DTP immunisation of steroid treated preterm infants

Preterm infants respond well to the three doses of diphtheria, tetanus, and whole cell pertussis (DTP) vaccine, but dexamethasone treatment may impair immunogenicity.\(^1\) We investigated whether four, rather than three, DTP doses may be preferable for primary immunisation of steroid treated preterm infants. Twelve infants born at < 30 weeks gestation who had received dexamethasone for chronic lung disease were given doses of DTP vaccine combined with Hib (ActHIB DTP: Pasteur-Mérieux-MSD) at 2, 3, and 4 months of age. A fourth dose was administered six weeks after the third immunisation (table 1). With the use of standardised enzyme linked immunosorbent assay (ELISA) methods, paired sera obtained before and after eight weeks after the fourth DTP dose were analysed at the Health Protection Agency (Porton Down, Wilts, UK) for antibody titres against diphtheria toxoid (DT), tetanus toxoid (TT), and three pertussis antigens (filibrinial agglutinogens 2+3 (FIM), pertussis toxin (PT), filamentous haemagglutinin (FHA)). A pre-fourth DTP serum sample was available for 12 infants, and 11 infants had paired sera. Median (range) gestational age was 25 weeks (24–29) and birth weight was 830 g (550–1239). The median (range) duration of dexamethasone treatment was 15 days (3–153), and cumulative dose was 3.9 mg/kg (1.5–25.6).

Antibody titres of 0.1 IU/ml against DT and TT are considered to correlate with individual protection.\(^2\) After three doses, all infants had already achieved titres > 0.1 IU/ml against DT and TT, and titres remained above this concentration after the fourth dose. No significant increase in antibody titres against diphtheria or tetanus antitoxins resulted from the fourth DTP immunisation (table 2). Despite a trend towards higher mean pertussis antibody titres after four DTP doses compared with after three doses, the increase was not significant in any of the three pertussis antibodies. Although there are no reference protective antibody concentrations for pertussis, mean antibody titres achieved against the three pertussis antigens after three DTP doses compared favourably with those in historical cohorts of UK term and preterm infants who received the accelerated DTP schedule.

All infants showed excellent immunogenicity to three dose DTP; a fourth dose did not improve antibody responses further. In a recent study using diphtheria/tetanus/acellular pertussis vaccine, responses of 15 preterm infants appeared unaffected by recent steroid treatment.\(^3\) These data suggest that dexamethasone treated preterm infants are able to mount satisfactory responses to a standard three dose DTP regimen administered at the same chronological age as term infants, and that supplementary doses are unnecessary in early infancy.

Acknowledgements

We warmly thank the parents and infants for participating in this study. We thank Carol Thornton and Moya Burraga at the Health Protection Agency for respectively performing the serological testing and assisting with data retrieval, and Dr Stephen Roberts for allowing study of one of his patients.

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### Table 1 Timing of vaccinations and serum samples

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>1st DTP</th>
<th>2nd DTP</th>
<th>3rd DTP</th>
<th>1st blood sample and 4th DTP</th>
<th>2nd (post-4th DTP) blood sample</th>
<th>Days between 4th DTP and 2nd blood sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 (60–89)</td>
<td>97 (92–121)</td>
<td>142 (127–170)</td>
<td>205 (164–218)</td>
<td>255 (229–274)</td>
<td>54 (31–59)</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (interquartile range). DTP, diphtheria, tetanus, and pertussis vaccine.

### Table 2 Geometric mean antibody titres (95% confidence intervals) for paired serology measurements after the 3rd and 4th DTP doses

<table>
<thead>
<tr>
<th>Diphtheria (IU/ml)</th>
<th>Tetanus (IU/ml)</th>
<th>Pertussis (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT</td>
<td>2.08 (1.39 to 3.10)</td>
<td>3.15 (1.67 to 5.93)</td>
</tr>
<tr>
<td>TT</td>
<td>2.11 (1.13 to 3.92)</td>
<td>3.12 (1.61 to 6.01)</td>
</tr>
<tr>
<td>FHA</td>
<td>1.41 (0.80 to 2.52)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Mean values were compared using Student’s t test for paired samples. Diphtheria and tetanus antibody concentrations are reported as IU/ml corrected against National Institute of Biological Standards and Control (NIBSC) reference sera 91/534 and 26/488 respectively; pertussis antibodies are reported as titres corrected against NIBSC reference serum 89/330.

### References


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In utero HIV infection in pregnancies complicated by tuberculosis in Durban, South Africa

At the core of the HIV-1 and tuberculosis (TB) epidemics, a defined effect of these combined pathogens on maternal and child health has been observed at King Edward VIII Hospital in Durban South Africa.\(^1\) Here we report on the adverse effect of maternal HIV-1 infection with TB disease on fetal acquisition of HIV-1.

In a prospective cohort study conducted at the hospital between April 1997 and July 1999, 92 HIV-1 infected pregnant women with active TB disease were investigated for intrauterine transmission of HIV-1. Intrauterine infection was diagnosed by a positive HIV-1 RNA polymerase chain reaction (PCR) (AmpliScorer; Amplicon) in a single laboratory which was participating in a continuing quality certification programme for HIV-1 RNA quantitation sponsored by the National Institutes of Health.

Eight newborns were HIV-1 RNA PCR positive by 72 hours of birth resulting in a 19% in utero transmission rate of HIV-1 for singleton live births exposed to maternal HIV-1 infection and TB disease in Durban. The rate of intrauterine transfer of HIV-1 in this category of ill women was much higher than the overall 5–10% in utero transmission rates recorded in resource-poor countries. Maternal CD4 (427 (278) v 318 (289) cells/ mm\(^3\) (mean (SD)); p = 0.37), plasma viral...
burden (median log 5.0 v 4.7), extrapulmonary sites of TB disease, and sputum smear or culture positive rates for Mycobacterium tuberculosis were no different between in utero transmitting and non-transmitting mothers. A further nine babies were HIV-1 PCR positive on follow up (intrapartum or post-partum transmission), resulting in an overall HIV-1 mother to child transmission rate of 40.4% (17/42).

This observation augments current knowledge on the impact of perinatal infections on mother to child transmission of HIV-1. High maternal viral burden and CD4 suppression, which are characteristic of advancing AIDS, have been associated with higher overall vertical transmission of HIV-1 and greater risk of rapidly progressive infant HIV-1. Here we quantify this intrauterine risk in HIV-1 infected pregnant women ill with TB disease, and suggest that, in these situations, regimens of antiretroviral therapy which are likely to reduce fetal acquisition of HIV-1 will need to be considered. These should supplement public health programmes to detect and prevent TB disease in HIV-1 infected pregnancies in endemic regions.

Table 1

<table>
<thead>
<tr>
<th>Study details</th>
<th>Peripheral VO2</th>
<th>Global VO2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mM HbO2/cm/min</td>
<td>mL O2/kg/min</td>
</tr>
<tr>
<td>1. Mild cooling of the hand (n=10)</td>
<td>1.38</td>
<td>5.4</td>
</tr>
<tr>
<td>Before</td>
<td>1.11</td>
<td>4.35</td>
</tr>
<tr>
<td>After</td>
<td>1.01</td>
<td>3.96</td>
</tr>
<tr>
<td>2. Moderate cooling of the hand (n=12)</td>
<td>1.06</td>
<td>2.58</td>
</tr>
<tr>
<td>Before</td>
<td>1.47</td>
<td>5.76</td>
</tr>
<tr>
<td>After</td>
<td>1.81</td>
<td>7.09</td>
</tr>
</tbody>
</table>

All values are means.

Discussion

Conversion of standard NIRS units into those normally recognised for VO2 has been achieved. This allows comparison between global, cerebral, and peripheral VO2 values and comparison between studies. The value of using a range of methods to measure tissue oxygenation is enhanced if the results can be compared through the use of standard units. For example, important relations between global and peripheral VO2 have been described.

In making the conversion, two key physical variables are used which have so far only been measured in adults. The skeletal tissue density value of 1.04 g/ml has been used for adult muscle studies. The differential path length factor (DPF) value of 3.59 (0.32) has been reported for adult forearm for inter-optrode distances over the range 1–6 cm. It has also been shown that the DPF is “almost constant” beyond 2.5 cm. In the studies illustrated in table 1, the inter-optrode distance is 3 cm for all infants, hence variation in the calculated peripheral VO2 resulting from changes in DPF is minimal.

Clearly if tissue density and DPF values become available for newborn forearm, then the calculations can be refined. In the meantime, this conversion still provides a valuable method for comparing the relation between cerebral and peripheral VO2. No previous NIRS research using peripheral VO2 methods has been reported using the proposed units. The units commonly used are confusing and difficult to understand. It is recommended that in future peripheral VO2 measurements are reported in mLO2/kg/min.

Quantification of peripheral oxygen consumption by near infrared spectroscopy

Oxygen consumption (VO2) is a measurement used to determine the metabolic rate, and is affected by: environmental temperature, body temperature, physical activity, blood flow, and nutrition. Measurements of VO2 have been used to study energy balance in newborn infants and to determine the optimal thermal environment for nursing preterm babies. More recently it has been suggested that measurements of peripheral VO2 may provide an indication of the need for circulatory support during critical care.

Methods

The basic units for expressing peripheral VO2 by NIRS using the arterial occlusion method are mM HbO2/cm/min (mM HbO2/cm/litre/min). This can be converted into μmol O2/kg/min using 4 x 10-3 (1.04 x 3.59 x 1), on the basis that the molecular ratio of Hb to O2 is 1:4, and the density of skeletal tissue is 1.04 g/ml. The distance between the light transmitting and receiving probe is L cm, and the path length correction factor is taken as 3.59. This is required to correct for scattering of light within the tissues. This equation reduces to 0.7L.

Conversion of μmol O2 into mL can be achieved using the molecular mass of oxygen (M(r)) which is 16 and the density (d(r)) which is 1.429 g/L. Consequently 1 μmol O2 is converted into mL using:

(M(r) x 10^-3)/(d(r) x 10^-3) = 1.1

Therefore conversion from mM HbO2/cm/min into mL O2/kg/min requires a multiplication factor of 1.1 x 107/L. In studies where L = 3 cm the conversion factor is simply 3.92.

Results

We used data from previous studies to examine the feasibility. Peripheral VO2 was measured by NIRS using arterial occlusion and the oxyhaemoglobin (HbO2) decremental slope. Global VO2 values were obtained by open circuit calorimetry. Table 1 gives the converted values of peripheral VO2 for comparison with global VO2 values.

References


References

Umbilical disinfection: lessons from history

A baby girl was born by spontaneous vaginal delivery at 38 weeks to a healthy mother in a district hospital. She was the second child in the family; there was no family history of concern, her mother was well, and the pregnancy had been uneventful. Breast feeding was established, and mother and baby were discharged home the following day with no specific advice as to umbilical care. At 10 days of life there was a yellowish discharge from her umbilicus; this was treated with topical fucidin by the general practitioner. Six days later there were increasing difficulties with breast feeding as the infant became more listless. The following morning, the mother noted swelling of the left knee; on admission a few hours later the infant was hypotonic, sleepy, and afebrile with a discharging umbilicus.

Aspirate from a tense effusion of the left knee, umbilicus, and blood cultures all grew Staphylococcus aureus, which was sensitive to flucloxacillin but resistant to fusidin. The infant was treated with intravenous antibiotics and a joint washout by a paediatric orthopaedic surgeon that day. The baby appears to have had a good outcome: six months later she showed normal development and equal limb length. This case shows a systemic complication consequent to umbilical colonisation and sepsis by a staphylococcal resistant to fusidin.

In the nineteenth century, staphylococcosis were among the first bacterial organisms to be clinically identified as the causative agent in epidemics of peripneumonic neonaotonum, a putrinal skin condition associated with death. It was found that newborns are rapidly colonised by staphylococci, streptococci, or Escherichia coli on the umbilical stump; infection or toxin production readily led to sepsis. The application of antiseptic treatments became critical to reducing epidemics of perinatal illness.

Over the last 25 years, the use of umbilical antiseptics has almost disappeared in British hospitals. Concerns about the potential toxicity of chlorhexidine, the unsightly appearance of triple dyes, and the limitations of other methods combined with a low incidence of pathology has resulted in a non-invasive approach in most maternity units. A Cochrane review has concluded that, in the developed world it is a disease of the most immature and unwell infants. Treatment is needed more often in extremely premature babies, taking place in 14% of those born before 26 weeks’ gestation. Treatment of severe ROP was originally by cryotherapy, but is now more commonly undertaken with laser, either as transpupillary or trans-scleral diode photocoagulation. C reactive protein (CRP) is an acute phase protein first discovered in the 1930s. It is a component of the innate immune system. Increased production is thought to be beneficial because of its ability to bind phosphocholine and thus recognise foreign pathogens. Tissue damage including burns, trauma, and surgery is known to increase CRP.

Babies undergoing treatment for ROP often have regular CRP measurements to help identify the onset of sepsis. There is currently no evidence as to whether cryotherapy or laser photocoagulation cause a rise in CRP irrespective of sepsis.

To ascertain whether CRP is affected by treatment of ROP, a retrospective case note review of infants treated with laser photocoagulation was undertaken. The notes of 16 infants (11 female and five male) requiring treatment for ROP (ROP 2 stage 2, treated between 24 weeks and 6 days) were reviewed. Fifteen of the babies received laser photocoagulation by transpupillary diode laser, and one received trans-scleral diode treatment. CRP concentration (suppl 107):CD001057. The data were non-parametric. A Wilcoxon signed rank test was used to determine whether the null hypothesis (lasering does not alter CRP concentration) was correct. This study did not find a significant difference in CRP concentration after surgery. (Sample size means this study has a 90% power to show significance (p < 0.05) difference in CRP concentration of 20.)

Our negative findings give some reassurance that if, after treatment for retinopathy, there is concern about infection, a raised CRP concentration is unlikely to be a result of the procedure and more likely to reflect sepsis. However, a prospective study of CRP concentrations after treatment for retinopathy will be necessary to confirm our findings.

References


Effect of laser photocoagulation for retinopathy of prematurity on CR reactive protein

Retinopathy of prematurity (ROP) is the major cause of blindness in premature babies, and in the developed world it is a disease of the most immature and unwell infants. Treatment is needed more often in extremely premature babies, taking place in 14% of those born before 26 weeks’ gestation. Treatment of severe ROP was originally by cryotherapy, but is now more commonly undertaken with laser, either as transpupillary or trans-scleral diode photocoagulation. C reactive protein (CRP) is an acute phase protein first discovered in the 1930s. It is a component of the innate immune system. Increased production is thought to be beneficial because of its ability to bind phosphocholine and thus recognise foreign pathogens, Tissue damage including burns, trauma, and surgery is known to increase CRP.

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References