Effect of Albumin Administration on Phototherapy for Neonatal Jaundice

Y. K. WONG, G. R. SHUTTLEWORTH, and B. S. B. WOOD

From the Birmingham Maternity Hospital, Queen Elizabeth Medical Centre, Edgbaston, Birmingham

Wong, Y. K., Shuttleworth, G. R., and Wood, B. S. B. (1972). *Archives of Disease in Childhood*, 47, 241. **Effect of albumin administration on phototherapy for neonatal jaundice.** Two clinical trials were designed to test the effect of albumin administration before phototherapy for non-haemolytic neonatal jaundice. The first with 18 hours of phototherapy showed that the albumin-treated group (23 infants) had higher and more prolonged jaundice than the group (27 infants) given phototherapy alone.

In the second study on 29 infants there were two groups as before, but the duration of phototherapy was increased to at least 48 hours and a third untreated group was included. These results showed significant differences between all three groups, the cases receiving phototherapy alone having the shortest and those receiving no specific therapy, the longest duration of jaundice.

Those patients given albumin intravenously had significantly greater albumin-binding capacity at the end of treatment.

It has been shown that administration of intravenous albumin raises the intravascular fraction of bilirubin (Odell, 1959a and b) and that albumin-enriched exchange transfusion increases the plasma's capacity to hold bilirubin within the extracellular space (Kitchen, Krieger, and Smith, 1960; Odell, Cohen, and Gordes, 1962; Waters and Porter, 1964; Sproul and Smith, 1964; Comley and Wood, 1968) and may decrease the risk of cellular damage (Wood, Comley, and Sherwell, 1970). Since phototherapy was introduced (Cremer, Perryman, and Richards, 1958), it has been shown to lower plasma bilirubin levels in neonatal jaundice (Broughton *et al.*, 1965; Lucey, Ferreiro, and Hewitt, 1968).

The present study was planned to observe the effect of albumin administered intravenously before phototherapy. It was also hoped to discover whether the light acted on the extravascular or intravascular component of bilirubin mass; thus, if light breaks down bilirubin in the extravascular space, then administration of albumin should decrease its effect by withdrawing bilirubin into the intravascular component. Conversely, administration of albumin should enhance the effect of phototherapy if it destroys the bilirubin circulating in the blood stream.

Trial I: Material and Methods

Infants whose plasma bilirubin levels rose above 15 mg/100 ml were allocated alternately to one of two regimens. Infants with haemolytic disease due to rhesus or possible ABO incompatibility (i.e. mother group O, infant group A or B) were excluded from the results.

Group I: Phototherapy for 18 hours only.

Group II: Administration of 1.5 g/kg body weight of human albumin intravenously followed immediately by 18 hours of phototherapy (combined group).

The same light source (Air Shields) and the same distance were maintained.

Total bilirubin was measured by the spectrophotometric method of Scott (1959) and direct bilirubin was measured by a micromodification of the method of Powell (1944).

Albumin solution was reconstituted by adding 100 ml water to 24 g freeze dried albumin (Lister Institute).

Twenty-seven infants were given phototherapy; 23 were given albumin followed by phototherapy. The uneven number was due to rejection of cases which on review might have been ABO incompatible. The 2 groups are evenly matched on birthweight, gestation, pretreatment plasma bilirubin, and age at onset of phototherapy (Fig. 1 and 2).

Results

The effectiveness of treatment was assessed in

FIG. 1.—Birthweight compared with gestation in the two groups. Average number: ○, 23, ●, 27; average gestation: ○, 37.0, ●, 37.2; average BW: ○, 2.69 kg, ●, 2.88 kg.

two ways; firstly the average overall duration of jaundice from birth until the average plasma bilirubin fell to around 12 mg/100 ml, and secondly the average time taken from the start of study to the plasma bilirubin reaching the same level.

Table I shows that the overall duration of jaundice was less in the group given phototherapy only but the difference did not reach a significant level. The rate of fall of bilirubin from the onset of phototherapy was slightly quicker in the group without

TABLE I

Overall Duration of Jaundice

Time (in hours) from birth to fall of bilirubin level to around 12 mg/100 ml

	Mean Duration (1 SD)	Mean Bilirubin Level (mg/100 ml) (1 SD)
Combined group	188 (53.2)	12.6 (0.98)
Phototherapy only group	165 (46.9)	12.5 (1.04)

Difference not significant.
1 SD = 1 standard deviation.

FIG. 2.—Age at onset of therapy. Average age at onset of treatment: ○, 93 hours, ●, 96 hours. Pretreatment plasma bilirubin level (av.): ○, 17.3 mg/100 ml, ●, 17.2 mg/100 ml.

albumin but the difference is not significant (Table II). Direct bilirubin levels remained less than 1 mg/100 ml in all cases.

It was felt that these differences might be enhanced if a longer period of phototherapy were given, so a second trial was planned, and this time the opportunity was taken to include controls in order to show whether delaying phototherapy until the plasma bilirubin level was greater than 15 mg/100 ml could contribute significantly to therapy.

TABLE II

Mean Duration of Jaundice

Time (in hours) from onset of therapy to bilirubin level around 12 mg/100 ml

	Mean Duration (1 SD)	Mean Bilirubin Level (mg/100 ml) (1 SD)
Combined group	95 (65)	12.6 (0.98)
Phototherapy only group	72 (52)	12.5 (1.04)

Difference is not significant.

Trial II: Material and Methods

The criteria for entry was as in Trial I but the infants were allocated to one of three groups by random selection.

Group I: Phototherapy only.

Group II: Administration of albumin at the same dosage as before followed immediately by phototherapy (combined group).

Group III: Controls: these infants had neither phototherapy nor albumin but were subjected to similar nursing care and blood sampling.

Total and direct bilirubin estimations were as in Trial I. Plasma albumin was measured by a modification of the bromocresol green dye binding method of Bartholomew and Delaney (1966). Residual albumin binding capacity (RABC) was measured using the

HBABA dye method of Porter and Waters (1966) and expressed as g albumin reserve/100 ml plasma (Wood *et al.*, 1970). Phototherapy was given for at least 48 hours in the first two groups. If the infants' bilirubin was still above 12 mg/100 ml at the end of 48 hours, then phototherapy was continued until the bilirubin had fallen below this level. Biochemical estimations were carried out at the same intervals in all three groups.

The three groups were reasonably well matched (Fig. 3 and Table III). In addition, the packed cell volume (Table IV) showed comparable changes during the period of study.

The combined group originally contained 9 infants but one required an exchange transfusion when the plasma bilirubin level rose to above 20 mg/100 ml, so

the results are based on the remaining 8. The 8 infants given phototherapy all responded satisfactorily and required no further treatment. Of the 12 controls, 4 had bilirubin levels approaching 20 mg/100 ml and so they were given other forms of treatment, leaving 8 for comparison.

Results

(a) **Plasma bilirubin level and duration of jaundice.** Fig. 4 and Table V showed on this occasion that the controls were jaundiced for a significantly longer time ($P < 0.01$) compared to

FIG. 3.—Age at onset of study. Average age at onset of study: ○, 84 hours, ●, 90 hours, X, 87 hours. Plasma bilirubin level at onset of study (av.): ○, 17.2 mg/100 ml, ●, 16.2 mg/100 ml, X, 15.6 mg/100 ml.

TABLE III
Trial II Composition of 3 Groups

	No.	Mean Birthweight (kg) (1 SD)	Mean Gestation (wk) (1 SD)
Combined	8/9	2.41 (0.38)	37.0 (2.14)
Phototherapy only	8/8	2.76 (0.59)	37.4 (3.42)
Controls	8/12	2.85 (0.94)	36.5 (2.51)

TABLE IV
Mean Packed Cell Volume (venous specimens)

	Before Phototherapy (1 SD)	48 hours (1 SD)
Combined group	56.0 (7.48)	53.7 (7.58)
Phototherapy only	59.7 (5.71)	52.3 (7.46)
Controls	55.6 (6.74)	51.0 (4.90)

FIG. 4.—Average overall duration of jaundice.

TABLE V
Mean Duration of Jaundice:

Time (in hours) from onset of therapy (or observation) to bilirubin level around 12 mg/100 ml

	Mean Duration (1 SD)	Mean Bilirubin Level (mg/100 ml) (1 SD)
Combined group	68.8 (10.6)	11.1 (0.50)
Phototherapy only group	45.9 (15.3)	10.9 (0.80)
Controls	100.9 (26.2)	11.3 (0.522)

The mean duration of jaundice of the phototherapy only group is significantly shorter than either the combined group ($P < 0.02$) or the controls ($P < 0.01$). The combined group's mean duration is significantly shorter ($P < 0.01$) than the controls.

the 2 treated groups. Comparing the 2 methods of treatment the duration of jaundice of those given phototherapy alone was significantly shorter ($P < 0.02$) than the combined group. This is shown graphically in Fig. 5. As before, there were no significant changes in the direct bilirubin levels.

FIG. 5.—Average duration of jaundice from onset of study.

(b) **Residual albumin-binding capacity (RABC).** The difference, either an increase (plus) or a decrease (minus), in RABC levels before and after the 48-hour period of treatment (or observation) in each infant was calculated. These differences were averaged and are given in Table VI with one standard deviation.

TABLE VI
Mean Differences in RABC at End of Phototherapy

	Mean (g/100 ml) (1 SD)	
Combined group	0.786 (0.536)	$\left. \begin{array}{l} \text{P} < 0.02 \\ \text{NS} \end{array} \right\} \text{P} < 0.05$
Phototherapy only group	0.086 (0.331)	
Controls	0.113 (0.494)	

(c) **Plasma albumin level.** The difference in albumin levels is calculated as in (b) above and in Table VII. The phototherapy only group had significantly lower plasma albumin levels than the other two.

Discussion

The long-term results of phototherapy are uncertain. Animal experiments have shown undesirable side effects (Noell *et al.*, 1966; Kuwabara and Gorn, 1968; Sisson *et al.*, 1969), but so far none has been reported in the human though some minor differences in growth pattern of questionable clinical significance have been reported (Hodgman and Teberg, 1970). On the other hand, the risks involved in exchange transfusions are well known.

TABLE VII

Trial II: Mean Difference of Albumin Levels at 48 Hours

	Mean (g/100 ml) (1 SD)	
Combined group	0.56 (0.56)	$\left. \begin{array}{l} \text{P} < 0.01 \\ \text{NS} \\ \text{P} < 0.05 \end{array} \right\}$
Phototherapy only group	-0.38 (0.38)	
Controls	0.175 (0.65)	

It is shown here that in non-haemolytic jaundice, even if phototherapy is delayed until the plasma bilirubin level has reached 15 mg/100 ml, there is still a sufficient time margin for the light to work before the critical level of 20 mg/100 ml is reached. When albumin is combined with phototherapy, plasma bilirubin levels fall more slowly and in one case the treatment failed to control the bilirubin rise and resort was made to exchange transfusion. Albumin therapy raises the RABC and may still have a place in cases where the albumin binding of bilirubin is low and this needs further evaluation.

The results also suggest that phototherapy is effective mainly on extravascular bilirubin and this is in line with the manifest reduction in skin staining when the infant is under the light.

The incidental finding of a decrease in the mean albumin concentration in the group receiving phototherapy alone compared to the control group is only significant at 5% level but is perhaps suggestive of a possible side effect of phototherapy. That these results may not be due to chance is supported by comparing plasma albumin levels in the control and the combined groups. If the combined group had been given albumin only and had not been exposed to light one would have expected the plasma albumin levels to be significantly higher than the controls (Wood *et al.*, 1970) but they were not. This also suggests that phototherapy has some effect on plasma albumin as well as bilirubin levels and justifies speculation.

If this observed decrease in albumin concentration is a true effect of phototherapy, it is unlikely to be due to the direct action of light on albumin since no change in albumin concentration was found when bilirubin and albumin were exposed to light *in vitro* (Wong and Inman, 1971, unpublished). Further, since the alteration in the PCV after 48 hours was similar in all three groups, the observed decrease is unlikely to be due to osmotic effects and fluid shift. It is tempting to speculate therefore that phototherapy may influence the

metabolism of albumin in some way or it may produce an effect on cellular membranes either by a direct effect of light or by the production of substances within the cell which may influence membrane permeability (Ostrow, 1971).

We gratefully acknowledge support for one of us (Y.K.W.) by the endowment Fund of the United Birmingham Hospitals. One phototherapy unit was kindly loaned by Air Shields. Professor T. Whitehead gave much help and advice on the biochemical aspects and Dr. John Waterhouse on the statistical side of the study. We are grateful to the residents and nursing staff of the neonatal unit at the Birmingham Maternity Hospital for care of the infants during the period.

REFERENCES

- Bartholomew, R. J., and Delaney, A. M. (1966). Sulphonphthalins as specific reagents for albumin: determination of albumin in serum. *Proceedings of the Australian Association of Clinical Biochemists*, **1**, 214.
- Broughton, P. M. G., Rossiter, E. J. R., Warren, C. B. M., Goulis, G., and Lord, P. S. (1965). Effect of blue light on hyperbilirubinaemia. *Archives of Disease in Childhood*, **40**, 666.
- Comley, A., and Wood, B. (1968). Albumin administration in exchange transfusion for hyperbilirubinaemia. *Archives of Disease in Childhood*, **43**, 151.
- Cremer, R. J., Perryman, P. W., and Richards, D. H. (1958). Influence of light on the hyperbilirubinaemia of infants. *Lancet*, **1**, 1094.
- Hodgman, J. E., and Teberg, A. (1970). Effect of phototherapy on subsequent growth and development of the premature infant. In *Bilirubin Metabolism in the Newborn*. (Birth Defects: Original Article Series, Vol. VI, No. 2), p. 75. Ed. by D. Bergsma. Williams and Wilkins (for National Foundation—March of Dimes), Baltimore.
- Kitchen, W. H., Krieger, V. I., and Smith, M. A. (1960). Human albumin in exchange transfusion. *Journal of Pediatrics*, **57**, 876.
- Kuwabara, T., and Gorn, R. A. (1968). Retinal damage by visible light: an electron-microscopic study. *Archives of Ophthalmology*, **79**, 69.
- Lucey, J., Ferreiro, M., and Hewitt, J. (1968). Prevention of hyperbilirubinemia of prematurity in phototherapy. *Pediatrics*, **41**, 1047.
- Noell, W. K., Walker, V. S., Bok Soon Kang, and Berman, S. (1966). Retinal damage by light in rats. *Investigative Ophthalmology*, **5**, 450.
- Odell, G. B. (1959a). Studies in kernicterus I. The protein binding of bilirubin. *Journal of Clinical Investigation*, **38**, 823.
- Odell, G. B. (1959b). The dissociation of bilirubin from albumin and its clinical implications. *Journal of Pediatrics*, **55**, 268.
- Odell, G. B., Cohen, S. N., and Gordes, E. H. (1962). Administration of albumin in the management of hyperbilirubinemia by exchange transfusions. *Pediatrics*, **30**, 613.
- Ostrow, J. D. (1971). Photocatabolism of labeled bilirubin in the congenitally jaundiced (Gunn) rat. *Journal of Clinical Investigation*, **50**, 707.
- Porter, E. G., and Waters, W. J. (1966). A rapid micromethod for measuring the reserve albumin binding capacity in serum from newborn infants with hyperbilirubinemia. *Journal of Laboratory and Clinical Medicine*, **67**, 660.
- Powell, W. N. (1944). A method for the quantitative determination of serum bilirubin with the photoelectric colorimeter. *American Journal of Clinical Pathology*, **14**, (Tech. Sect., 8), 55.
- Scott, P. (1959). An ultramicromethod for the estimation of plasma bilirubin in neonates. *Newsletter of the Association of Clinical Biochemists*, No. 24, November 1959, p. 11.
- Sisson, T. R. C., Glauser, S. C., Glauser, E. M., Tasman, W., and Chulkarat, P. (1969). Retinopathy due to phototherapy in newborn piglets. *Federation Proceedings*, **28**, 440.
- Sproul, A., and Smith, L. (1964). Bilirubin equilibration during exchange transfusion in hemolytic disease of the newborn. *Journal of Pediatrics*, **65**, 12.
- Waters, W. J., and Porter, E. (1964). Indications for exchange transfusion based upon the role of albumin in the treatment of hemolytic disease of the newborn. *Pediatrics*, **33**, 749.
- Wood, B., Comley, A., and Sherwell, J. (1970). Effect of additional albumin administration during exchange transfusion on plasma albumin-binding capacity. *Archives of Disease in Childhood*, **45**, 59.

Correspondence to Dr. B. S. B. Wood, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET.