positive mouth cultures (31 *C albicans*, five *C parapsilosis*) and in 25 of these dummy cultures also grew candida (20 *C albicans*, five *C parapsilosis*). Only eight children without dummies had candida positive mouth cultures (using Yates' correction: $\chi^2=7.5$ $P<0.01$). Only four of the children using dummies who had negative mouth swabs had positive dummy cultures.

Ten children who used dummies had mouth swabs which were positive for candida on more than two occasions (repeatedly positive) and dummy cultures were also repeatedly positive for all except one of these children. No child who did not suck a dummy had repeatedly positive mouth swabs.

Discussion

Our study suggests that dummy sucking in early childhood is associated with greater prevalence of thrush and with more frequent and more persistent mouth colonisation by candida. Where candida is present in the mouth, it is usually cultured from the dummy also. Objects placed in the mouth are likely to reflect oral flora but we were surprised that dummy sucking predisposed to oral colonisation and infection with candida.

Candida is a common mouth commensal and its prevalence in our study is no more than that found in other studies.^{2,3} Positive cultures may reflect the density as well as the prevalence of candida colonisation. Thus our finding of a greater prevalence of Candida in the mouths of children with dummies may indicate either an absolute increase in prevalence of colonisation or, possibly, denser colonisation. Low density colonisation may explain why the

correlation between dummy and mouth cultures in children who used dummies was not total. The finding of clinical thrush in only a minority of infants with positive mouth swabs suggests that gastrointestinal contamination from dummies should be considered in infants with candida napkin rash when there is no clinical evidence for oral thrush.

Foreign bodies in the mouth such as dummies and false teeth⁴ predispose to candidal infection. Abramovits⁵ described a child in whom oral thrush did not respond to treatment until the child's dummy was confiscated. Our study also suggests that persistent oral and dummy infection go together. The dummy's role as pacifier may be more important to mothers than its aesthetic and health disadvantages. If this is the case, mothers need advice on effective treatment for infected dummies as well as for their children's thrush.

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Septicaemic low birthweight neonates treated with human antibodies to endotoxin

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SUMMARY In a double blind controlled study antilipopolysaccharide gammaglobulin given intramuscularly did not reduce mortality in low birthweight babies suffering from septicaemia. It did, however, reduce the recovery period of survivors from 310 to 120 hours.

Antimicrobial agents frequently fail in the treatment of Gram negative septicaemia, in part because they do not inactivate circulating endotoxins.¹ Adults suffering from Gram negative bacteraemia and shock have successfully been treated with an intravenous antiserum to endotoxin.¹

Since the production of intravenous gammaglobulin is difficult, an intramuscular lipopolysaccharide

specific gammaglobulin was tested to determine its possible efficacy in reducing mortality in Gram negative septicaemia.

Trial design

This was a double blind, placebo controlled trial. Patients regarded as clinically septicaemic, with a positive limulus amoebocyte lysate test,² were entered into the study and investigated by routine methods for further evidence of infection. These patients were given a daily intramuscular injection of a coded preparation of human antilipopolysaccharide at a concentration of 1600 µg/ml or a placebo of albumin adjusted to a similar viscosity for three consecutive days. The preparation of these antibodies has been described previously.³ At the end of the trial the code was broken and the patients divided into treated or placebo group.

Patients and methods

Low birthweight infants (less than 2.5 kg) in the Neonatal Unit of King Edward VIII Hospital, Durban, who had clinical features of sepsis and were positive for lipopolysaccharide by the limulus amoebocyte lysate assay, were entered into the trial. Informed parental consent was obtained in all cases.

Routine investigations for confirmation of infection on entry to the study were as follows. Blood samples were drawn for anaerobic and aerobic culture, full blood count, and C reactive protein. Cultures of cerebrospinal fluid, urine, stool, umbilicus, and any superficial septic lesions were taken. Serum bilirubin values, blood urea nitrogen, and electrolytes were estimated whenever necessary. Immune complexes were tested by a modification of the method described by Theofilopoulos.⁴

Most statistical comparisons between groups were based on the χ^2 test, except for 'time to recovery' in which the non-parametric, two sample median test was used because the data did not follow a normal distribution. 'Recovery' was the period from onset of disease to full clinical improvement.

Management

All patients were initially given soluble penicillin and gentamicin in recommended dosages until culture and sensitivity results were obtained, after which antibiotic treatment was altered accordingly. Patients in the trial were given a daily intramuscular injection into the thigh of either antilipopolysaccharide or placebo as described above, within three hours of entry and for three days.

Results

Of 57 patients investigated, 36 had a positive result for the limulus amoebocyte lysate test and were entered into the trial. At the conclusion of the trial 16 patients were found to have received antilipopolysaccharide and 20 placebo.

Patients with positive limulus amoebocyte lysate tests. No significant differences were found in weight, gestational age, sex, in blood and cerebrospinal fluid parameters, period of recovery, period of survival, and mortality between the treated and placebo groups with positive test results.

Thirty seven per cent (6 of 16) of the patients who had been treated with antilipopolysaccharide died, compared with 35% (7 of 20) of the placebo treated group (N.D.).

It became clear after the results had been analysed that the limulus amoebocyte lysate test gave a high incidence of false negative results and was not, therefore, a precise indicator of septicaemia in the newborn. (This is the subject of a separate report, to be published.) Therefore, blood culture positive patients only were considered to have definite evidence of infection and were analysed separately.

Evaluation of patients with positive blood cultures. Nineteen (53%) of the total 36 patients who had positive limulus amoebocyte lysate tests also had positive blood cultures (*Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas*). Ten had received the antilipopolysaccharide and nine placebo.

Table Patients with positive cultures

	Antilipopolysaccharide group	Placebo group	P value
No	10	9	—
No of boys	4	3	—
Weight (kg), mean (SD)	1.49 (0.22)	1.49 (0.36)	NS
Gestational age, mean (SD)	32 (1.49)	32.2 (2.2)	NS
Deaths, no (%)	4 (40)	3 (33.3)	NS
Period of survival (hours), mean (SD)	60.5 (73.5)	38.6 (29.2)	NS
Time to recovery (hours) (survivors only)	120 (48)	301 (210)	<0.001

These two groups were comparable for weight, gestational age, and sex. Overall mortality and period of survival among those who died were not significantly different in the two groups (4 of 10 in the study group and 3 of 9 in the placebo group). The survival periods were 12, 14, 48, and 168 hours in the group receiving antilipopolysaccharide and 17, 27, and 72 hours in the placebo group. The former group had a significantly shorter time to recovery, however, than the placebo group (mean (SD), 120 (48) hours v 302 (210) hours respectively, $P < 0.001$) (Table).

Immune complexes

Serial blood samples up to 14 days after treatment showed no increase in the concentrations of immune complexes.

Discussion

In this study intramuscular antilipopolysaccharide did not significantly reduce mortality or the period of survival in neonates with proved Gram negative septicaemia. Most deaths in the placebo group occurred within 48 hours of admission to hospital. The slow absorption of antibodies given intramuscularly may have contributed to the lack of effect.⁵ There was a trend, however, towards prolonged survival in those who subsequently died in the antilipopolysaccharide treated group. The difficulties in diagnosis of neonatal sepsis, possible differences in individual reticulo-endothelial function, or additional organ failure of low birthweight babies may contribute to the poorer efficacy of this treatment in these seriously ill neonates compared with adults.

In this study the limulus amoebocyte lysate test did not seem to be reliable in the first week of life for detecting Gram negative septicaemia. The diagnosis of neonatal septicaemia remains extremely difficult and can only be confirmed by blood culture, which may take 24 to 48 hours. Delay in instituting treatment may result in death and there is, therefore, an urgent need for a rapid and reliable diagnostic test.

Theoretically, raised concentrations of immune complexes due to the binding of lipopolysaccharide

by antilipopolysaccharide could induce immune complex disease. These studies have shown, however, that no such adverse reaction developed and antilipopolysaccharide IgG seems safe, therefore, for clinical use. Moreover, antilipopolysaccharide did reduce the recovery period of survivors in the treated group compared with the placebo group, as has been seen in other similar studies.⁶

These results indicate the need for further similar studies in neonatal septicaemia, using antilipopolysaccharide antibodies given intravenously. These are currently being prepared at the Natal Institute of Immunology. A purer preparation in which the specific pathogenic components of the endotoxin antigens have been defined may pave the way for the production and therapeutic use of human monoclonal antibodies.

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