LETTERS TO THE EDITOR

Need to avoid bias in controlled trials

EDITOR,—It is accepted practice that in all quantitative research statistical tests should be used to estimate the likelihood that findings arose by chance and that authors should avoid overinterpreting data where these tests suggest that the likelihood is high. It is also accepted that to avoid bias in the analysis of randomised controlled trials clinically important endpoints must be specified in advance.

A recent report of a clinical trial of two different surfactant preparations illustrates the dangers of neglecting these guidelines.1 Although infants in the group treated with one of the preparations appeared to fair better on the pre-determined clinical endpoints, none of the differences approached conventional levels of significance. The paper also reports data on a number of intermediate measures of oxygenation and ventilatory requirements, outcomes which the authors specifically state were not established at the design stage, where on some occasions, although statistically insignificant, other differences do reach conventional levels of significance.

The authors state that statistical tests were performed in an attempt to rule out this possibility. However, it is not clear from the presentation how any of the differences were interpreted, nor what were the criteria used to determine which differences were considered significant. It is also not clear from the paper whether the authors used a pre-determined hierarchy of outcome measures on which the results were based or if the results were interpreted on an ‘as you please’ basis.

In the discussion the authors begin by noting the need for caution in the interpretation of the results from this small study but, unfortunately, did not provide their own interpretations. They interpret the data on intermediate endpoints as demonstrating improved lung function in babies treated with Curosurf and devote much of the discussion to trying to rule out these results being caused by other factors. They conclude the paper by stating their belief that Curosurf is more effective at improving oxygenation and reducing ventilatory requirements than Survanta, but they remind readers of the ‘trend’ towards lower incidence of adverse outcomes in the Curosurf group and suggest the need for additional studies, which are confirmed in a large randomised controlled trial.2 The clear implication of their comments is that they believe that they have demonstrated that Curosurf is more effective than Survanta.

The correct interpretation of the data presented is that the results would be compatible with Curosurf being either considerably better or considerably worse than Survanta at preventing the development of adverse clinical outcomes. The authors specifically mention that patients treated with Curosurf had a lower incidence of pneumothorax, intracerebral haemorrhage grades 3-4, and mortality; in fact, the adjusted 95% confidence limits of the odds ratios for each of these outcomes associated with being treated with Curosurf rather than Survanta are 0·08-2·88, 0·02-2·54, respectively, which suggests a high probability that these results are due to chance. There is always a temptation to overinterpret data from studies which are too small to provide answers to the questions addressed. In this particular paper there is the added concern that the drug favoured by the authors’ discussion, on the basis of appropriate interpretation of the data, is manufactured by the company which sponsored the research.

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Raised cerebral artery blood flow velocity

EDITOR,—Scherjon et al’s findings3 of raised cerebral artery blood flow velocity (CABFV) in infants who had evidence of fetal brain sparing were very similar to our previously published findings4 of a raised CABFV at 3 days of age in small for gestational age (SGA) infants weighing less than 1500 g. Two thirds of the patients in our study had evidence of fetal redistribution of blood flow, with absent end diastolic flow in the umbilical artery. Postnatally, we also found persistently lowered coeliac axis, superior mesenteric artery, and renal artery blood flow velocities, indicating that ongoing redistribution of blood flow in SGA babies affects the whole circulation.3

Scherjon et al did not find an association between blood pressure and CABFV, whereas we found that for appropriately grown infants a multiple regression analysis of cerebral blood flow parameters, age, and body weight shows a significant correlation between blood pressure, carbon dioxide tension, and CABFV.4,5 We carried out an identical multiple regression analysis, using data from 16 SGA infants weighing less than 1500 g at birth who had invasive monitoring of blood pressure through umbilical or peripheral arterial lines. Measurements of blood flow velocity in the anterior cerebral artery were obtained in the same way as for the appropriately grown infants.4 For the SGA infants there was no effect of blood pressure, although there was an effect of carbon dioxide tension (table).

Correlation coefficients from multiple regression analysis of effects of mean arterial blood pressure (MABP), Pco2 and Pao2 on anterior cerebral artery blood flow velocity

<table>
<thead>
<tr>
<th>MABP</th>
<th>Pco2</th>
<th>Pao2</th>
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<tbody>
<tr>
<td>Appropriately grown</td>
<td>0·70**</td>
<td>0·64***</td>
</tr>
<tr>
<td>SGA (n=16)</td>
<td>0·14</td>
<td>0·60*</td>
</tr>
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*p<0·05, ***p<0·001.

We suggest that Scherjon et al’s failure to find an effect of blood pressure on CABFV may be due to the lack of such effects in the SGA group only. The antenatal experiences of the fetus may modify the responses of many parts of the circulation, producing both baseline changes and differences in the way the circulation responds to factors such as blood pressure. Circulatory data from appropriately grown and SGA babies should probably be analysed separately, and as we understand more, it may be that our management of the circulation should also be different in these babies.

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1 Scherjon SA, Oosting H, Kok JH, Zondervan HA. Effect of fetal brain sparing on the early