Acta Paediatrica Academiae Scientiarum Hungaricae, Vol. 18 (1), pp. 53—59 (1977)

Oxygen therapy and massive pulmonary haemorrhage in newborn infants

M. Fekete, M. Horváth, L. Bárdosi, J. Mestyán

Department of Paediatrics and Institute of Pathology, University Medical School, Pécs

Received 11th August, 1976

A significant rise in the frequency of neonatal pulmonary haemorrhage was observed in the year when intensive oxygen therapy by CPAP and IPPV ventilation was started. To clarify the role of oxygen therapy the neonatal deaths occurring in two periods of different oxygen treatment were analysed and compared in respect of all clinical features which may be involved in the pathogenesis of pulmonary haemorrhage. In conclusion it is suggested that the local effect of oxygen is probably an additional but significant pathogenetic factor in the condition.

Massive pulmonary haemorrhage (MPH) is in general thought to be the cause of 1—10% of neonatal deaths. The pathogenesis of MPH is still controversial. Diagnosis *in vivo* can rarely be achieved in due time and no successful treatment has yet been reported. Perinatal asphyxia [4, 15, 17, 22, 27], hyaline membrane disease [27], lesions of the central nervous system [4, 14, 15], aspiration [11, 25], pneumonia [10, 21], hypothermia [6, 9], septicaemia [3, 17], congenital heart malformations [3, 4, 16, 22], coagulation defects [1, 12, 26], transfusion and infusion therapy [22], oxygen- and respirator therapy [7, 20, 23, 24, 28] had all been suggested as causative or at least predisposing factors. Despite the obvious interrelationships existing between suspected mechanisms, the long list truly reflects the lack of solid knowledge. Nevertheless the recent theory of Adamson et al. [2] and Cole et al. [13] seems to synthesize all the former explanations by suggesting that hypoxia and acidosis trigger a vicious circle leading to haemorrhagic pulmonary oedema.

The average frequency of MPH in our patient material was 4.5% (range, 1.0—9.2) in the six-year period 1967 to 1972 [17]. A frequency of 8.2% (14 out of 170 neonatal deaths) was recorded in 1973, and in 1974, when CPAP and respirator (IPPV) therapy attained wide use in our special care baby unit, a significant ($\chi^2 = 4.66$; $p < 0.05$) rise was noted (17.3%, i.e. 28 out of 162 deaths). As the role of high FiO_2 in causing MPH had been suggested [7, 20, 23, 28] we have tested this possibility in a retrospective clinical study.

Methods

Newborn infants who died during two different periods of oxygen therapy, i. e. from 1st January to 31th December,

1973, and from 1st January to 31th December, 1974, were studied. All data which may have been related to the frequency of MPH were analysed and compared in the two groups of neonates (170/1973 and 162/1974). Postmortem examination was performed on all babies who succumbed. Autopsy reports were reviewed and MPH cases selected on the basis of gross and histologic findings. No distinction was made between interstitial and intraalveolar haemorrhage.

Clinical data listed below were compared in the two populations of patients: 1) pathologic pregnancy; 2) delivery by Caesarean section or breech presentation and/or forceps; 3) perinatal asphyxia; 4) hypothermia on admission; 5) birth weight; 6) gestational age; 7) intrauterine nutrition (dysmaturity); 8) infusion therapy; 9) blood transfusion therapy; 10) oxygen therapy; 11) postmortem finding. For statistical analysis, the 2K contingencial tables were used with χ^2 test, except for comparing oxygen therapy.

Definitions. Perinatal asphyxia: the baby needed resuscitation at birth; the five minute Apgar score was less than 7; on admission IRDS or postasphyxic syndrome was diagnosed on the basis of the acid-base status, X-ray and/or clinical signs.

Hypothermia: rectal temperature below 36 °C on admission.

Infusion therapy: 5—10% glucose +4.2% sodium bicarbonate infusion by Braun—Melsungen perfusor, maintenance volume per day.

Blood transfusion therapy: 10—15 ml/kg ACD blood not older than 72 hours, by Braun—Melsungen perfusor.

Oxygen therapy: $FiO_2 \geqq 40\%$ via head-box; CPAP breathing $FiO_2 \geqq 40\%$ with a pressure of 5—12 H_2O cm; IPPV ventilation with 60—100% oxygen by Bennett PR-2 respirator. Duration of oxygen therapy was expressed in days.

Postmortem finding: gross finding which was thought to be the primary cause of death.

Results

Results are shown on Figs 1 and 2, and in Tables I to III. It can be seen that the two populations studied were remarkably similar ($p > 0.05$—$p > 0.3$) in respect of all data compared except for oxygen therapy (Table II). Whilst in 1973, 140 patients received oxygen therapy via head-box for 1.9 days, in 1974, 120 babies were treated in the same way for 2.5 days on the average, 80 infants received CPAP ventilation and 23 babies had IPPV for 1.6 and 1.3 days, respectively. The difference in intensity and duration of oxygen therapy during the two periods is obvious.

In 1973, 7.6% (13 infants) and in 1974, 12.9% (21 infants) of the cases had blood transfusions within 24 hours prior to death. The difference was significant statistically ($p < 0.05$). Furthermore, nearly two thirds of the infants could only be classified from the point of view of intrauterine nutrition and development. This was due partly to the gestational age of a number of patients being unknown and partly to the considerable number of infants with a gestational age of less than 28 weeks (33 in 1973 and 30 in 1974).

In 1974, the number of those with subtotal pulmonary atelectasis as a single autopsy finding decreased considerably, while the number of infants with atelectasis associated with intraventricular or subependymal haemorrhage increased significantly ($p < 0.05$). The frequency of other kinds

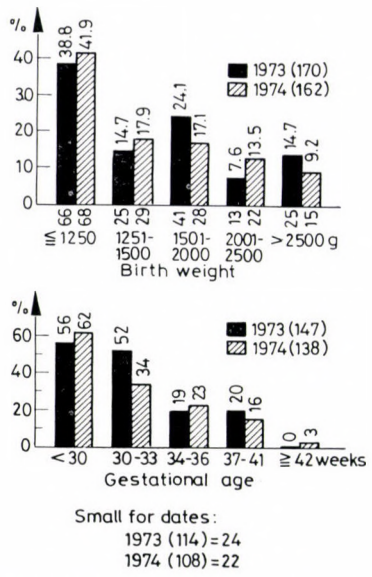

FIG. 1 Birth weight and gestational age of newborn infants who died in 1973 and 1974. Top: percentage values; bottom: number of babies. Only the number of infants is given in the lower part of the figure (gestational age distribution).

of extracranial and extrapulmonary haemorrhage remained unchanged (14 in 1973 and 16 in 1974).

On Table III, clinical data of MPH cases are shown. It can be seen that except oxygen therapy, the various parameters showed a similar frequency in the two groups of infants. The duration of oxygen therapy calculated per patient was significantly ($\chi^2 = 5.64$; $p < 0.02$) longer in 1974 than in 1973. Similarly as that for all deaths in the two test periods, a relative rise in the frequency

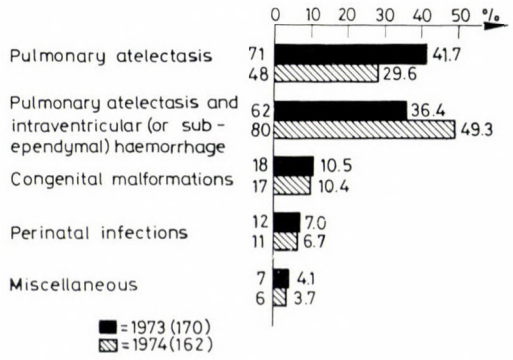

FIG. 2 Gross postmortem findings in newborn infants who died during the two periods. Right: percentage values; left: number of infants.

TABLE I

Clinical data of newborn infants who died in 1973/1974

	1973		1974	
	No.	per cent	No.	per cent
Number of patients	*170*	100	*162*	100
Pathological pregnancy	*74*	43.6	*63*	38.9
Delivery by Caesarean section, or breech presentation or forceps	*34*	20.0	*31*	19.2
Perinatal asphyxia	*121*	71.1	*118*	72.8
Hypothermia on admission				
< 34 °C	*87*	51.1	*84*	51.8
34.0 – 35.0 °C	*15*	8.8	*23*	14.1
35.1 – 36.0 °C	*37*	21.7	*31*	19.1
Infusion therapy within 24 hours prior to death	*151*	88.8	*149*	91.9
	142	83.5	*142*	87.6
Blood transfusion therapy within 24 hours prior to death (*)	*39*	22.9	*55*	33.9
	13	7.6	*21*	12.9

*$p < 0.05$

TABLE II

Oxygen therapy in newborn infants who died in 1973/1974

Duration of oxygen therapy (day)	Head-box — $FiO_2 \geqq 40\%$		CPAP — $FiO_2 \geqq 40\%$		IPPV — 60 – 100% oxygen	
	1973	*1974*	*1973*	*1974*	*1973*	*1974*
1	82	54	–	50	–	18
2	29	20	–	21	–	7
3	10	11	–	10	–	3
4	6	14	–	2	–	–
5	6	7	–	2	–	–
6	7	14	–	–	–	–

1973 — 1.9 days/patient — Head-box (140 patients)
1974 — 2.5 days/patient — Head-box (120 patients)
1.6 days/patient — CPAP (85 patients)
1.3 days/patient — IPPV (23 patients)

TABLE III

Clinical data of newborn infants who died of MPH

	1973	1974
Number of patients	14/170	28/162
Perinatal asphyxia	9/14	20/28
Prematurity	12/14	27/28
Small for dates	3/14	5/28
Hypothermia	11/14	23/28
Respiratory distress syndrome	6/14	15/28
Postasphyxic syndrome	4/14	8/28
Perinatal infection, septicaemia	1/14	1/28
Rhesus haemolytic disease	1/14	1/28
Congenital heart malformation	0/14	0/28
Infusion therapy	14/14	27/28
Blood transfusion therapy	4/14	10/28
Oxygen therapy		
Head-box $FiO_2 \geq 40$ % (days)	30/14	40/28
CPAP $FiO_2 \geq 40$ % (days)	0/14	38/28
IPPV 60 – 100 O_2 (days)	0/14	11/28
Postmortem findings		
Pulmonary atelectasis	8/14	7/28
Pulmonary atelectasis associated with intraventricular or subependymal haemorrhage	4/14	19/28
Septicaemia	1/14	1/28
Rhesus haemolytic disease	1/14	1/28
Hyline membrane (histology)	3/14	5/28

of intraventricular and subependymal haemorrhage could be observed in 1974 among MPH patients too.

DISCUSSION

A causal relationship between oxygen therapy and MPH had first been suggested by Shanklin and Wolfson [28] on the basis of clinical observations. Kistler et al. [19] observed damage of pulmonary capillary endothelium in subjects breathing high concentration oxygen which favours transudation and oedema formation. Increased capillary pressure due to left ventricular failure has also been suggested to have a role in the capillary endothelial damage and disseminated intravascular coagulation was found in rats kept in 100% oxygen [31]. Boothby and deSa [7] concluded that the increased frequency of pulmonary haemorrhage was probably related to the use of oxygen at high concentration and $FiO_2 > 80\%$ for longer than 24 hours may be dangerous. Recently Kotas et al. [20] have reported on extensive intraalveolar and interstitial pulmonary haemorrhage in newborn animals evoked by high environmental oxygen concentrations. They emphasized the role of reduced alveolar collateral ventilation due to pulmonary immaturity and also of the higher absorption coefficient of oxygen in comparison with that of air.

In spite of evidence of the role of oxygen in causing or predisposing to MPH, the argument could not be

rejected that the grave pathological condition *per se* would lead to MPH. If this is correct, MPH should be considered a 'preterminal syndrome'. After all, in the light of the work of Adamson et al. [2] and Cole et al. [13] it seems much more likely that cardiorespiratory and circulatory changes caused by asphyxia play the primary role and the local effect of oxygen is probably only one, though not an insignificant, additional factor.

The results of the present study support the probability of a causal relationship of intensive oxygen therapy and pulmonary haemorrhage. The two compared populations of newborn infants were closely similar in respect of all parameters but oxygen therapy. The fact should, however, be emphasized that the severity and duration of asphyxia and the effect of treatment could not be evaluated in this study. For this reason the pathogenetic role of oxygen therapy can only be assumed but not regarded as proven.

The rise in frequency of intraventricular and subependymal haemorrhages in the total population studied and among babies with MPH in the year of intensive oxygen therapy is puzzling. The effect on cerebral circulation of a hyperoxyemia or of CPAP and IPPV has not so far been elucidated. It may, however, be supposed that CPAP with a pressure of less than 12 H_2O cm does not reduce cardiac output in general, but can be dangerous in patients with hypovolaemia and/or heart failure [18].

The risks of oxygen therapy are well known. The present results draw attention to the possibility of a less widely known complication and emphasize the need for a strict indication and control of oxygen administration.

References

1. Aballi, A. J., de Lamerens, S.: Coagulation changes in the neonatal period and early infancy. Pediat. Clin. N. Amer. **9**, 758 (1962).
2. Adamson, T. M., Boyd, R. D. H., Normand, I. C. S., Reynolds, E. O. R., Shaw, J. C. L.: Haemorrhagic pulmonary oedema (massive pulmonary haemorrhage) in the newborn. Lancet **1**, 494 (1969).
3. Ahvenainen, E. K., Call, J. D.: Pulmonary hemorrhage in infants. Amer. J. Path. **28**, 1 (1952).
4. Ahvenainin, E. K.: Massive pulmonary haemorrhage in the newborn. Ann. paediat. Fenn. **2**, 44 (1956).
5. Arey, J. B., Dent, J. J.: Causes of fetal and neonatal death with special reference to pulmonary inflammatory lesions. J. Pediat. **42**, 1 (1953).
6. Arneil, G. C., Kerr, M. M.: Severe hypothermia in Glasgow infants in winter. Lancet **2**, 756 (1963).
7. Boothby, C. B., deSa, D. J.: Massive pulmonary haemorrhage in the newborn. A changing pattern. Arch. Dis. Childh. **48**, 21 (1973).
8. Bound, J. P., Butler, N. R., Spector, W. G.: Classification and causes of perinatal mortality. Brit. med. J. **2**, 1191 (1956).
9. Bower, M. D., Jones, L. F., Weeks, M. M.: Cold injury in the newborn. Brit. med. J. **1**, 303 (1960).
10. Browne, F. J.: Pneumonia neonatorum. Brit. med. J. **1**, 469 (1922).
11. Ceballos, R.: Aspiration of maternal blood in the etiology of massive pulmonary hemorrhage in the newborn infant. J. Pediat. **72**, 390 (1968).
12. Celander, O.: In: Nutricia Symposium on the adaptation of newborn infant to extrauterine life, Jonxis, J. P. H., Visser, H. K. A., Troelstra, J. A., (eds) Thomas, Springfield, Ill. 1964.
13. Cole, V. A., Normand, I. C. S., Reynolds, E. O. R., Rivers, R. P. A.: Pathogenesis of hemorrhagic pulmo-

nary edema and massive pulmonary hemorrhage in the newborn. Pediatrics **51,** 175 (1973).
14. Driscoll, S. G., Smith, C. A.: Neonatal pulmonary disorders. Pediat. Clin. N. Amer. **9,** 325 (1962).
15. Esterley, J. R., Oppenheimer, E. H.: Massive pulmonary hemorrhage in the newborn. I. Pathologic considerations. J. Pediat. **69,** 11 (1966).
16. Fedrick, J., Butler, N. R.: Certain cause of neonatal death. IV. Massive pulmonary haemorrhage. Biol. Neonat. **18,** 243 (1971).
17. Fekete, M., Járai, I., Mestyán, Gy.: Pulmonary haemorrhage in the newborn. Acta paediat. Acad. Sci. hung. **9,** 85 (1968).
18. Hoodson, W. A., Belenkey, D. A.: Management of respiratory problems. In: Neonatology. Avery, G. B. (ed.) J. B. Lippincott Co., 1975.
Kistler, G. S., Caldwell, P. R., Weibel, E. R.: Dvelopment of fine structural damage to alveolar and capillary lining cells in oxygen poisoned rat lungs. J. Cell Biol. **33,** 60 (1967).
20. Kotas, R. V., Wells, T. J., Mims, L. C., Trainer, E. J., Wiles, C. L.: A new model for neonatal pulmonary hemorrhage research. Pediat. Res. **9,** 161 (1975).
21. Landing, B. H.: Pulmonary lesions of newborn infants (A statistical study). Pediatrics **19,** 217 (1957).
22. McAdams, A. J.: Pulmonary haemorrhage in the newborn. Amer. J. Dis. Child. **113,** 255 (1967).
23. Mead, J., Takishima, T., Leith, D.: A model of pulmonary elasticity. J. appl. Physiol. **28,** 596 (1970).
24. Normand, I. C. S., Reynolds, E. O. R., Strang, L. B. J.: Passage of macromolecules between alveolar and interstitial spaces in foetal and newly ventilated lungs of the lamb. J. Physiol. **210,** 151 (1970).
25. Rhaney, K., McGregor, A. R.: Pneumonia in the newborn resulting from the inhalation of gastric contents. Arch. Dis. Childh. **23,** 254 (1948).
26. Roberts, T. J., Davies, A. J., Bloom, A. L.: Coagulation studies in massive pulmonary haemorrhage of the newborn. J. clin. Path. **19,** 334 (1966).
27. Rowe, S., Avery, M. E.: Massive pulmonary hemorrhage in the newborn. II. Clinical considerations. J. Pediat. **69,** 12 (1966).
28. Shanklin, D. R., Wolfson, S. L.: Therapeutic oxygen as a possible cause of pulmonary haemorrhage in premature infants. New Engl. J. Med. **277,** 833 (1967).
29. Sivanesan, S.: Neonatal pulmonary pathology in Singapore. J. Pediat. **59,** 600, 1961.
30. Thorburn, M. J.: Neonatal death and massive pulmonary haemorrhage in Jamaica. Arch. Dis. Childh. **38,** 589 (1963).
31. Wood, C. D., Perkins, G. F., Smith, A. G., Reaux, J. M.: Response of the cardiovascular system in oxygen toxicity. Aerospace Med. **43,** 162 (1972).

Dr. M. Fekete
József A. u. 11.
H-7623 Pécs, Hungary