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Apnoea of immaturity

2. Mortality and handicap

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SUMMARY One hundred and three consecutive infants $\leqslant$ 32 weeks' gestation with recurrent apnoea of immaturity were reviewed, and survival was assessed and related to timing of treatment. The sickest infants were treated after between one and three episodes of apnoea with bradycardia, and mortality was 70%. Of those in whom treatment was postponed because apnoea was considered mild, 34% subsequently required mechanical ventilation, and 23% died. Among a small group of 20 survivors seen at ages 9–24 months, 4 (20%) have major handicaps. The possible place for earlier treatment is discussed.

A controlled trial of theophylline and continuous positive airways pressure (CPAP) was undertaken for treating apnoea in preterm infants and is reported on page 761. Despite agreed criteria for treatment, therapy was often delayed for many hours or days and several eligible infants remained untreated because of reluctance to treat apparently mild apnoea with either agent. This paper reports the mortality of treated and untreated infants and considers the effect of delaying therapy. A group of 20 treated survivors was followed up to ascertain the incidence of handicap.

Method

Details of the controlled trial are reported in the previous paper (page 761), including definitions of recurrent apnoea.[1] All admissions to the two neonatal units during the 27-month study were reviewed and the nurses' records of apnoeic attacks extracted from the notes. Medical notes and investigations were checked to exclude infants with secondary apnoea (as previously defined[1]). The time of starting treatment was noted and related to the time at which the infant fulfilled the trial entry criteria. Deaths up to age one year were recorded.

The 20 surviving infants from the controlled trial were seen (by R A K J) at ages 9 to 24 (median 12) months for full neurological examination, vision and hearing testing, and assessment using Griffiths's mental development scales.[2 3] Griffiths[2] recommended correcting for prematurity until the first birthday but this method produces an apparent sudden fall in developmental quotient (DQ) at 12 months. A sliding-scale correction was therefore applied reducing by one-twelfth for each month of life with no correction by one year. Infants were considered to have major handicap in the presence of DQ below 70, cerebral palsy, visual or hearing loss likely to require special education. Minor handicap comprised DQ 70–84, or partial vision or hearing loss.

The design of the controlled trial allowed for infants failing to respond to one treatment being changed to the other. Unfortunately, the unexpectedly poor response to CPAP meant that most survivors from that group subsequently received theophylline; 9 survivors had received theophylline alone, 4 CPAP alone, and 7 both treatments. Comparison of outcome for the two treatments was thus not possible, and the results are given for the group as a whole.

A questionnaire (available from us) was devised by the clinical psychologist (D L) to assess behavioural problems at ages 9 to 12 months, and was given to 15 mothers (omitting 5 older children). It was similar to one used in a large study of preschool children,[4] with questions on feeding, sleeping, teething, general mood, and management difficulties. It was also given to 20 mothers of normal infants aged 7 to 10 months (10 boys, 10 girls), picked at random from local child health clinic attenders. Infants were placed in one of 3 categories: slight difficulties or none, moderate difficulties, and pronounced difficulties.

In addition to the detailed assessment on these 20 infants, babies not entered into the trial were followed routinely in the outpatient departments of the two hospitals or by their referring paediatricians, and details were available in all but 6 survivors.

Results

Incidence of apnoea. Among 362 infants of gestation ≤32 weeks, 103 (28%) developed recurrent apnoea for which no cause apart from immaturity could be found. If infants who died having had intermittent positive pressure ventilation (IPPV) throughout life were excluded, apnoea occurred in 35% of those who breathed spontaneously; the incidence rose with decreasing gestation from 12% at 32 weeks to 83% at 24 weeks (r 0·94, P<0·001). Apnoea secondary to specific causes such as sepsis was also more common in the most immature and 91% of infants below 29 weeks' gestation who breathed spontaneously developed either primary or secondary apnoea compared with only 31% of infants of 29 to 32 weeks' gestation.

Mortality related to time of treatment. Of the 103 infants with apnoea, 68 (66%) survived. Eight started treatment at their referring hospital and one was not treated because of extreme immaturity at 24 weeks; Table 1 shows the outcome for the remaining 94. Only 23 were treated as soon as trial criteria were met; apnoea was generally very severe with 12 needing immediate IPPV and 3 others having IPPV after poor response to theophylline or CPAP; 16 (70%) died. Of the 71 not treated immediately, 7 subsequently required IPPV, and 33 were treated with theophylline or CPAP, 17 of whom were later ventilated. Thirty-one infants remained untreated, apnoea continuing in 20 (infants having 5 to 26 further attacks spread over days or weeks). In only 11 did apnoea resolve with no treatment (<5 further attacks). The mortality in 71 infants with delayed treatment or none was 23%.

Outcome at follow-up. The DQ for 20 treated survivors was 92·9 ± 14·7 (mean ± standard deviation). Four infants have major handicaps: one is nearly blind from bilateral retrolental fibroplasia (DQ 94); one has severe sensorineural deafness (DQ 78); one has spastic diplegia and global retardation (DQ 56); one has spastic quadriplegia, deafness, and severe general retardation (DQ 46). All 4 had required prolonged IPPV for apnoea. Thus 4 of 8 infants surviving IPPV had major handicaps compared with none of 12 infants surviving without ventilation (Fisher's exact test P<0·05). The 4 infants with major handicaps had had more prolonged episodes of apnoea than those without handicaps (Wilcoxon's rank sum test P<0·05). Of the 32 infants in the controlled trial, 16 died or had major neurological handicaps and the need for IPPV for apnoea carried a bad prognosis (Table 2).

Table 1 *Outcome in 94 infants related to timing of treatment*

Timing of treatment	*Survival without ventilation*	*Mechanical ventilation*	*Death*
Immediate (n=23)	4	15	16
Delayed (n=40)	13	24	15
None (n=31)	30	0	1

Table 2 *Outcome in 32 infants ventilated or not ventilated for apnoea*

	Normal	*Dead or handicapped*
Given IPPV (n=17)	4	13
Not given IPPV (n=15)	12	3

χ^2 (Yates's correction) = 8·03 P<0·01.

Two infants (one severely handicapped) have had further episodes of apnoea. One of these and 2 others had had repeated hospital admissions with chest infections and in two, chest *x*-ray films suggest bronchopulmonary dysplasia. There was no apparent excess of behavioural difficulties; only 2 of 15 infants had pronounced problems compared with 3 of 20 term controls. The mean scores for the questions on general mood and management difficulties were the same as in the term controls.

Of the total of 68 infants surviving recurrent apnoea, 16 (24%) are known to have major handicaps after 1 to 2 years' follow-up. Of the 30 untreated survivors, 6 are handicapped.

Discussion

Despite strict criteria for treating recurrent apnoea, delay was common because of reluctance of nursing or junior medical staff to start treatments they considered hazardous. The infants treated the earliest had the worst prognosis, but their apnoea was often very severe needing immediate intubation and IPPV. Of the 71 in whom treatment was delayed, 34% later required IPPV and 23% died, so the condition was hardly benign. The fact that all but 11 of 103 infants had further apnoea after fulfilling the initial criteria suggests that this was a reasonable basis for treatment. Of those treated after delay with either theophylline or CPAP, both established forms of therapy, 17 of 33 responded poorly requiring IPPV, compared with only 3 of 11 infants given theophylline or CPAP promptly.

The occurrence of major handicap in 4 of 20 survivors all of whom had required IPPV is comparable with the 25% reported by Stewart *et al.*[5] in infants surviving ventilation for apnoea. The lack of behavioural problems is perhaps surprising in view of the prolonged maternal separation. Follow-up studies of preterm infants reporting excess difficulties have concerned older children.[6 7] It is

possible that after 9 to 12 months, memory of recent neonatal dangers makes parents more tolerant of their infants' behaviour.

The finding of major handicap in 24% of infants surviving recurrent apnoea is presumably not a true estimate of the outcome for all such infants as only the smallest and most sick will be transferred to neonatal intensive care units. Nevertheless the high incidence of handicap even among those whose apnoea was considered too mild to treat, suggests that the symptom of apnoea should never be considered 'physiological'. Any attempt to treat apnoea assumes that the episodes themselves cause damage and that abolishing apnoea and bradycardia will reduce handicap.

This assumption, although unproved, is reasonable in view of the marked hypotension and hypoxaemia which may occur and which might lead to ischaemic brain damage.[8] However, many preterm infants with apnoea will have had adverse perinatal factors—such as intrauterine hypoxia, breech delivery, and low Apgar scores—themselves associated with poor outcome. Prophylactic theophylline from birth has been shown to reduce apnoea[9] and prophylactic CPAP to reduce both apnoea and mortality[10] but both studies used as controls infants from previous years, ignoring the effect of other improvements in neonatal and obstetric care. A prospective randomised controlled trial of early or prophylactic treatment is needed to see whether more aggressive therapy can reduce mortality and long-term handicap.

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