Conclusions

The conference considered present and future issues relating to the management of RhD negative pregnant women in a thorough, balanced, and fair way. Some cynics have criticised the conclusions of the conference panel because the blood products industry were co-sponsors and inevitably this would have been expected to have led to a recommendation to increase the use of anti-D. This is unfair criticism. The evidence of scientific effectiveness of routine anti-D prophylaxis is very robust and on that conclusion alone, the practice must be recommended.

The important question providers of health care will have to answer is: is the present hidden or spontaneous RhD sensitisation rate acceptable? If the answer to that is "no" then offering routine anti-D prophylaxis to RhD negative pregnant women in the third trimester may be cost effective in the long term. The dose which seems to be preferred is 500 IU anti-D at 28 and 34 weeks.

Finally, and as a more immediate priority, all professionals involved in pregnancy care should improve the implementation of the 1991 guidelines. Specifically, there needs to be a tightening up of the practice of the administration of anti-D to RhD negative women and the use of Kleihauer testing at the time of sensitising events in pregnancy. This advice is especially relevant to those working in accident and emergency departments and in primary care.

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- 1 Consensus statement from the Royal College of Physicians of Edinburgh/ Royal College of Obstetricians and Gynaecologists Consensus Conference on Anti-D Prophylaxis 7&8 April 1997. *Transfus Med* 1997;7:143-4.
- 2 Hadley AG, Kumpel BM. The role of Rh antibodies in haemolytic disease of the newborn. *Balière's Clin Haematol* 1993;6:423-44.
- 3 Hughes RG, Craig JL, Murphy WG, Grear IA. Causes and clinical consequences of Rhesus (D) haemolytic disease of the newborn: a study of a Scottish population, 1985-1990. *Br J Obs Gynaecol* 1994;101:297-300.
- 4 Ghosh S, Murphy WG. Implementation of the Rhesus prevention programme. A prospective study. *Scot Med J* 1994;39:147-9.
- 5 Gilling-Smith C, Toozs-Hobson P, Potts DJ, Touquet R, Beard RW. Management of bleeding in early pregnancy in accident and emergency departments. *BMJ* 1994;309:574-75.
- 6 Bowman JM, Pollock JM. Rh isoimmunisation during pregnancy: antenatal prophylaxis. *Can Med Assoc J* 1978;118:623-7.
- 7 Bowman JM, Pollock JM. Antenatal prophylaxis of Rh isoimmunisation: 28-weeks gestation service program. *Can Med Assoc J* 1978;118:627-30.
- 8 Bowman JM, Pollock JM. Failures of intravenous Rh immune globulin prophylaxis: an analysis of the reasons for such failures. *Transfus Med Rev* 1987;1:101-12.
- 9 National Blood Transfusion Service Immunoglobulin Working Party. Recommendations for the use of Anti-D immunoglobulin. *Prescribers' Journal* 1991;30:137-45.
- 10 Ascarì WQ, Levine P, Pollack W. Incidence of maternal Rh immunisation by ABO compatible and incompatible pregnancies. *BMJ* 1969;i:399-401.
- 11 Combined Study Group. Prevention of Rh-haemolytic disease: results of the clinical trial. A combined study from centres in England and Baltimore. *Br Med J* 1966;ii:907-14.
- 12 Medical Research Council. Report of a working party on the use of Anti-D immunoglobulin for the prevention of isoimmunisation of Rh-negative women during pregnancy. *Br Med J* 1974;i:75-80.
- 13 World Health Organisation. *Technical Report Series, No 468. Prevention of Rh Sensitization*. Geneva: WHO, 1971.
- 14 Commission of the European Communities. Committee for Proprietary Medicinal Products. *Core Summary of Product Characteristics for Human Anti-D Immunoglobulin*. Brussels: CEC 1994 (111/34463/92EN).
- 15 Polesky HF, Sebring ES. Evaluation of methods for detection and quantification of fetal cells and their effect on Rh IgG usage. *Am J Clin Pathol* 1981; (Suppl 1):525-29.
- 16 Duguid JKM, Bromilow I. Value of Kleihauer testing after administration of Anti-D immunoglobulin. *BMJ* 1994;309:240.
- 17 UK NEQAS. *Provisional Report*. Potters Bar: National Institute for Biological Standards and Control, 1994.
- 18 Letsky EA, De Silva M. Preventing Rh Immunisation - much scope for improvement. *BMJ* 1994;309:213-14.

Pump up the volume? The routine early use of colloid in very preterm infants

Rarely does a very low birthweight infant escape at least 10 ml/kg of colloid in the first few hours of life. Most units do not give volume routinely on admission, in the same way that most units don't prescribe routine antibiotics, yet almost every very preterm baby gets both, as routinely as vitamin K or a photograph for the mother. In the case of antibiotics there is usually some feature of the history or examination that can be invoked to suggest a risk of infection, even if the mother had an elective caesarean section. In the case of colloid there is always a slight metabolic acidosis, or a lowish temperature on arrival from labour ward, or a casual tweak of the big toe by a passing consultant which, of course, provides conclusive proof of hypovolaemia.

A few hours later the baby is warmer and pinker, peripheral perfusion is improved (the ritual toe tweak evokes a satisfied hmm rather than a tut-tut), the base deficit is less, so the colloid must have worked. But is this necessarily cause and effect? These improvements may well have occurred without specific treatment.

The clinical instinct to improve peripheral perfusion and blood pressure fairly quickly after birth is not purely cosmetic in very preterm infants who are at major risk of both haemorrhagic and ischaemic cerebral lesions. Both intraventricular haemorrhage (IVH) and periventricular leucomalacia have been attributed to hypotension and cerebral hypoperfusion,¹ but does routine volume expansion prevent these complications of prematurity?

In 1985 Beverley *et al*² randomised 80 infants who were <1500 g birthweight or <32 weeks of gestation, or both, to

a regimen of 10 ml/kg fresh frozen plasma (FFP) on admission and again 24 hours later, or to a control group who were to be given "small volumes" of purified protein fraction only if they became hypotensive. The authors excluded seven of these neonates from their analysis, two in the treatment arm who had an IVH or died before treatment with FFP, and five controls who required FFP on clinical grounds for severe hypotension or coagulopathy. Including these cases and analysing by intention to treat, there were seven deaths and five severe IVHs (grades III or IV according to Papile's classification)³ in the treatment group. There were eight deaths and 10 severe IVHs in the control group. These differences were not significant. The authors' analysis included minor degrees of IVH and suggested a benefit of routine volume expansion. This was attributed to the haemodynamic effects of the FFP rather than any effect on impaired coagulation status, because clotting studies were similar in the two groups at 48 hours.

In 1996 the Northern Neonatal Nursing Initiative Trial Group reported a much larger multicentre randomised controlled trial of infants of under 32 weeks of gestation.⁴ They compared a control group with a group given FFP routinely, and also a group who were volume loaded with a gel based colloid, to assess the independent effect of colloid infusion without any beneficial effect on coagulation status. Fairly aggressive volume loading was used. Each of the treatment groups received 20 ml/kg over 15 minutes in the first few hours of life and another 10 ml/kg the following day. Because cerebral ultrasound scanning may fail to detect clinically significant ischaemic lesions and is

therefore an inadequate proxy for long term outcome, they chose survival without major disability at 2 years as their endpoint. It is a huge credit to those who organised and carried out this trial that they managed to recruit 776 babies from 21 hospitals in the Northern Region, and achieved 100% follow up. The result was clearcut. Neither the number of deaths, nor the number of survivors with major disability, differed between the two treatment groups and the controls. Not surprisingly, infants in the control group were more likely than those in the two treatment groups (20% *vs* 8%) to need colloid infusions to correct anaemia or hypotension during the first 48 hours.

Any true difference between the outcomes for higher risk babies in these groups might have been diluted by the inclusion of relatively large preterms in the 30–32 weeks gestational age range (who might be expected to benefit less from early colloid) and the exclusion of 61/834 babies (who might be expected to benefit more from routine volume expansion) on the grounds of severe illness or extreme prematurity. It is also possible, if unlikely, that a slower or smaller colloid infusion may have shown a net benefit, but the rapid rate of infusion of a large bolus of colloid in this study led to sudden increases in venous pressure in some babies leading to cardiac or cerebral sequelae. Despite these minor reservations about applicability to the extremely preterm infant, this very large trial used a more clinically valid endpoint than the smaller Beverley study, and the assessments were carried out blind to initial treatment allocation. Routine colloid infusion in the first hours of life in all preterm infants of <32 weeks of gestation is therefore of no value, which leaves clinicians in the difficult position of needing to make clinical decisions.

Such a decision seems straightforward in the slightly grey, hypothermic, ventilated 24 week gestational age infant just admitted from the labour ward. The entire arm goes white when you lift it to insert an intravenous cannula, the base deficit is 13 mmol/l, and colloid is probably appropriate even before arterial access is achieved and blood pressure measured. The results of the controlled trial do not help in this situation, as such cases would have been excluded or lost in the analysis among the much larger numbers of 31 week gestational age infants. The decision is even easier in the well perfused, vigorous 31 week old gestational age baby with minimal respiratory disease in whom arterial access is deemed unduly invasive. Most neonatologists are unlikely to give colloid to such a baby (unless constrained by a trial protocol) and now the evidence supports that gut reaction. We can now cite the results of a large trial in our arguments with senior house officers and specialist registrars who tend to be very aggressive in their use of volume and have a very low threshold for “treating” mild metabolic acidosis.

Unfortunately, the current evidence does not help in the less clearcut cases, and we are limited in our means of assessing which preterm infants do need colloid. Capillary refill times correlate poorly with hypovolaemia in adults.⁵ They have been evaluated in older children in whom peripheral temperature is an important confounder.⁶ Recent work has established a normal range in neonates in different thermal environments in a neonatal unit, and has suggested that the chest or forehead are preferable sites to assess capillary refill.⁷ However, there are no data testing the accuracy of capillary refill time for the detection of hypovolaemia in the recently born who often have very marked vasomotor instability. Of course I can hmm, and tut-tut, and toe tweak with the best of them (and in future I shall tweak the forehead), because we have little else to judge objectively. Measurement of urine output is obviously unhelpful as a means of assessing circulating volume in the first few hours of life. Central venous pressure

(CVP) measurements are rarely used, but are easily available in those babies in whom an umbilical venous catheter is sited and passes into the right atrium. Skinner *et al*⁸ published some normative data from 13 babies with respiratory disease, eight of whom were preterm, but there is very little published on the use of CVP monitoring in “medical” neonatal patients. Skinner *et al* concluded that CVP monitoring was useful for detecting trends, and in some circumstances individual measurements of CVP could help in clinical decision making. For instance, in ventilated neonates a CVP of 0 mm Hg was likely to be associated with other signs of hypovolaemia. It is important to realise the effect of intrathoracic pressure and respiratory status on the CVP, and that negative values do not necessarily represent hypovolaemia in the spontaneously breathing baby.⁸

Lyon *et al*⁹ studied central–peripheral temperature differences in infants with birthweights of < 1000 g and concluded that in the first few days of life thermoregulation is immature, so central and peripheral temperatures are similar. Both are directly affected by external temperature, so the baby is effectively poikilothermic. Central–peripheral temperature gaps of > 2°C became more frequent after three days of life when babies became more competent at vasoconstriction, but even then were more likely to represent thermal stress than hypovolaemia. Continuous monitoring showed that a clinically significant temperature gap was associated with other indicators of hypovolaemia for only 11% of the time, so dual temperature monitoring is not going to inform decisions about colloid infusions on day 1. Actual measurements of circulating plasma volume have been made in neonates using dye dilution techniques^{10–11} but these are very much research procedures. It is probably more important in any case to look at the functional effect of a reduced circulating volume. Electrodes for continuous monitoring of tissue pH have been available for many years¹² without having any impact on neonatal practice, perhaps because it is assumed that the additional information from an invasive electrode adds little to intermittent arterial pH measurements.

Venous oxygen tensions or saturations may be better than arterial values as a guide to tissue oxygen delivery, and measurements made from right atrial samples taken from an umbilical venous catheter have been suggested as a reasonable proxy for the pulmonary artery samples used in adult intensive care.¹³ Non-invasive measurements of peripheral venous oxygen saturation¹⁴ or cerebral venous oxygenation^{15–17} are possible using near infra-red spectroscopy, but the complexity of the current methodology precludes routine application.

Blood pressure can be measured directly and accurately, but hypotension represents a decompensation we should be aiming to avoid rather than treat. Of course, even the definition of hypotension and the appropriate treatment are still in doubt. The appropriate level of mean blood pressure for intervention in very preterm infants remains controversial. Should treatment with colloid be the mainstay of treatment of “hypotension”? It often seems to work, but evidence suggests that early “hypotension” is not usually due to hypovolaemia.¹⁰ Should we therefore resort to inotropes at an earlier stage, as suggested by Gill and Weindling?¹⁸ Dopamine seems to be an effective agent for increasing the blood pressure, but may peripherally vasoconstrict without increasing ventricular output,¹⁹ and may exacerbate pulmonary vasoconstriction.^{19–20} Dobutamine may have theoretical advantages, but seems to be a less effective pressor.¹⁹

The trial in the Northern Region was nearly as good as it could be, and it may lead to some moderation and common sense in the use of blood products such as FFP,

cryoprecipitate, and human serum albumin (HAS). Times have changed since SHOs were selected at interview on the basis of their blood group and used as walking whole blood donors every time they suggested a baby needed colloid. The routine use of FFP in the absence of confirmed coagulopathy is now discouraged, and both the Beverley² and the Northern Neonatal Network trial⁴ support that approach. HAS is still used frequently, and it is a blood product even if it comes in a cardboard box. There is certainly a case for further evaluation of synthetic alternatives to colloid treatment in neonates: one such is crystalloid. However counterintuitive it might seem, recent evidence from a small randomised trial by King W So *et al*²¹ shows that physiological saline is no less effective than albumin for the treatment of early hypotension in preterm infants and is associated with less fluid retention.

It should be easier to sort out what fluid to use for volume expansion than to decide to whom to give it and when. Toes will continue to be tweaked until there are simple objective techniques to assess hypovolaemia in preterm neonates.

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- 1 Miall-Allen VM, de Vries LS, Whitelaw AGL. Mean arterial blood pressure and neonatal cerebral lesions. *Arch Dis Child* 1987;62:1068-9.
- 2 Beverley DW, Pitts-Tucker TJ, Congdon PJ, Arthur RJ, Tate G. Prevention of intraventricular haemorrhage by fresh frozen plasma. *Arch Dis Child* 1985;60:710-13.
- 3 Papile L, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal haemorrhage: a study of infants with birthweight less than 1500 grams. *J Pediatr* 1978;92: 529-34.
- 4 Northern Neonatal Nursing Initiative Trial Group. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996; 348:229-32.
- 5 Baraff LJ. Capillary refill: is it a useful clinical sign? *Pediatrics* 1993;92:723-4.
- 6 Gorelick MH, Shaw KN, Baker MD. Effect of ambient temperature on capillary refill in healthy children. *Pediatrics* 1993;92:699-702.
- 7 Strozik KS, Pieper CH, Roller J. Capillary refilling time in newborn babies: normal values. *Arch Dis Child* 1997;76:F193-F6.
- 8 Skinner JR, Milligan DWA, Hunter S, Hey EN. Central venous pressure in the ventilated neonate. *Arch Dis Child* 1992;67:374-7.
- 9 Lyon A, Pikaar ME, Badger P, McIntosh N. Temperature control in very low birthweight infants during the first five days of life. *Arch Dis Child* 1997;76:F47-F50.
- 10 Barr PA, Bailey PE, Sumners J, Cassady G. Relation between arterial blood pressure and blood volume and effect of infused albumin in sick preterm infants. *Pediatrics* 1977;60:282-9.
- 11 Anthony MY, Goodall SR, Papouli M, Levene MI. Measurement of plasma volume in neonates. *Arch Dis Child* 1992;67:36-40.
- 12 Bhat R, Vidyasagar D, Asonye UO, Papazafiratu C. Continuous tissue pH monitoring in critically ill neonates. *J Pediatr* 1980;97: 445-50.
- 13 O'Connor TA, Hall RT. Mixed venous oxygenation in critically ill neonates. *Crit Care Med* 1994;22:343-6.
- 14 Yoxall CW, Weindling AM. The measurement of peripheral venous oxyhaemoglobin saturation in newborn infants by near infrared spectroscopy with venous occlusion. *Pediatr Res* 1996;39:1103-6.
- 15 Wyatt JS, Cope M, Delpy DT, Wray S, Reynolds EOR. Quantification of cerebral oxygenation and haemodynamics in sick newborn infants by near infrared spectrophotometry. *Lancet* 1986;ii:1063-6.
- 16 Yoxall CW, Dawani N, Weindling AM, Peart I. Measurement of cerebral venous oxyhaemoglobin saturation in children by near infrared spectroscopy with partial jugular venous occlusion. *Pediatr Res* 1995;38:319-23.
- 17 Wolf M, Duc G, Keel M, Niederer P, von Siebenthal K, Bucher H-U. Continuous noninvasive measurement of cerebral arterial and venous oxygen saturation at the bedside in mechanically ventilated neonates. *Crit Care Med* 1997;25:1579-82.
- 18 Gill AB, Weindling AM. Randomised controlled trial of plasma protein fraction versus dopamine in hypotensive very low birthweight infants. *Arch Dis Child* 1993;69:284-7.
- 19 Roze JC, Tohier C, Maingueneau C, Lefevre M, Mouzard A. Response to dobutamine and dopamine in the hypotensive very preterm infant. *Arch Dis Child* 1993;69:59-63.
- 20 Zaritsky A, Chernow B. Use of catecholamines in pediatrics. *J Pediatr* 1984;105:341-50.
- 21 So KW, Fok TF, Ng PC, Wong WW, Cheung KL. Randomised controlled trial of colloid or crystalloid in hypotensive preterm infants. *Arch Dis Child* 1997;76:F43-F6.