Annotations

Intervention after birth asphyxia

Despite improvements in fetal monitoring and neonatal resuscitation, every district general hospital has a number of full term infants every year who suffer from the effects of severe lack of oxygen before or during delivery. Approximately six per 1000 full term infants develop hypoxic-ischaemic encephalopathy and one per 1000 will die or survive with severe neurological disability.¹ In Great Britain, 300-400 children per year survive birth asphyxia with serious brain damage.

Paediatricians have vigorously tried to improve standards of neonatal resuscitation in the delivery ward but have found hypoxic-ischaemic encephalopathy a difficult problem to treat. A common attitude is that the damage has been done before arrival in the neonatal intensive care unit and treatment is too late to repair neural cell death. The prognosis has seemed so hopeless in some cases that withdrawal of intensive care has seemed the kindest solution.² Are we being too negative about the encephalopathy? This annotation discusses the emerging evidence that management after initial resuscitation may influence neurological outcome.

Hypoxic-ischaemic encephalopathy

After resuscitation a proportion of infants become neurologically abnormal during the next 48 hours. This encephalopathy can be clinically classified into: mild (irritability, poor sucking, and hypotonia), moderate (convulsions, lethargy, and appreciably abnormal tone), and severe (comatose with prolonged seizures and respiratory failure).³ Out of 24 infants with moderate encephalopathy, one died and five survived with severe handicap. Out of 21 with severe encephalopathy, 13 died and three survived with severe handicap. Of the infants with mild encephalopathy, only one became handicapped and this child had a congenital myopathy.¹

Convulsions

Generalised tonic-clonic convulsions should be treated as they tend to interfere with respiration and raise intracranial pressure. We start treatment with phenobarbitone 20 mg/kg intravenously as a loading dose.⁴ If convulsions continue, paraldehyde 3 ml/kg/

hour of a 5% solution is given intravenously until the seizures stop.⁵ Continued seizures are treated with phenytoin 20 mg/kg and diazepam 0.3 mg/kg intravenously.

Postasphyxial seizures can be very resistant to treatment and intravenous clonazepam, lignocaine, chlormethiazole, and sodium valproate can be considered in such cases. Whether one should treat a comatose, ventilated baby who is having subtle seizures or purely electrical seizures is arguable. Neonatal seizures deplete the brain of high energy substrates and interfere with brain cell division⁶ but large doses of anticonvulsants may have adverse effects: particularly respiratory and circulatory depression. It used to be thought that high dose barbiturate might have a protective effect after hypoxia by reducing cerebral metabolic requirements. A trial of thiopentone in severely asphyxiated infants, however, gave no evidence of benefit. Indeed hypotension was a troublesome side effect of thiopentone.⁷

Control of raised intracranial pressure

The brain commonly reacts to severe hypoxia by developing oedema over a period of 24-48 hours. The skull is able to accommodate some degree of brain swelling by squeezing cerebrospinal fluid out of the cranium. Moreover, neonates can tolerate some further brain swelling without the pressure rising because of the unfused sutures and the open fontanelles. Severe cerebral oedema can exceed the cranial compliance, however, and cause the pressure to rise above the normal upper limit of 6 mm Hg (0.80 kPa).⁸ We have used the same subarachnoid pressure catheter technique as Levene *et al*⁹ to monitor intracranial pressure in asphyxiated neonates and have confirmed their findings that raised pressure in some infants can be temporarily lowered by intravenous mannitol, that sustained intracranial hypertension (>15 mm Hg (2.00 kPa)) resistant to treatment has a very bad prognosis, and that some infants can have severe encephalopathy and bad outcome without raising intracranial pressure above 10 mm Hg (1.33 kPa).⁹

We have extensively investigated non-invasive measurement of intracranial pressure via the fon-

tanelle and have found it too inaccurate for clinical decision making.¹⁰ Although we have had no complications from subarachnoid catheterisation in 25 cases, the technique is highly invasive and has the potential to cause meningitis. No study has yet shown that invasive intracranial pressure monitoring and mannitol treatment improves later outcome.

Dexamethasone has been used for certain types of cerebral oedema associated with tumour or abscess. There is no evidence, however, that it gives benefit after birth asphyxia.¹¹

Hyperventilation to produce hypocapnoea has been used to reduce raised intracranial pressure in adults. However, this effect is achieved by reducing cerebral blood flow which seems undesirable.

Circulatory support

Neonates are generally not good at raising arterial pressure in response to raised intracranial pressure (Cushing response) and the combination of low arterial pressure and raised intracranial pressure is particularly devastating. We have not found any normal survivors from a cerebral perfusion pressure (mean arterial pressure—intracranial pressure) below 20 mm Hg (2.67 kPa).

Hypovolaemia may be associated with asphyxia because of shunting of blood from the vasoconstricted fetus to the placenta, from blood loss, or from hypoxic capillaries leaking plasma into the interstitial space. Peripheral vasoconstriction, mean arterial pressure below 40 mm Hg (5.33 kPa), and metabolic acidosis are suggestive of hypovolaemia. Colloid at 10 to 20 ml/kg should be given intravenously and larger volumes may be necessary. Myocardial ischaemia may also occur with reduced cardiac output. This diagnosis would be suggested by finding cardiomegaly on chest radiography and ischaemic ST changes on electrocardiography. If arterial pressure remains low despite volume replacement, a dopamine infusion should be started after any remaining metabolic acidosis has been corrected with sodium bicarbonate. The dopamine infusion can start at 5 µg/kg/minute but should be increased to 10, 15, or 20 µg/kg/minute if mean arterial pressure does not reach 40 mm Hg (5.33 kPa).¹²

Cerebral protection

Studies of hypoxia in experimental animals have indicated that processes continuing for some hours after a hypoxic insult has ceased can bring about further cerebral damage. These mechanisms include a prolonged fall in cerebral blood flow (the no reflow phenomenon),¹³ calcium loading of mito-

chondria activating phospholipase,¹⁴ release of oxygen free radicals,¹⁵ and excitatory amino acids such as glutamate.¹⁶ Steen *et al* showed that the calcium channel blocker nimodipine improved survival when given after complete cerebral ischaemia in primates.¹⁷ Thiringer *et al* carried out a randomised trial of oxygen free radical scavengers (methionine, mannitol, and magnesium sulphate) and the calcium channel blocker lidoflazine in lambs subjected to acute umbilical cord occlusion.¹⁸ She found that the lambs treated within 5 minutes of resuscitation retained cerebral blood flow better than controls. The treated lambs also had better somatosensory evoked potentials and cerebral cortical function. There are no published studies on glutamate antagonists, free radical scavengers, or calcium channel blockers in human neonates.

Prognosis

Nelson and Ellenberg found that an Apgar score of <4 at 20 minutes gave a 57% chance of cerebral palsy in survivors.¹⁹ Steiner and Nelligan found that all full term infants who failed to establish respiration by 30 minutes subsequently had spastic quadriplegia and mental retardation.²⁰ It has been a common practice to discontinue further resuscitation if there is no respiratory effort after 30 minutes. Infants with severe encephalopathy who have persistently raised intracranial pressure (>15 mm Hg (2.00 kPa)) resistant to mannitol also have an extremely poor outlook. In the future, electroencephalography, cerebral blood velocity by Doppler, and phosphorus magnetic resonance spectroscopy may help to give us an accurate prognosis at an early stage. Asphyxiated infants who are assessed very early to have a bad prognosis are the ones who should be considered for therapeutic trials of cerebral protection.

References

- Levene MI, Sands C, Grindulis H, Moore JR. Comparison of two methods of predicting outcome in perinatal asphyxia. *Lancet* 1986;i:67-8.
- Whitelaw A. Death as an option in neonatal intensive care. *Lancet* 1986;ii:328-31.
- Levene MI, Kornberg J, Williams THC. The incidence and severity of post-asphyxial encephalopathy in full term infants. *Early Hum Dev* 1985;11:21-6.
- Painter MJ, Pippenger C, Macdonald H, Pitlick P. Phenobarbital and diphenylhydantoin levels in neonates with seizures. *J Pediatr* 1978;92:315-9.
- Giacioia GP, Gessner PK, Zaleska MM, Boutwell WC. Pharmacokinetics of paraldehyde disposition in the neonate. *J Pediatr* 1984;104:291-5.
- Wasterlain C, Plum F. Vulnerability of developing rat brain to electroconvulsive seizures. *Arch Neurol* 1973;29:38-45.
- Eyre JA, Wilkinson AR. Thiopentone induced coma after severe birth asphyxia. *Arch Dis Child* 1986;61:1084-9.

- ⁸ Kaiser A, Whitelaw A. Normal cerebrospinal fluid pressure in the newborn. *Neuropediatrics* 1986;**17**:100–2.
- ⁹ Levene MI, Evans DH, Forde A, Archer LNJ. Value of intracranial pressure monitoring of asphyxiated newborn infants. *Dev Med Child Neurol* 1987;**29**:311–9.
- ¹⁰ Kaiser A, Whitelaw AGL. Non-invasive monitoring of intracranial pressure—fact or fancy? *Dev Med Child Neurol* 1987;**29**:320–6.
- ¹¹ Levene MI, Evans DH. The medical management of raised intracranial pressure following severe birth asphyxia. *Arch Dis Child* 1985;**60**:12–6.
- ¹² Perez CA, Reimer JM, Schreiber MD, Warburton D, Gregory GA. Effect of high dose dopamine on urine output in newborn infants. *Crit Care Med* 1986;**14**:1045–9.
- ¹³ Ames A, Wright RL, Kowada M. Cerebral insult II. The no reflow phenomenon. *Am J Pathol* 1968;**52**:437–53.
- ¹⁴ White B, Wiegenstein JG, Winegar CD. Brain ischemic anoxia. Mechanisms of injury. *JAMA* 1984;**251**:1586–90.
- ¹⁵ McCord JM. Oxygen-derived free radicals in post-ischemic tissue injury. *N Engl J Med* 1985;**312**:159–63.
- ¹⁶ Meldrum B, Evans M, Griffiths T, Simon R. Ischemic brain damage: the role of excitatory activity and of calcium entry. *Br J Anaesth* 1985;**57**:44–6.
- ¹⁷ Steen PA, Gisvold SE, Milde JH, *et al*. Nimodipine improves outcome when given after complete cerebral ischemia in primates. *Anesthesiology* 1985;**62**:406–14.
- ¹⁸ Thiringer K, Hrbek A, Karlsson, Rosen KG, Kjellmer I. Postasphyxial cerebral survival in newborn sheep after treatment with oxygen free radical scavengers and a calcium antagonist. *Pediatr Res* 1987;**22**:62–6.
- ¹⁹ Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. *Pediatrics* 1981;**68**:225–32.
- ²⁰ Steiner H, Nelligan G. Perinatal cardiac arrest. Quality of the survivors. *Arch Dis Child* 1975;**50**:696–702.

A WHITELAW
Department of Paediatrics and
Neonatal Medicine,
Hammersmith Hospital,
DuCane Road,
London W12 0HS