Correspondence

Effect of exogenous surfactant on total respiratory system compliance

Sir,

I should like to comment on the paper by Milner et al on the effect of the Cambridge artificial surfactant on lung compliance of intubated preterm babies at birth.1

In 1980 Fujiwara2 claimed that an ‘artificial surfactant’ dramatically improved the oxygenation of babies with respiratory distress syndrome. Since then there has been considerable interest in exogenous surfactant treatment. Four years later, however, there are few published reports with results of clinical trials that can be interpreted with confidence. In most studies there are too few babies and no controls, or unsatisfactory controls.3-6 Even the careful study of Halliday7 did not include enough babies to show conclusive results.

The publication of Milner’s paper1 adds another example of tantalisingly inconclusive data to the published reports. It is such a small study that it is not possible to make any satisfactory conclusion. The reasons for this study being unsatisfactory are:

(1) There is no consideration of the numbers of babies needed in their trial to show a significant difference between the compliance measurements of the surfactant treated babies and the controls. For this trial the way to calculate the number of babies needed is firstly to determine what change in compliance could be considered a significant improvement or ‘the smallest medically relevant difference’. Milner mentions that there was no ‘significant improvement’ without defining what he considered to be significant. Obviously this value depends on the accuracy and reproducibility of the compliance measurements. Compliance varied three to fourfold among the controls before (0-21 to 0-61 ml/cm H₂O) and after saline (0-15 to 0-69 ml/cm H₂O). With this enormous variation the smallest acceptable difference would need to be quite large, that is, a 50% change. The mean lung compliance of the controls before saline was 0-36, therefore a 50% change would be 0-18. Using the relevant Table in ‘Statistics in Practice’8 it can be calculated (using this value of 0-18 and the sample’s standard deviation of 0-22) that a trial size of 70 babies would be needed to detect a 50% change in compliance at the one per cent level with an 80% power. Realistically, it might be surprising if surfactant treatment at this stage altered compliance by as much as 50%. To detect a smaller difference, however, a trial with many more babies would be needed. Milner’s study with only 16 babies has a power of less than 20%, that is only a 20% chance of detecting a significant difference at a one per cent level and not much more at the level of five per cent.

(2) The paper concentrates on the acute effect of surfactant treatment on static lung compliance without discussing why it was an appropriate measurement. Milner’s own published data9 show that newborn babies do not always accept lung inflation passively and often respond with a rejection reflex or an augmented inspiration. Both profoundly alter the tidal volume and therefore the calculation of compliance. Also the expiratory tidal volume might be reduced because the inhaled air is trapped in the lung as the peripheral airways collapse during expiration. Factors like this suggest that the measurement of compliance in this situation may produce results that are difficult to interpret. Perhaps functional residual capacity or thoracic gas volume would be more reliable measurements if they could be made accurately.

(3) Surfactant treated babies received a dose immediately after birth. The ‘before treatment’ measurement of compliance was therefore made before the second dose. This fact was not considered to be relevant by the authors even though the treated babies had a ‘before treatment’ compliance on average 50% higher than the control group (mean (SD) 0-54 (0-19) vs 0-36 (0-22) ml/cm H₂O). This, like the rest of the compliance data, was not statistically significant because the numbers are too small for such a large variation in the compliance measurement.

(4) The babies were not randomised to this particular study. They were extracted from a larger randomised trial.

Four years after Fujiwara’s original paper the role of exogenous natural or artificial surfactant remains undecided; I believe that it is counterproductive to publish small series of anecdotal data and then draw unsubstantiated conclusions from them.

COlIn J MORLEY
University of Cambridge Clinical School,
Addenbrooke’s Hospital,
Cambridge CB2 2QQ

Professor Milner and co-workers comment:

Firstly, Dr Morley criticises the number of babies in our study.1 Our aim as stated in the paper was to see whether artificial surfactant given during resuscitation produced changes similar to those seen when added to animal models. For this, we considered that small numbers were adequate, similar indeed to those published by Dr Morley himself.10 We also stated that this type of study could not determine when artificial surfactant altered outcome and entirely agree that for this, vastly larger numbers would be required.

In his second point, he claims that our measurements might be inaccurate due to respiratory efforts by the babies. We were, of course, very careful to exclude inflations where the baby made any respiratory efforts whatsoever. Also we know of no conclusive evidence that air is trapped in the lungs during expiration immediately after delivery and would be grateful to receive a reference on this.
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C J Morley

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