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SHORT REPORT

Randomised double blind placebo controlled trial of inhaled fluticasone propionate in infants with chronic lung disease

M W Beresford, R Primhak, N V Subhedar, N J Shaw

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In a double blind randomised controlled trial, 30 infants with chronic lung disease received fluticasone propionate or placebo for one year. There were no significant differences between treatment groups in the incidence of any day or night time symptoms or any other outcome measures.

Chronic lung disease of prematurity (CLD) is associated with significant respiratory morbidity in the early years of life.[1 2] Systemic corticosteroids reduce the duration of respiratory support in infants at risk of developing CLD.[3] Inhaled corticosteroids reduce symptoms in wheezing infants.[4] No randomised controlled studies have assessed the efficacy of inhaled corticosteroids as prophylactic therapy in CLD. We report the results of a randomised double blind placebo controlled trial of inhaled fluticasone propionate in infants with CLD, which aimed to determine whether the regular use of an inhaled corticosteroid reduces respiratory morbidity.

Infants studied required supplementary oxygen at 36 postmenstrual weeks. They were excluded if they were ventilated or receiving systemic corticosteroids at this time. Local research ethics approval was granted and written informed parental consent obtained. Infants were randomised to receive 250 µg twice daily of inhaled fluticasone propionate or placebo via metered dose inhaler (with spacer and face mask) for a one year study period. Treatment allocation was double blinded. Primary outcome was the incidence of reported symptom free days. Secondary outcomes included symptom frequency (assessed using a symptom diary), growth parameters, and hospital admissions. It was estimated that placebo treated infants may experience symptoms on 50% of days. Sample size calculation, looking for a 20% reduction in symptom frequency in fluticasone treated infants (80% power, 95% confidence) revealed that 63 infants were required in each treatment arm. After two years recruitment, it became evident that the original sample size would not be achieved in a reasonable time. A decision was taken to stop the trial but to report available data for use in designing future studies or systematic reviews.

Thirty infants were randomised to the study; 15 received fluticasone (table 1). Two infants in the fluticasone treated group and three in the placebo arm withdrew from the trial without completing diaries. Three infants had no symptom diaries complete despite continuing treatment, one from the fluticasone arm and two from the placebo arm of the trial.

There were no significant differences between treatment groups in the incidence of any day or night time symptoms (table 2). The median (interquartile range) duration of continuous oxygen therapy was 181 days (133–301) for fluticasone and 119 days (56–280) for placebo treated infants ($p = 0.4$), while the median duration of inhaler usage was 350 days (113–373) and 242 days (97–301) respectively ($p = 0.4$).

Table 1 Patient characteristics

	Fluticasone (n=15)	Placebo (n=15)
Male	8 (53%)	9 (60%)
Gestation (wk)	27 (25 to 28)	28 (27 to 30)
Birth weight (g)	864 (755 to 1058)	1120 (820 to 1430)
Z score	0.17 (–0.43 to 0.84)	–0.21 (–0.45 to 0.57)
Birth OFC (cm)	25.2 (23.8 to 30)	26.2 (23.5 to 28.6)
Z score	0.24 (–1.18 to 1.17)	0.06 (–0.95 to 0.50)
Respiratory support		
Total ventilated days	17 (13 to 34)	15 (7 to 25)
Maximum PIP (cmH_2O)	25 (20 to 28)	26 (20 to 32)
Maximum (Fi_{O_2}) (%)	71 (55 to 100)	100 (70 to 100)
Characteristics at recruitment		
Age (corrected weeks)	39 (38 to 43)	40 (37 to 42)
Weight (g)	2458 (2100 to 2870)	2390 (2042 to 2637)
Z score	–1.57 (–3.05 to –1.01)	–1.76 (–2.70 to –1.27)
OFC (cm)	33.6 (32.2 to 35.5)	33.5 (32.4 to 34.0)
Z score	–0.55 (–2.46 to 0.78)	–0.77 (–1.56 to 0.29)
Supplemental oxygen (l/min)	0.25 (0.1 to 0.4)	0.15 (0.05 to 0.3)

Results expressed as median (interquartile range).
OFC, occipitofrontal circumference; PIP, peak inspiratory pressure; Fi_{O_2}, fractional inspired oxygen.

Table 2 Incidence of respiratory symptoms reported in diaries

	Fluticasone (n=12)	Placebo (n=10)	p value
Data days per patient	296 (66 to 358)	220 (85 to 313)	0.42
Incidence of day time symptoms (% days)			
None	67 (50 to 85)	81 (48 to 97)	0.50
One or more episodes	33 (15 to 50)	19 (3 to 52)	0.50
Two or more episodes	11 (3 to 25)	7 (0 to 20)	0.37
Reliever used during day	1 (0 to 12)	3 (0 to 12)	0.72
Incidence of night time symptoms (% nights)			
None	76 (58 to 94)	80 (44 to 95)	0.87
Woke once or more	24 (6 to 42)	20 (5 to 56)	0.87
Woke twice or more	6 (4 to 20)	7 (9 to 37)	0.67
Reliever used at night	4 (0 to 26)	1 (0 to 6)	0.50

Results expressed as median (interquartile range).

There was no significant difference between treatment groups with respect to weight gain expressed as Z score or increase in hospital admissions for respiratory illness, number of courses of oral corticosteroids, or the use of bronchodilator therapy during the study period.

Fluticasone is a potent inhaled corticosteroid[5] and the lack of a major clinical effect might be a result of poor treatment adherence, an insensitive outcome measure, or a type II error. Double blinding of participants optimised the chance of detecting a significant treatment effect. Stratification by centre compensated for potential variation in management regimes. Efficacy of an inhaled prophylactic therapy depends on adequate and regular administration. Parents were trained in the inhaler technique and regularly monitored. Being a pragmatic trial, no objective measure of treatment adherence (for example, weighing of canisters) was adopted. Use of symptom diaries, though easy to complete and regularly supervised, relies on parental motivation and interpretation of symptoms. The eight infants either withdrawing or not completing symptom diaries were excluded from analyses. No data were available for the primary outcome measure and therefore they could not be included in an intention to treat analysis.

This study provides useful data regarding respiratory symptomatology in placebo treated infants with CLD. Approximately 19% of infants with CLD treated with placebo had short episodes of cough or wheeze during the day and 20% had similar episodes sufficient to wake them at least once at night. These are substantially lower frequencies than our estimated values for sample size calculation (50%) and indicate that a much larger sample size would be need to detect important differences in symptom frequency in this population.

In conclusion, this is a small, negative outcome study that does not encourage clinicians to start inhaled corticosteroids prophylactically in infants with CLD. A larger clinical trial of treatment in symptomatic children with CLD would be the next appropriate step.

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Authors' affiliations
M W Beresford, N V Subhedar, N J Shaw, Royal Liverpool Children's NHS Trust, Alder Hey, UK
R Primhak, Sheffield Children's Hospital NHS Trust, UK

Correspondence to: Dr N J Shaw, Neonatal Unit, Liverpool Women's Hospital, Liverpool L8 7SS, UK; ben.shaw@lwh-tr.nwest.nhs.uk

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