

Outcome at 5–6 years of prematurely born children who received morphine as neonates

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Abstract

Aim—To assess outcome at 5–6 years in a cohort of very preterm infants (<34 weeks of gestation) who had been randomly allocated within a controlled clinical trial to receive morphine or non-morphine treatment in the neonatal period.

Methods—Assessments were made on 87 children at 5–6 years who had been recruited in the neonatal period to two sequential controlled studies (1989–92). Infants requiring mechanical ventilation had been randomly allocated to receive either morphine (n=62) or other (n=33) solutions starting on the first day of life. Each child was seen by a single experienced observer and assessed at 5–6 years using the WPPSI-R, Movement ABC, and the Child Behaviour Checklist. The performance of children exposed to morphine was compared with that of those in the non-morphine group. Blood samples for thyroid stimulating hormone (TSH) measurement were obtained from children whose parents gave consent.

Results—There was no significant difference in any of the three test scales between infants in the two groups, but there was a trend towards better performance in all three tests in the morphine group. Assessment of TSH values in a subgroup of the survivors showed no difference in thyroid function between the two groups.

Conclusion—Exposure to morphine in the neonatal period to facilitate mechanical ventilation does not seem to have any adverse effects on intelligence, motor function, or behaviour when these children are assessed at 5–6 years of age.

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Sedation with opiates is widely used during mechanical ventilation of prematurely born infants in Britain. Morphine is associated with a significant reduction in catecholamine concentration in ventilated babies¹⁻³; and an increase in catecholamine in preterm ventilated infants is believed to be due to neonatal stress. Extreme catecholamine responses in sick preterm infants have been associated with neonatal death.⁴ Sedation by means of opiates is therefore assumed to be of some benefit to babies, but there has been no evidence of improved outcome on follow up studies of surviving infants.

There is also the possibility that opiates may have an adverse effect on outcome. Children who have been born to opiate abusing mothers can have behaviour problems, poor concentration, and delayed early language development,⁵⁻⁷ but these data are confused by the multiple risk factors associated with maternal drug misuse. Animal studies have shown a detrimental effect on developing brain structure, particularly in the hypothalamus and the cortex^{8,9} when opiates were given over a few days in the perinatal period. It has been suggested that cognitive impairment may be due to the effect of opiates on reducing thyroid stimulating hormone (TSH) in rats.¹⁰ There are no data on the endocrine effects available in human infants who have been exposed to pharmacological doses of morphine for short periods.

To rationalise the common practice of using opiate sedatives or non-depolarising muscle relaxants during mechanical ventilation, we previously undertook two randomised control studies of morphine in ventilated preterm infants.^{1,2} We followed up the surviving infants until 5–6 years to assess whether brief exposure to exogenous opiate has measurable effects on subsequent neurological or behavioural performance. Blood was also taken to determine whether early opiate exposure may have had a long term effect on thyroid stimulating hormone activities.

Methods

The survivors of two randomised studies are the subject of this follow up study. The first in 1989–90¹ enrolled 95 ventilated infants of <34 weeks of gestation who were randomly allocated to receive either morphine (50–100 µg/kg/hour) alone (n=29), pancuronium alone (n=28), or both morphine (dose as above) and pancuronium (n=38). The median time of exposure to either drug was 5 days. The second trial² in 1991–2 was a double blind, randomised control trial of morphine (loading dose 100 µg/kg/hour for 2 hours, followed by 25 µg/kg/hour, to achieve a steady state concentration of 200 ng/ml¹¹) or 5% dextrose solution infused at the same rate as morphine. Forty one ventilated infants of gestational age <34 weeks were studied (morphine n=21, placebo n=20). The median time of exposure of the morphine was 56 hours. The dose of pancuronium used during both trials was 50–100 µg/kg, used as required.

Each child was assessed using three scales: the full scale Weschler Preschool and Primary Scale of Intelligence(WPPSI-R),¹² the Movement ABC (Movement Assessment Battery for

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Table 1 Pre-randomisation characteristics of infants followed up

Number followed up	Morphine (n=57)	Non-morphine (n=30)	Comparative statistics	
			χ^2 statistic	p value*
Male	27 (47%)	17 (57%)	0.68	0.41
Female	30 (53%)	13 (43%)		
Social class I-III	35 (61%)	23 (77%)		
Social class IV and V	22 (39%)	7 (23%)		
	Median (interquartile range)	Median (interquartile range)	Point estimate	95% CIs
Gestational age (weeks)	29 (27-31)	29 (27-30)	1.0	-1.0 to 2.0
Birth weight (g)	1300 (970-1590)	1200 (815-1740)	80	-160 to 300

* χ^2 analysis.

**Mann-Whitney U test.

Children),¹³ and the Child Behaviour Checklist,¹⁴ the latter being completed by a parent. In children with major disability, tests were undertaken to the level of the child's ability. All the children were seen at their homes except for five who were seen at school, and all were assessed by one experienced paediatrician (RJM) who was blinded to the randomisation group. Disability was defined as cerebral palsy, intelligence quotient <70, blindness or severe sensorineural hearing loss requiring hearing aids.

Consent to see the children was initially obtained from the GP and hospital consultant and then from the parents. Signed consent for the TSH blood test was obtained separately from the consent for the other assessments. The United Leeds Teaching Hospitals Trust Ethics Committee had approved the study before its start.

During the course of the study, two different TSH assays were used: the Kodak Amerlite TSH-30 ultrasensitive immunometric technique (Kodak Clinical Diagnostics Ltd, Amersham, UK) and the Technicon immuno-1 heterogeneous sandwich magnetic separation assay (Bayer Corporation, NY, USA). Both of these assays were standardised to the WHO second international standard IRP 80/558 and the results expressed in mIU/l.

The scores from all the assessments were analysed using the Mann-Whitney U test as none of them was normally distributed within the group. A cohort of 96 children was deemed to have an 85% chance of detecting a significant difference in IQ of 10 points between the morphine and the control group ($p=0.05$).

Results

A total of 136 babies were recruited to these two studies, of whom 95 survived; 62 had

received morphine and there were 33 controls in the non-morphine group. Of the 95 surviving children, 87 (91.6%) were seen and assessed at 5-6 years of age, blinded to allocated treatment groups (morphine group $n=57$ and non-morphine group $n=30$). Details of these infants are shown in table 1 and there was no significant differences in the baseline characteristics. Of the eight children who were not seen, three could not be traced, two refused permission to be assessed, two did not reply to three letters, lived outside Leeds and were not on the telephone, and one child came from a travelling family. Five of the children not seen had received morphine and three had not. Of these children, one is known to have diplegic cerebral palsy and learning difficulties and three are attending normal school without apparent clinically significant problems (all in the morphine group). Information on the other four children is not available (two morphine, two non-morphine), two of whom may have left the country as they had non-British parents.

The fate of the infants originally recruited to the study is shown in table 2. At follow up the children's ages ranged from 5 years to 6.99 years with a mean age of 5.7 years. Fifteen of the children assessed were disabled (11 morphine, 4 non-morphine). Four of these were unable to do the WPPSI-R or Movement ABC assessments due to severe disability, and one child with quadriplegic cerebral palsy was only able to do the verbal component of the WPPSI-R. Of the 11 disabled children able to complete fully the assessments, eight had cerebral palsy (two quadriplegia, four diplegia, two hemiplegia), one had severe learning difficulties, one had septo-optic dysplasia with learning difficulties and one had Dubowitz syndrome and learning difficulties. All the children seen were included in the analyses. The children who were unscorable on IQ and motor assessments were given a nominal score of 30 for the WPPSI-R and the maximum score of 40 for the ABC.

There was no significant difference in combined death and disability rates between the morphine and non-morphine groups for the 136 children in the original cohorts (table 2). For the 95 survivors up to 5 years of age, there was no significant difference between the two groups for disability. Table 3 shows the results of cerebral ultrasound examinations carried out in the neonatal period. There was no significant difference in the number of

Table 2 Primary outcomes (death and disability)

	Morphine	Non-morphine	χ^2 analysis	
			χ^2 statistic	p Value
Number at trial entry	88	48		
Death before assessment	26 (30%)	15 (31%)		
Alive at assessment	62 (70%)	33 (69%)	0.05	0.82
Survivors at assessment				
Disabled	11 (13%)	4 (8%)		
Normal	46 (52%)	26 (54%)		
Status unknown	5 (6%)	3 (6%)		
Death and disability	37 (42%)	19 (40%)	0.07	0.80
Assuming unknowns, favour morphine group	37 (42%)	22 (46%)	0.18	0.67
Assuming unknowns, favour non-morphine group	42 (48%)	19 (40%)	0.83	0.36

Table 3 Neonatal cerebral ultrasound diagnoses

	Morphine (n=88)	Non-morphine (n=48)	Comparative statistics	
			χ^2 statistic	p Value
Ultrasound report not available	18 (20%)	13 (27%)	0.78	0.38
Ultrasound report available	70 (80%)	35 (73%)		
<i>Ultrasound diagnosis</i>				
Normal	40 (45%)	27 (56%)		
Germinal matrix haemorrhage	12 (14%)	2 (4%)		
Intraventricular haemorrhage	5 (6%)	3 (6%)		
Parenchymal venous infarction	11 (13%)	2 (4%)		
Cystic leucomalacia (cPVL)	2 (2%)	1 (2%)		
<i>Diagnoses of major clinical significance</i>				
Venous infarction + cPVL	13 (15%)	3 (6%)		p value* 0.23

* χ^2 analysis.

**Fisher's exact test.

Table 4 Assessments

	Morphine Median (interquartile range)	Non-morphine Median (interquartile range)	Mann-Whitney U	
			Point estimate	95% CIs
Age at assessment (years)	5.9 (5.6–6.0)	5.7 (5.0–5.9)	0.1	0.01 to 0.56
Intelligence (IQ)	98 (85–112)	94 (81–109)	2.0	–6.0 to 11.0
Motor impairment (ABC)	9 (5.3–21.5)	12 (6.9–22.8)	–2.0	–5.5 to 2.0
Behaviour problems (CBCL)	24 (14–42)	29 (16–41)	–3.0	–12 to 3

infants with ultrasound abnormalities of major prognostic importance (cystic leucomalacia and parenchymal venous infarction) between the morphine and non-morphine groups.

The results of the assessment of the 87 children seen at 5–6 years are shown in table 4. There were no significant differences in IQ, motor impairment, and behaviour problems, but there was a trend in all three scores in favour of those children treated with morphine in the neonatal period.

Thirty nine children consented to having a blood test for TSH measurement; 24 were in the morphine group and 15 were in the non-morphine group. There was no difference between the two groups on the Mann Whitney U analysis: morphine group median = 1.68 mIU/l, non-morphine group median = 1.65 mIU/l, point estimate of difference = –0.01 mIU/l; 95% confidence intervals: –0.53 to 0.39; p=0.92.

Discussion

The ontogeny of brain opiate receptors is not clear, but in rats the adult distribution of u-receptors is complete by the sixth postnatal day.⁸ Morphine is a specific agonist of u-receptors and naloxone effectively antagonises these receptors as well as other receptor subtypes. Endogenous opiates have important effects on moulding neuronal organisation in the developing brain,¹⁵ and astrocytes within the brain are very sensitive to the effects of local opiate concentrations in terms of growth.¹⁶ Endogenous opiates seem to inhibit neuronal growth and proliferation.¹⁷ In animal models, neuronal development has been disrupted by exogenous opiate exposure. Very short term morphine exposure of both the fetal and neonatal rat causes a down-regulation in u-receptors, particularly in the hypothalamus⁸ and other nuclei.¹⁸ This effect was seen only after four days of morphine exposure and was reversed following longer term exposure.¹⁸

Brief exposure of the mature fetal rat to morphine also significantly reduced neuronal packing density¹⁹ in the cortex, increased glial elements,⁸ reduced dendritic length⁸ and number of dendritic branches.²⁰ This effect may be mediated as a direct action of short term morphine exposure on astrocytic DNA synthesis.¹⁶ Changes in the behaviour of juvenile rats who had been exposed to morphine at an early developmental age have also been reported.²¹

In view of these potential adverse effects on neuronal development in animal models, the results of this clinical study are reassuring in that morphine showed no detrimental effects on the intelligence of 5–6 year old children who received it in the first days of neonatal life. There was a trend for children treated in the morphine group to have better scores for all three areas of assessment than the non-morphine group. The study was not originally designed to test assessment at 5–6 years as a primary outcome measure and it is clear from the power calculation on the numbers in our follow up cohort that we would only have enough children in the study to show a difference of 10 IQ points. The conclusion that morphine has no effect on outcome must therefore be tentative, but based on these data it is unlikely that there would be an adverse effect.

Morphine exposure seems to have a specific effect on hypothalamic nuclei which may affect pituitary hormone release. In particular, hypothalamic function involving thyroid function control has been adversely affected. Mess *et al*¹⁰ gave a single small dose of morphine (0.2 μ g) on the day of birth to male newborn rats and showed that these animals had a nearly 20% reduction of serum TSH concentration when they reached maturity. The reduction in basal secretion of TSH was even greater when the morphine exposure occurred before birth when the animals were more immature. It is thought that this action occurs as the result of morphine acting on the monoaminergic neurons in hypothalamic related nuclei. The long term effect on reducing TSH activities may be one mechanism by which morphine affects later cognitive development. We were able to measure TSH values in a proportion of the children in our follow up cohort and there were no significant differences in TSH activities between the two groups.

Over 90% of the surviving children have been traced and assessed as part of this study. All the children were assessed by one experienced neurodevelopmental paediatrician who undertook all the assessments. We feel that the high compliance and the single observer assessment overcomes many of the problems of longer term follow up of prematurely born infants. Overall, 20% of the total cohort assessed had significant disability defined as cerebral palsy, mental retardation (IQ <70), blindness or severe sensorineural hearing impairment. This figure is somewhat higher than many reports for premature infants, but our cohort is a very high risk one with a prerequisite for the need for mechanical

ventilation. In light of this we do not feel that the proportion with disability is excessive.

There is no evidence that post randomisation neonatal insults have biased these results. It could be argued that there may have been more adverse neonatal events in the non-morphine group, masking potentially harmful effects of morphine. The neonatal cerebral ultrasound diagnoses of the two groups were not significantly different (table 3), although it would be unwise to assume that any post-randomisation insults are outside the influence of morphine. Randomisation is the best mechanism of controlling for both known and unknown confounding influences and the pre-randomisation characteristics of the groups were similar (table 1).

The results of the previous two studies have shown that morphine reduces catecholamine response, suggesting that the morphine was given at an effective dose to reduce stress. Although concentrations of catecholamines have been reported to correlate with death,⁴ there are no data available on their correlation with disability. This will be the subject of another study currently in preparation. It has been suggested that reducing the catecholamine response may be detrimental to the outcome of babies as this may blunt a normal physiological mechanism. This study suggests that morphine sedation causes no harm to babies when used for a short time in the neonatal period.

In summary, these results show that children who received morphine as neonates showed no significant difference in IQ, motor impairment, or behaviour compared with those who did not receive morphine or other opiate. The trend in the results, although slight, is in favour of the morphine group. We suggest that this shows that morphine can safely be used as a sedative and analgesic in the neonatal intensive care unit.

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