLER ECHOCARDIOGRAPHY
This was performed by a single operator (GH) using an ATL Ultramark IV ultrasound scanner with a 7.5 MHz multifrequency imaging transducer combined with a 5 MHz Doppler transducer. A Doppler signal was recorded from the centre of the main pulmonary artery just distal to the pulmonary valve, and measurements of the time to peak velocity and right ventricular ejection time made from the Doppler waveform. The TPV:RVET(c) was calculated at 12 hours, and the mean a:A ratio for the first 24 hours after delivery.

Results
Twenty-two babies were entered into the study in each group. Table 1 gives a summary of their details. There were no differences between the two groups in terms of male:female ratio, gestation, birth weight, antenatal dexamethasone exposure, or postnatal surfactant use. The two groups were comparable in terms of initial degree of illness, with similar CRIB scores and mean a:A ratios for the first 24 hours.

The intraobserver variability for TPV:RVET(c) was calculated at 12 hours, and the mean a:A ratio for the first 24 hours after delivery.

DATA ANALYSIS
Statistical calculations were performed using Intercooled Stata v.4. All data were tested for normality, and parametric or non-parametric tests applied accordingly. Within group comparisons were made using the paired t test or Mann-Whitney two sample statistic. As a summary measure for TPV:RVET(c), the area under the curve of TPV:RVET(c) v day of study was used for the first seven days and the first 14 days after delivery.

Discussion
The aim of this study was to examine the effect of delaying sodium supplementation until 6% or more of birth weight had been lost on the rate of PAP alteration, as measured by Doppler derived TPV:RVET(c) from the main pulmonary artery. We have shown that the different sodium regimens were not associated with any difference between the groups. When within group changes were analysed, the early supplemented group had a statistically significant rise in TPV:RVET(c), indicating a lower PAP, at an earlier stage than the late supplemented group.
There are three methods for estimating PAP in preterm infants using echocardiography: systolic time intervals, tricuspid regurgitation, and ductal flow velocities. Kitabatake et al showed an inverse relation between TPV:RVET and PAP in adults, which was also shown to hold true in children when the ratio was corrected for heart rate. However, very few neonates have been included in validation studies, so the applicability of the method to the preterm population is uncertain. In addition, TPV:RVET may correlate well with PAP, but it does not reliably distinguish babies with high PAP from those with normal pressure; a TPV:RVET ratio of 0.30 can occur with a mean PAP of 15 mm Hg or 45 mm Hg. There are potentially large intraobserver and interobserver variabilities in the measurements, and the sampling point for the pulsed wave Doppler is critical in determining the result. In our study, the intraobserver variability for TPV:RVET(c) was 11% which is comparable to published values of 14.7% and 12.3%, and 12% (figure adjusted to take into account different method of calculation).2

The method of applying the modified Bernoulli equation to the flow velocity of tricuspid regurgitation to derive the fall in pressure between the right ventricle and right atrium has been validated in adults, and 10–12 day old infants. It is reproducible and accurately reflects PAP in the absence of pulmonary valve disease, but there are problems when applying the technique to preterm infants. The modified Bernoulli equation underestimates falls in pressure if the orifice through which the blood is flowing is less than 3.5 mm and if the velocity of the jet is less than 3 m/s, both of which are within the range of values encountered in the preterm infant. Also, the modified Bernoulli equation ignores viscous friction forces; preterm infants often have a high packed cell volume, which will lead to a high viscosity and an underestimate of the PAP.

The modified Bernoulli equation can also be applied to the flow velocity of blood through the patent ductus arteriosus to determine the pressure difference between the aorta and the pulmonary artery, allowing calculation of the PAP if aortic pressure is known. However, the modified Bernoulli equation was derived to be applied to flow through a distinct orifice whereas the patent ductus arteriosus is a tunnel-like structure, leading to underestimates of PAP. In addition, as the ductus constricts, it will produce a very small orifice leading to an underestimate of PAP, as with tricuspid regurgitation.

Walther et al examined the course of postnatal cardiopulmonary adaptation in healthy and sick term babies during the first 24 hours after delivery. They did not use the Doppler time ratios in their analysis but looked at patterns of ductal flow and aortopulmonary pressure differences. They showed that in healthy term infants most measurable cardio-pulmonary changes had occurred by eight hours after delivery. However, in the sick term babies, there was still a measurable degree of ductal shunting and raised PAP at 24 hours, the end point of their study. Evans and Archer used TPV:RVET to compare the rate of circulatory adaptation between healthy term babies and healthy preterm babies. They found no differences between the two groups on the initial assessment at less than six hours after delivery, but on subsequent assessments, TPV:RVET was significantly higher in the term babies, indicating a lower PAP. This was maintained until the final assessment at four days after delivery, by which time TPV:RVET in the preterm infants had risen to that of the term infants. This showed that the rate of cardiopulmonary adaptation is slower in healthy preterm infants when compared with healthy term infants.

Evans and Archer also compared the changes in TPV:RVET in preterm infants with and without HMD. In the preterm infants without HMD, TPV:RVET rose rapidly to reach normal values by 60 hours after delivery, after which values remained constant. In contrast, although there were no differences between the two groups over the first 15 hours after delivery, TPV:RVET rose more slowly in the group with HMD, so that by 24 hours after delivery the ratio was significantly lower. In babies with HMD, TPV:RVET never reached a normal value, but also reached a plateau at 45–60 hours after delivery, which was maintained until the end of the study at 150 hours. Skinner et al using tricuspid regurgitation, also found that the rate of fall in PAP in babies with HMD was much slower than in healthy preterm babies and that it did not fall to a level comparable to that of healthy preterm infants until about 160–240 hours after delivery. These data are in keeping with a rate of fall in PAP after delivery that is slower in preterm infants and slower still in sick infants. Evans and Archer also examined the changes in TPV:RVET over a longer time period during recovery from HMD in preterm infants. They found three distinct patterns of change with time in TPV:RVET. One group of infants had a rapid rise in TPV:RVET as the Fio₂ fell, indicating rapid postnatal adaptation; another group had a delay of greater than 24 hours in the rise of TPV:RVET after the Fio₂ fell to < 0.5. These infants were significantly more premature than the first group. In the third group, TPV:RVET never rose to normal values, but gradually fell after an initial rise, despite a median follow up time of 58 days, indicating a persistently elevated PAP. This last

Key messages
- Delaying routine sodium supplementation until after the onset of postnatal weight loss has a beneficial effect on oxygen requirement after preterm birth.
- The adverse effect of routine sodium supplementation is not mediated by alterations in pulmonary artery pressure but by impaired loss of extracellular fluid from the pulmonary interstitium.

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We have shown that early sodium supplementation has a detrimental effect on oxygen dependency\textsuperscript{12,13} and also delays the postnatal contraction of the extracellular fluid compartment.\textsuperscript{14} We have also shown that, regardless of the timing of sodium supplementation, postnatal extracellular fluid loss appears to be triggered by a surge in atrial natriuretic peptide.\textsuperscript{28} Increased release of atrial natriuretic peptide may be expected as a result of increased left atrial stretch as pulmonary venous return rises postnatally. A failure to lose extracellular fluid and therefore, as sodium is the principal extracellular electrolyte, the associated sodium load may be a consequence of either an intake that exceeds sodium excretory capacity or a delayed fall in pulmonary vascular resistance and delayed rise in pulmonary blood flow. The results reported here show that the babies in both groups had a delayed rise in TPV:RVET(c) similar to that seen in the second group of babies described by Evans and Archer.\textsuperscript{7} However, we found no differences between our two groups in TPV:RVET(c) throughout our study period of 15 days. Indeed TPV:RVET(c) rose more quickly in the early sodium supplemented group, suggesting that, in this group, cardiopulmonary adaptation occurred more quickly with a more rapid fall in PAP. It is of note that, despite this more rapid adaptation, the early sodium supplemented group had a greater risk of persisting oxygen requirement\textsuperscript{12} and a delayed loss of extracellular fluid.\textsuperscript{14} The conclusion to be drawn therefore is that the delayed loss of extracellular fluid was primarily a consequence of a sodium intake (4 mmol/kg/day) that exceeded sodium excretory capacity and that the poorer outcome in terms of oxygen dependency was mediated by increased lung interstitial fluid. Although this intake would be unlikely to exceed excretory capacity for long, as the capacity to excrete a sodium load matures during the first days after birth,\textsuperscript{27} the regulation of fluid balance during the first few days after preterm delivery is clearly of critical importance. This conclusion lends further support to our previously stated view\textsuperscript{11} that clinical management, in this case the timing of starting a routine sodium supplement after preterm birth, should be tailored individually and delayed until the onset of postnatal extracellular volume contraction, marked clinically by weight loss. The key message of this study is that the benefit that we have previously shown,\textsuperscript{11,15} namely that delaying routine sodium supplementation until after the onset of postnatal weight loss, is not mediated by any change in PAP.


\textsuperscript{19} Intercooled Stata version 4.0 [computer program]. College Station, TX: Stata Corporation, 1995.


\textsuperscript{24} Teirstein PS, Yock PG, Popp RL. The accuracy of Doppler ultrasound measurement of pressure gradients across irregular, dual, and tunnel-like obstructions to blood flow. \textit{Circulation} 1985;74:577–94.


