Medical management of raised intracranial pressure after severe birth asphyxia

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SUMMARY The effects of dexamethasone and 20% mannitol infusion in reducing raised intracranial pressure were assessed in severely asphyxiated newborn infants. Intracranial pressure was measured continuously by a percutaneously placed subarachnoid catheter, and cerebral perfusion pressure was calculated from this and blood pressure data. Dexamethasone treatment, assessed in seven infants, produced an overall fall in intracranial pressure which was sustained for at least six hours, but this was coincident with a simultaneous reduction in systemic blood pressure with no change in the cerebral perfusion pressure. Mannitol, studied on nine occasions, produced a fall in intracranial pressure in each case, together with an overall rise in cerebral perfusion pressure 60 minutes after starting the infusion; this was sustained for a further four hours. We can find little to support the routine use of dexamethasone in severe perinatal asphyxia but mannitol infusion seems of value in treating raised intracranial pressure associated with cerebral oedema.

The incidence of birth asphyxia causing cerebral disturbance is unknown but is probably in the order of 1·5 to 6 per 1000 live births. It is arguably the commonest cause of perinatal brain injury associated with long term neurological handicap.[1]

The management of severe birth asphyxia is both supportive and directed towards avoidance of, or treatment for, cerebral oedema. Supportive treatment includes control of convulsions, avoidance of hypotension, and prevention of metabolic disturbances. The management of cerebral oedema is entirely empirical as methods have not been available for the reliable diagnosis of this condition. Where intracranial hypertension is thought to be present, dehydration, corticosteroids, and osmotic agents have been recommended. There have been no studies on the medical management of raised intracranial pressure in the severely asphyxiated human newborn. We report the effects of dexamethasone and mannitol on lowering raised intracranial pressure as measured directly from the subarachnoid space.

Patients and methods

Ten mature infants who had suffered severe perinatal birth asphyxia were studied. A fine catheter was inserted percutaneously into the subarachnoid space through the anterior fontanelle[2] and connected to a silicon diaphragm transducer by means of a saline filled, low compliance manometer connecting tube. This procedure had been approved by the hospital ethical committee, and informed signed consent was obtained from all parents before placement of the catheter.

The infants were managed with relative dehydration and given approximately 10% less fluid than normal term babies. In ventilator dependent infants, the mechanical ventilation was adjusted to achieve a $Paco_2$ of between 3·5 and 4·0 kPa (26 to 30 mm Hg). Raised intracranial pressure was diagnosed if the pressure measured from the subarachnoid space reached an arbitrary level of 10 mm Hg or more, and was sustained for two hours or more. Under these circumstances medical treatment was introduced. Dexamethasone (4 mg intravenously) was used first and if after six hours the intracranial pressure still exceeded 10 mm Hg, 20% mannitol was infused (1 g/kg) over 20 minutes. Intracranial pressure was monitored continuously and displayed on a multichannel chart recorder. In six infants, systolic and diastolic blood pressure was also recorded continuously from an umbilical aortic catheter and displayed on the same chart as intracranial pressure.

Both pressure channels were zeroed at regular intervals, and the transducers relevelled with the mid point on the infant's head each time they were moved. In the other infants, blood pressure was measured by an oscillometric method (Dinamap). Cerebral perfusion pressure was calculated by subtracting the mean intracranial pressure from the mean arterial blood pressure.[3]

For the purposes of illustration, the intracranial and cerebral perfusion pressures at the time of giving dexamethasone or mannitol (zero time) have been taken as 100%, and changes expressed as a proportion of the value at that time. Statistical analysis was performed using the Wilcoxon matched pairs, signed rank test on the raw data.

Results

Seven infants fulfilled the criteria for treatment of raised intracranial pressure (Table 1). The duration of intracranial pressure monitoring was 12 to 76 hours (median 48 hours). The recordings were analysed for a period from six hours before dexamethasone treatment until 24 hours after the drug had been given or monitoring ended. Table 1 shows the duration of monitoring for each infant studied, as well as the intracranial pressure at the time of treatment. In three infants (cases 1, 3, and 6) raised intracranial pressure was still a problem six hours after dexamethasone treatment and they received mannitol infusions 7, 7·5, and 18 hours later. In five of the seven infants the intracranial pressure fell within one hour of dexamethasone and in a sixth within two hours. In one infant there was no reduction in intracranial pressure over the 24 hour period after treatment. The relative change in intracranial pressure after dexamethasone for the seven infants is shown in Fig. 1. It can be seen that intracranial pressure gradually rose for six hours before dexamethasone injection and then fell to its lowest point six hours afterwards. There was a statistically significant reduction in intracranial pressure after two hours (P<0·05). After six hours there was a gradual increase in pressure.
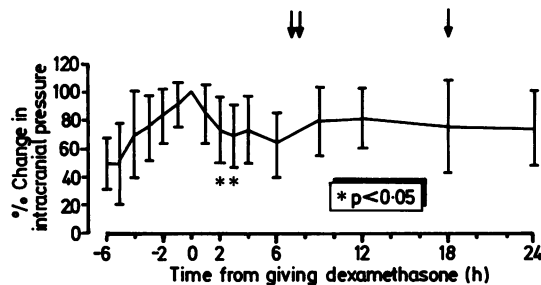

Fig. 1 *Intracranial pressure measurements (mean (SD)) in seven infants before and after dexamethasone injection.*

Arrows indicate the start of mannitol infusion in three infants with persistently raised intracranial pressure.

Continuous blood pressure monitoring was not possible in one infant and cerebral perfusion pressure could not be calculated. Table 1 details the cerebral perfusion pressure in seven infants given dexamethasone. This fell within one hour of the injection in four infants and rose by just 2 mm Hg in the remaining two. At six hours the cerebral perfusion pressure was below that at zero time in two infants and had risen by less than 5 mm Hg in a further two. In only one child was there a noticeable increase in cerebral perfusion pressure at six hours. Fig. 2 shows graphically the relative changes in
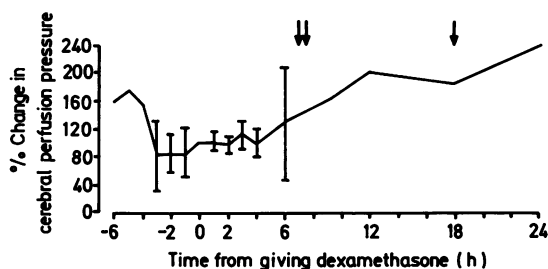

Fig. 2 *Cerebral perfusion pressure (mean (SD)) in six infants before and after dexamethasone injection.*

After six hours the SD could not be calculated because of small numbers.

Table 1 *Details of seven infants treated with dexamethasone*

Infant no	Gestational age (wks)	Birthweight (g)	Duration of ICP monitoring (hrs)	ICP at zero time (mm Hg)	CPP at zero time (mm Hg)
1	40	3100	38	14	—
2	40	3000	76	14·5	33
3	35	2520	50	37	7
4	39	2990	12	10	39
5	40	3820	15	12·5	35
6	40	3560	52	10	31
7	40	3820	48	11	70

ICP=intracranial pressure; CPP=cerebral perfusion pressure.

cerebral perfusion pressure after dexamethasone treatment in six infants for six hours before and 24 hours after injection. There was little change until six hours after the injection of dexamethasone.

Mannitol 20% was used on nine occasions in four infants who had raised intracranial pressure six hours after dexamethasone treatment. Intracranial pressure at the time of mannitol infusion varied from 11 to 40 mm Hg (Table 2). All infants were studied for 60 minutes before and 300 minutes after infusion. Intracranial pressure fell within 20 minutes after eight infusions, and in all cases by 60 minutes. Fig. 3 shows the overall change in intracranial pressure before and after treatment with mannitol. There was a gradual rise for 60 minutes before mannitol and a significant drop within 20 minutes of starting the infusion (P<0·02). By 40 minutes there had been overall a 35% drop (P<0·01) and this was sustained for at least a further four hours. The cerebral perfusion pressure could be calculated on six occasions and its value at zero time is shown in Table 2. Cerebral perfusion pressure improved by 5 to 28 mm Hg in every case by 60 minutes from the start of the infusion. Fig. 4 shows this data plotted as a proportion of cerebral perfusion pressure at zero time. There was no appreciable change for 40

Table 2   Details of the effects of 20% mannitol infusions in four infants

Infusion No	Infant No	ICP at zero time (mm Hg)	CPP at zero time (mm Hg)
A	1	14	—
B	1	18	—
C	2	18	—
D	2	11	41
E	3	23	3
F	3	40	19
G	6	12	27
H	6	12·5	26·5
I	6	18	28

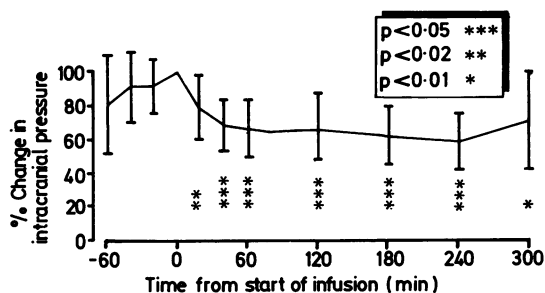ICP=intracranial pressure; CPP=cerebral perfusion pressure.

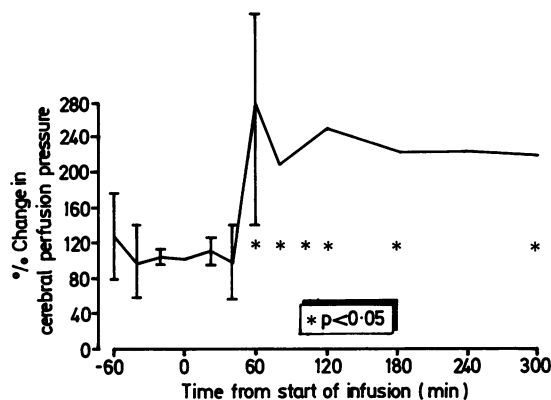Fig. 3   Intracranial pressure (mean (SD)) before and after nine infusions of 20% mannitol.

Fig. 4   Cerebral perfusion pressure (mean (SD)) before and after six infusions of 20% mannitol.

minutes before and 40 minutes after starting the infusion, but by 60 minutes there had been a significant increase in the cerebral perfusion pressure (P<0·05) which was sustained for at least a further 240 minutes. Serum electrolytes and urinary specific gravity were evaluated daily and no disturbances in these measurements were found in any patient.

Discussion

We have previously shown that intracranial pressure can be measured continuously from the subarachnoid space,[2] and we have found no complications related to this method. Direct monitoring can be used to assess the effects of various drugs on reducing raised intracranial pressure in severely asphyxiated mature infants. We found that both dexamethasone and 20% mannitol seemed to produce at least a short term reduction in this. Monitoring of intracranial pressure must be made in conjunction with measurement of mean arterial blood pressure in order to assess cerebral perfusion pressure. Both dexamethasone and mannitol cause a reduction in intracranial pressure with a simultaneous reduction in systemic blood pressure. In the case of mannitol, this blood pressure reduction seems to be transient with subsequent recovery and improvement in cerebral perfusion pressure, but after dexamethasone treatment there is no improvement in cerebral perfusion pressure over six hours and subsequent improvement may be due to the use of mannitol.

No reliable data exists on normal intracranial pressure in newborn infants. In a few of the babies we have monitored, pressures within the subarachnoid space rarely exceeded 3 to 4 mm Hg. We set an

arbitrary level for intracranial hypertension at 10 mm Hg but this may be too low. Attention to the intracranial pressure in relation to the cerebral perfusion pressure is probably the most relevant factor.

This is the first report of the effect of drugs on intracranial pressure in the asphyxiated newborn. The results are presented as a pilot study and we have made no effort to present these observations as part of a controlled study. Indeed, it seems unlikely at this time that we could insert a subarachnoid catheter and ignore intracranial hypertension and until further experience with this technique is obtained we feel that a controlled study is difficult to justify ethically.

The role of dexamethasone in the management of perinatal birth asphyxia is disputed. Two recent books which discuss the management of birth asphyxia recommend the early use of corticosteroids,[4] [5] while Volpe,[1] in a comprehensive monograph on neonatal neurology, disregards the use of these agents. There are few experimental data from controlled studies to support the use of dexamethasone in the management of perinatal asphyxia. The existing experimental work cannot easily be applied to the newborn. The use of experimental animals with brains of different maturity to those of term humans, and methods for producing asphyxia which poorly mimic perinatal asphyxia are major criticisms of such work. In addition, there are few histological studies on the asphyxiated newborn brain. Studies on five day old rats, whose brain at that age is at a comparable stage of development with the term human brain, showed that treatment with dexamethasone *before* asphyxia resulted in less severe effects on the brain than in untreated animals.[6] Treatment after asphyxia with doses of dexamethasone comparable to those used in the human newborn were ineffective in treating or preventing cerebral oedema.[7]

It has been suggested that cerebral oedema is caused by either cytotoxic or vasogenic damage.[8] Histological studies showing brain oedema to be associated with both an increase in extracellular fluid in the white matter and with noticeable swelling of the astrocytes support this.[9] In clinical practice it is likely that both vasogenic (extracellular oedema) and cytotoxic (cell swelling) occur together. Published reports suggest that dexamethasone has effects primarily on vasogenic oedema and to a lesser extent on cell swelling.[10] This agent finds its major role in the treatment of focal cerebral oedema associated with tumour or abscess, neither of which bear a close resemblance to the generalised brain swelling after perinatal asphyxia.

The adverse effects of steroids must also be considered. There is a large body of data on the theoretical and actual hazards after pharmacological doses of steroids on the developing brain. These include immediate effects on cell division, differentiation, myelination, and electrophysiological reactions as well as less obvious latent effects.[11] In a follow up study Fitzhardinge *et al*[12] found that a group of infants treated with hydrocortisone in the first 24 hours of life had a slightly increased incidence of gross neurological and electroencephalographic abnormalities compared with a control group. In addition, gross motor development was poorer in the treated group.

The conclusions from our study on dexamethasone are limited. Corticosteroid agents probably have their maximal action in reducing oedema between 24 and 48 hours after administration and we have not been able to monitor intracranial pressure for that period of time. It is, however, unlikely that any clinical study could monitor intracranial pressure for this duration without treating persistently raised pressure with other drugs. Once cerebral oedema was severe enough to cause raised intracranial pressure, dexamethasone did not improve cerebral perfusion pressure in the short term but reduced intracranial pressure at the expense of the blood pressure. A smaller but more frequent dose of steroid may conceivably be more effective but we can find no evidence that glucocorticoids have a beneficial effect in birth asphyxia.

As in the case of steroids, osmotic agents have not been scientifically assessed in the management of birth asphyxia. There is a theoretical risk of rebound cerebral oedema if mannitol enters the brain through a damaged blood-brain barrier and is then excreted from the systemic circulation. In order to avoid this, controlled management with intracranial pressure monitoring is necessary. To our knowledge this has not previously been performed in the newborn. Our results suggest that mannitol is an effective agent in the management of raised intracranial pressure caused by cerebral oedema. In this study, intracranial pressure fell in all infants after mannitol infusion. More importantly, there was a noticeable improvement in cerebral perfusion pressure 60 minutes after starting the drug, and this was sustained for at least four hours. There is only one published report on the use of mannitol after perinatal asphyxial insult. Mannitol was given either early (before 2 hours of age) or late (after 2 hours) but a control group was not studied.[13] The authors concluded that early treatment was beneficial but statistical analysis was not performed. We would tentatively recommend the cautious use of 20% mannitol in the treatment of raised intracranial pressure after perinatal cerebral asphyxia.

In conclusion, measurement of intracranial and cerebral perfusion pressures allows the controlled use of drugs in the treatment of intracranial hypertension. We can find little evidence that dexamethasone improves cerebral perfusion pressure, at least in the first six hours after its use, and its role in the management of birth asphyxia must remain uncertain. Mannitol, however, seems to be effective in lowering intracranial pressure and improving cerebral perfusion pressure, and its cautious use is recommended if intracranial pressure monitoring is available.

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