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 at the design stage.

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 not on others, differences do reach conventional levels of significance.

In the discussion the authors begin by noting the need for caution in the interpretation of the results from this small study but, unfortunately, do not heed their own warning. 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 explanations other than that Curosurf is the more effective agent. They conclude the paper by stating their belief that Curosurf is more effective at improving oxygenation and reducing ventilatory requirements than Surfactant in the first 24 hours, remind readers of the 'trend' towards lower incidence of adverse outcomes in the Curosurf group and suggest the need for these results 'to be confirmed in a larger randomised controlled trial'. The clear implication of their comments is that they believe that they have demonstrated that Curosurf is more effective than Surfactant.

The correct interpretation of the data presented is that the results would be compatible with Curosurf being either considerably better or considerably worse than Surfactant 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 Surfactant are 0.08-2.88, 0.02-1.78, and 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 inappropriate interpretation of the data, is

manufactured by the company which sponsored the research.

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1 Speer CP, Gefeller O, Groneck P, Laufkötter E, Roll C, Manssler L, *et al.* Randomised trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. *Arch Dis Child* 1995; 72: F8-13.

Dr Gefeller, Professor Speer, et al comment:

A well known dilemma of small-sized clinical trials refers to the repeated observation that they fail to reveal significant differences between the treatment groups, especially when treatment success is assessed using dichotomous outcome variables.¹ For example, a reduction in a treatment complication from 20% to 10% yields a P value of 0.345 (two-tailed Fisher's exact test) in a comparison of 40 patients randomised to each of two treatment groups (and thus is far away from any claim of a significant difference). However, when evaluated in a trial of 200 patients in each group, the same difference is highly significant (P=0.007).

Dr Logan criticises our small-sized randomised clinical trial of two treatment regimens of natural surfactant preparations (Curosurf *v* Surfactant) in neonatal respiratory distress syndrome.² He blames us for 'overinterpreting' our data, and that we implied that Curosurf was more effective than Surfactant. We did not imply this, and we are sorry if Dr Logan misinterpreted our message. On the contrary, although we agree with his well known general comments on the analysis of randomised clinical trials, we believe that he has chosen an unsuitable example for his crusade against overinterpreted studies.

Specifically, our study was designed as a pilot study for a large scale study (explicitly stated in the paper). Thus, there was no necessity to establish a hierarchy of clinically important endpoints at the design stage. We recorded all relevant complications using standardised criteria and documented measures of oxygenation and ventilatory requirements at fixed time points specified in the study protocol. Our paper presented the results of this pilot trial with respect to all recorded endpoints. Without reiterating our Results section, we found a consistent picture favouring the Curosurf treatment regimen. The differences in complications did not reach significance (repeatedly emphasised in the paper), whereas the improvement in oxygenation and the reduction of ventilatory requirements for infants treated with Curosurf did so at several time points during the first 24 hours. We discussed in detail the limitations of our trial and ended our paper with the request that 'these findings need to be confirmed in a larger randomised trial'. Consequently, we are puzzled by Dr Logan's eloquent criticism of our findings.

We take exception to the comments made in the final sentence of Dr Logan's letter. We openly declared the source of funding of our trial and that it was designed, conducted, and analysed independently of the company according to GCP standards. We assume that since Dr Logan did not declare any financial support in his letter, he has no conflict of interest.

1 Frieman JA, Chalmers TC, Smith H, *et al.* The importance of beta, the type II error and sample size in the design and interpretation of the

randomized controlled trial. *N Engl J Med* 1978; 290: 690-4.

2 Speer CP, Gefeller O, Groneck P, *et al.* Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. *Arch Dis Child* 1995; 72: F8-13.

Raised cerebral artery blood flow velocity

EDITOR,—Scherjon *et al.*'s findings¹ of raised cerebral artery blood flow velocity (CABFV) in infants who had evidence of fetal brain sparing are very similar to our previously published findings² 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.^{2,3}

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 indicates 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 performed 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), PaCO₂ and PaO₂ on anterior cerebral artery blood flow velocity

	MABP	PaCO ₂	PaO ₂
Appropriately grown (n=34)	0.70***	0.64***	-0.31
SGA (n=16)	0.14	0.60*	0.48

*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 that 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

- neonatal cerebral circulation. *Arch Dis Child* 1994; 71: F11-5.
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 - Kempley ST, Gamsu HR. Arterial blood pressure and blood flow velocity in major cerebral and visceral arteries. I. Interindividual differences. *Early Hum Devel* 1993; 34: 227-32.
 - Kempley ST, Gamsu HR. Arterial blood pressure and blood flow velocity in major cerebral and visceral arteries. II. Effects of colloid infusion. *Early Hum Devel* 1993; 35: 25-30.

Dr Scherjon comments:

The most obvious difference in the analysis presented in the letter of Kempley *et al* and our study is that our analysis is based on 10 longitudinal measurements, instead of two point measurements. We are therefore able to analyse the contribution of several variables to a repeated measurement model.

We used values of MAP and PCO₂ (as did Kempley), but also analysed both variables as covariates changing over time. Thus the effect of MAP and PCO₂ both on the patient specific level of CBFV and the within patient time course on CBFV could be estimated. Secondly, our model included gestational age as a possible confounding variable. The latter seems to be essential in the interpretation of the results. Growth retardation (IUGR) was defined by a raised antenatal umbilical/cerebral pulsatility index ratio (U'/C''): an index indicating fetal haemodynamic redistribution and very strictly related to neonatal birthweight.¹ For this reply a more classic definition of SGA, using the fetal growth ratio (FGR), was used. The lower limit for appropriate fetal growth was 80%, corresponding to the 4.3 birthweight centile.²

If gestational age is not included in the model (table 1) MAP has a significant contribution to CBFV; if gestational age is included in the model its contribution disappears.

Interestingly, the interaction component between IUGR grouping and MAP_{trend} appeared to be significant only for the FGR definition. This suggests that there might be a different effect of MAP_{trend} on CBFV for IUGR compared with non-IUGR infants (IUGR defined by FGR and not by the U'/C'' ratio).

We therefore repeated the analysis for the

two growth retardation definitions. For the normal FGR infants and not for the normal U'/C'' ratio group, we found a significant contribution of the time course of blood pressure changes on CBFV changes, but the absolute levels of MAP seem to have no contribution to the model (table 2).

We agree with Kempley that there seems to be a different setting for the regulation of CBFV between appropriately grown and SGA neonates, although we did find the effect when FGR alone is used as the definition of SGA. We also could not show the effect for the absolute MAP values on CBFV. It might be, as was suggested in the original article, that SGA is associated with a more stable CBFV, and therefore this would explain the lower incidence of severe intracranial pathology found in the growth retarded group.

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Neonatal abstinence syndrome

EDITOR,—Our clinical experience of neonatal abstinence syndrome (NAS) differs from that in Liverpool described by Shaw and McIvor, who focused on methadone.¹ During the period 1989-94 inclusive, we identified 39 babies at risk of NAS. Of these, two (5%) had mothers with a history of drug use who denied current use, one (3%) mother took codeine, five (13%) used heroin, 22 (56%) used methadone and nine (23%) did not use opiates at all (largely alcohol and amphetamines). Of the mothers using methadone, five (23%) took methadone alone, eight (36%) took heroin in early pregnancy followed by methadone as part

of a detoxification regimen, and nine (41%) were polypharmacy users.

The median time to onset of withdrawal for the methadone group was 30 hours (range 0-7 days) and for the heroin group 1.5 (range 1-2) days. Median duration of medical treatment for the methadone group was 23 (range 0-80) days and for the heroin group, 4.5 (range 0-8) days. The median length of stay in hospital for the methadone group was 22.5 (range 6-107) days - one baby was successfully withdrawn from morphine at home under close supervision - the median for the heroin group was 12.5 (range 7-15) days.

Of the babies exposed to methadone, 18 (81%) were placed at home, the others being fostered. Follow up appointments at this hospital were kept by 12 (55%) babies, two (9%) attended for appointments at referring hospitals, two (9%) moved and were offered follow up with a local paediatrician (outcome unknown), and six (27%) were chronic non-attenders. Of the heroin group, one baby was adopted and the rest stayed with their mothers. Two (40%) were followed up on more than one occasion, one attended outpatients only once, and two (40%) never attended. There was one death in a baby exposed to methadone and heroin who died at the age of 6 weeks from meningococcal septicaemia.

Even though the Liverpool figures suggest an earlier and less severe withdrawal from methadone than has previously been suggested² we cannot be certain that the mothers were not taking heroin in addition to methadone. Our figures suggest a wider range of onset and a more protracted course of NAS with methadone. We would caution paediatricians to be aware of the pattern of local drug use before altering observation policy for NAS on the basis of one paper.

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Pros and cons of antiseptic cord care

EDITOR,—A recent letter points out that antiseptic agents may delay separation of the umbilical cord.¹ However, certain agents can hasten cord separation. This has public health implications. In many non-industrial settings the period from birth to cord separation is an important rite of passage during which varied social and dietary taboos are observed.

Among the pastoralist peoples of southern Sudan, where neonatal tetanus is common and seems to be related to traditional cord care techniques,² cord care kits were promoted in the 1980s. When I interviewed mothers of babies with tetanus neonatorum (n=35, unpublished data) none had used cord care kits. Seventy five per cent had applied earth to the cord which had been collected from a number of ritually important sites. When asked why this was done most replied that it helped to expedite the process of cord separation. In traditional village culture in this region mother and baby are segregated in the family hut and extensive dietary restrictions are enforced until the cord separates, when mother and infant become the focus of a collective feast. Women prefer

Table 1 Variables significantly contributing to the model: repeated measurements model

Model	U'/C'' ratio	U'/C'' ratio	FGR ratio	FGR ratio
Time	0.00	0.00	0.00	0.00
GA	Not included	0.00	Not included	0.00
IUGR	0.00	0.04	0.00	0.01
IUGR*MAP time course*	0.14	0.16	0.07	0.02
CO ₂ time course	0.00	0.00	0.00	0.00
CO ₂ level	0.00	0.00	0.00	0.00
MAP time course	0.23	0.26	0.56	0.38
MAP level	0.00	0.14	0.01	0.18

GA: gestational age; IUGR: fetal growth retardation as defined by U'/C'' ratio or FGR; MAP: mean arterial blood pressure; CO₂: transcutaneous PCO₂; *interaction component between MAP_{trend} and IUGR.

Table 2 Variables significantly contributing to the model: repeated measurements model

Model	U'/C'' ratio: normal (n=63)	U'/C'' ratio: raised (n=35)	FGR ratio: normal (n=70)	FGR ratio: low (n=33)
Time	0.00	0.00	0.00	0.00
Gestational age	0.01	0.04	0.01	0.03
CO ₂ time course	0.00	0.00	0.00	0.02
CO ₂ level	0.00	0.16	0.00	0.2
MAP time course	0.09	0.67	0.01	0.47
MAP level	0.36	0.27	0.56	0.17