BIOCHEMICAL CHANGES DURING EXCHANGE TRANSFUSION IN HYPERBILIRUBINEMIA IN TERM NEWBORN BABIES

AMIT JAIN, D. PURI*, and M.M.A. FARIDI

Departments of Pediatrics and Biochemistry*, University College of Med. Sciences & Guru Teg Bahadur Hospital, Delhi 110 095

ABSTRACT

Double volume (170 ml/kg body weight) exchange transfusion was done in 52 term infants in the first week of life for neonatal hyperbilirubinemia. The M:F ratio was 1.08:1 and 37 (71.1%) babies were of low birth weight. Causes of jaundice were hemolytic in 46.2% and non-hemolytic in 41.3% cases; in 13.5% babies no cause of jaundice could be found. After exchange transfusion a fall of 14.6% and 47.4% was observed in the hemoglobin and serum bilirubin levels respectively. There was significant ($p=0.0414$) rise in the mean mid exchange and post-exchange serum sodium levels as compared to pre-exchange values and it was found to be due to higher donor's serum sodium levels ($p=0.007$). There was no effect on the serum potassium levels during or after ET.

In general serum calcium levels significantly increased at mid-exchange period ($p=0.0029$) but post-exchange levels were same as pre-exchange. Donor's serum calcium level had no effect on the infant's serum calcium level ($p=0.993$). There was no change in the serum phosphate and blood urea levels during and after exchange-transfusion. The plasma glucose was significantly raised during and after ET and plasma glucose of the donors had significant effect on the infant's plasma glucose levels ($p=0.043$). Similarly plasma osmolality also showed significant increase during and after ET which was due to the effect of donor's plasma osmolality ($p=0.007$).

INTRODUCTION

Neonatal hyperbilirubinemia with mild to moderate elevation of serum bilirubin levels is generally considered to be an innocuous state. However, if serum bilirubin levels exceed a dangerous limit, that varies with birth weight, gestational age, chronological age and internal milieu of the body, bilirubin may cross blood brain barrier and bilirubin encephalopathy results. Kernicterus, a pathological description of bilirubin encephalopathy, rarely occurs when serum bilirubin levels are below 18-20 mg% term infants (1).

Despite advent of phototherapy as a therapeutic modality, exchange transfusion (ET) plays a significant role in the treatment of neonatal hyperbilirubinemia by eliminating serum bilirubin

quickly. In ET infant's blood is exchanged with adult blood by conventional discontinuation technique in 10 ml aliquotes. Total volume of donor's blood infused is usually double (170 ml/kg body wt) the total blood volume of the infant (85 ml/kg body wt) and it replaces about 87% of the infant's blood (1). A significant proportion of serum bilirubin is removed from the body which ensures immediate protection against the imminent bilirubin toxicity (2). Although it is considered to be a safe undertaking, many changes take place in various serum biochemical parameters, plasma osmolality and electrolyte profile in the recipient infants which may give rise to post operative complications including death, syncope and serious ECG changes. These changes result due to procedure per se and to infusion of large volume (170 ml/kg body wt) of adult blood that is qualitatively different from that of an infant (2,3,4,5). Many biochemical alterations following ET have not been studied in detail, hence this study.

Address for correspondence :

Dr. M.M.A. Faridi, Prof. of Paediatrics, at above address.

MATERIALS AND METHODS

The present prospective study was undertaken in the Neonatal Intensive Care Unit, Dept. of Pediatrics and Dept. of Biochemistry. Only term newborn infants of both sexes born at 37 to 41 completed weeks of gestation, calculated from last date of menstrual period of their mothers, in whom double exchange blood transfusion was done in the early neonatal period (age <7 days) by one of us (AJ) according to Cockington's criteria (6), were included in the study. Babies in whom partial exchange transfusion was done earlier or where ET was done with single or 1.5 volume of blood were excluded. In all 52 newborns fulfilled the criteria of inclusion with M:F of 1.08:1.

Complete history of pregnancy and delivery was elicited, birth weight of babies was recorded by electronic weighing scale (Secca, Germany), complete examination of the babies was carried out and breast feeding was offered within two hours of birth. When clinical jaundice was observed and baby fulfilled Cockington's criteria (6) for ET, following parameters were studied:

Before ET: Hemoglobin, blood urea, plasma glucose, serum electrolytes, total serum calcium, serum phosphate and plasma osmolality were measured in the first aliquot of blood drawn from the baby and in the donor's blood.

Mid-ET: All the above parameters in the baby's blood were estimated when 50% of the donor's blood was exchanged.

Post-ET: At the end of the procedure the last aliquot of blood drawn from the baby was collected and all the above parameters were estimated.

ET was done by standard method through umbilical route (1,2). An aliquot of 10 ml of blood was removed from the infant's body and the same amount of donor's blood was infused. The procedure was carried out with alternate removal of infant's blood and infusion of donor's blood with written record till whole of the donor's blood was transfused. The whole procedure took about 45 to 60 minutes. The donor's blood was collected 96-120 hours before ET in 17.3% cases while in 13.5% cases $\leq$ 48 hour old blood was used. In 69.2% cases

the blood was collected between 2 to 4 days prior to ET.

Serum electrolytes were estimated by micro-analyser (AVL 984-5). Total serum calcium was estimated by autozyme calcium kits and serum phosphate was measured by modified method of Fiske and Subbarow (7). Plasma glucose was done by Glucose-oxidase method using Ranbaxy kits; blood urea was estimated by Netelson method (8). Plasma osmolality was calculated by the following formula (9):

$$\text{Osmolality (mosm/l)} = 2[\text{Na}^+] (\text{mEq/l}) + [\text{Glucose}]18(\text{mg}\%) + \text{BUN}/2.8$$

The p value and significance for various biochemical parameters was calculated by one way analysis of variance with Tukey and Duncun tests and regression analysis was applied for analyzing effect of donor's blood; the data was processed on SPSS-PC computer version 5.

RESULTS AND DISCUSSION

Out of 52 neonates 71.1% were of low birth weight (<2500 gm). Cause of jaundice was hemolytic in 46.2% cases, with ABO blood group incompatibility accounting for 30.8% and Rh-incompatibility for 13.5% cases. Oxytocin induction/augmentation of labor was responsible for hemolytic jaundice in 1.9% cases only. Nonhemolytic causes of jaundice were septicemia (17.3%), cephalhematoma (3.8%) and low birth weight per se (19.2%) and no cause could be found in 13.5% cases. Most of the babies required ET between 24 to 72 hours of age (71.2%); 4 (7.7%) babies were between 4 and 7 days and one baby was subjected to ET with in 24 hours of birth. There was a fall of 14.6% in the hemoglobin level after ET which was higher in hemolytic cases (17.3%) in comparison to non-hemolytic cases (14.9%). A fall of 47.4% was observed in the serum bilirubin level which was slightly higher in the non-hemolytic cases (48.47% vs 46.1% in hemolytic cases). These observations are in conformity with other workers (1,2,5,13). The results of various parameters analysed are given in tables 1 and 2.

Table 1. Effect on electrolyte and biochemical parameters during and after exchange transfusion (ET) (N=52).

Time at ET Parameters	n=52 x $\pm$ SD	Significance
Pre ET Serum Sodium (mEq/l)	146.22 $\pm$ 5.66	P=0.0414
Mid ET Serum Sodium (mEq/l)	147.63 $\pm$ 5.32	
Post ET Serum Sodium (mEq/l)	148.83 $\pm$ 3.88*	
Pre ET Serum Potassium (mEq/l)	4.97 $\pm$ 1.27	N.S.
Mid ET Serum Potassium (mEq/l)	4.98 $\pm$ 1.08	
Post ET Serum Potassium (mEq/l)	4.74 $\pm$ 0.78	
Pre ET Serum Calcium (mEq/l)	9.08 $\pm$ 0.86	P=0.0029
Mid ET Serum Calcium (mEq/l)	9.73 $\pm$ 0.82*	
Post ET Serum Calcium (mEq/l)	9.31 $\pm$ 1.19	
Pre ET Serum Phosphate (mEq/l)	6.62 $\pm$ 1.69	P=<0.01
Mid ET Serum Phosphate (mEq/l)	6.46 $\pm$ 1.59*	
Post ET Serum Phosphate (mEq/l)	6.42 $\pm$ 1.59*	
Pre ET Plasma Glucose (mEq/l)	123.63 $\pm$ 68.48**	P<0.001
Mid ET Plasma Glucose (mEq/l)	166.10 $\pm$ 59.96**	
Post ET Plasma Glucose (mEq/l)	189.62 $\pm$ 57.04	
Pre ET Blood Urea (mEq/l)	44.00 $\pm$ 15.53	NS
Mid ET Blood Urea (mEq/l)	39.88 $\pm$ 14.98	
Post ET Blood Urea (mEq/l)	41.88 $\pm$ 14.44	
Pre ET Plasma Osmolality (mEq/l)	294.73 $\pm$ 10.84	P=0.0009
Mid ET Plasma Osmolality (mEq/l)	298.06 $\pm$ 11.00	
Post ET Plasma Osmolality (mEq/l)	302.31 $\pm$ 8.36	

Sodium: The mean pre-exchange transfusion serum sodium level was on higher side of the normal range (146.32 $\pm$ 5.66 mEq/l) possibly because the physiological loss of water in neonates is significant at this age (10). In the donor's blood the mean serum sodium level was high (156.99 $\pm$ 6.39 mEq/l) as a result of blood storage (11). There was rise in the mean mid-exchange (147.63 $\pm$ 5.32 mEq/l) and post-exchange (148.83 $\pm$ 3.88 mEq/l) serum sodium concentrations; the latter was significantly higher than the mean pre-exchange level (p=0.0414; Table 1,2). The progressive rise is attributed to the hyperosmolar sodium concentration in the donor's blood (p=0.007). These observations are in agree-

ment with those of the earlier workers who reported a transient but significant hypernatremia (11,12). Hypernatraemia increases the osmotic pressure which may lead to nervous disturbances by causing cerebral edema (10). Fernandez (13), however, did not observe any such significant alterations during exchange transfusion. The age of the donors' blood and chronological age of the infants, did not affect serum sodium.

Potassium: In the present study the mean serum potassium level in the donor's blood was observed to be very high (9.20 $\pm$ 2.54 mEq/l). This is in line with earlier reports that serum potassium

Table 2. Effect of Donor Blood on various neonatal pre and post exchange transfusion (ET) electrolyte and biochemical parameters.

Indices	Pre ET (n=52)	Post ET (n=52)	Donor (n=52)	Regression Equation	P-value
Serum Sodium (mEq/l)	146.32± 5.66	148.83± 3.88	156.99± 6.39	(Post-pre) S.Na=(0.24* Donor S. Sodium)±40.40	0.007
Serum Potassium (mEq/l)	4.97± 1.27	4.74± 0.78	9.20± 2.54	-	0.081
Serum Calcium (mg/dl)	9.08± 0.86	9.31± 1.19	7.75± 0.68	-	0.993
Serum Phosphorus (mg/dl)	6.62± 1.69	6.42± 1.59	6.21± 1.54	-	0.928
Plasma glucose (mg/dl)	123.63± 68.48	189.62± 57.04	280.88± 59.33	(Post-pre) Plasma glucose= (0.26* Donor Plasma glucose)± (8.57)	0.043
Blood Urea (mg/dl)	44.00± 68.48	41.88± 14.44	32.29± 11.49	-	0.864
Plasma Osmolality (mosm/kg)	294.73± 10.84	302.31± 8.36	319.14± 11.42	(Post-pre) P.Osmolality= (0.29* Donor P.Osmolality)± 99.49	0.007

levels increased with age of the stored blood due to passage of potassium from the erythrocytes to plasma (11,14,15). However, no significant rise in the recipient's blood was observed with its infusion in the present study ($p=0.081$; Table 1,2). The mean mid-exchange (4.98 ± 1.08 mEq/l) and post-exchange (4.74 ± 0.78 mEq/l) levels were also not significantly different from the mean pre-exchange level (4.97 ± 1.27 Eq/l). These results are in contrast with some earlier reports that infusion of stored blood elevates serum potassium concentration and that the hyperkalaemia gets further augmented due to decreased renal potassium excretion in infants and to subsequent development of acidosis (14,15,16).

Distribution kinetics of intravenously administered potassium reveal that transfer of potassium from plasma to other tissues is rapid (15). Hence even though ET was done with hyperkalemic donor blood, it did not elevate the serum potassium concentration, probably due to rapid transfer of the latter to other compartments which counteracted any rise in serum potassium concentration. Potassium is chiefly an intracellular cation; small rise in the tissue concentration of potassium may not produce any clinical manifestation. Further, there was no effect of the chronological age or date of collection of donors' blood on the serum potassium.

Calcium: The measurement of serum total calcium levels during the course of exchange transfusion showed an initial rise so that the mean mid-exchange level (9.73 ± 0.82 mEq/L) increased significantly ($p=0.0029$) compared to the mean pre-exchange level (9.08 ± 0.86 mEq/L), in spite of low mean serum calcium level in the donor's blood (7.75 ± 0.68 mg%). However, there was a subsequent fall in the mean post-exchange value (9.31 ± 1.19 mg%) which was not found to be significantly different ($p>0.05$) from the mean pre- and mid-exchange values. The initial rise had been observed by earlier workers also (13) and was reported to be due to the administration of calcium gluconate (100 mg for every 100 ml exchanged blood) in order to counteract any fall in serum ionized calcium levels (17,18,19). Such fall occurs due to calcium chelating properties of citrate which is present in high concentration in the donor's blood where it is used as an anticoagulant (19,20). However, in the present study calcium gluconate was not administered at all (1). Increase in the mean mid-exchange total serum calcium level was possibly due to a rapid rise in serum citrate concentration which has a calcium mobilizing effect on bones (1,3,17). Later the citrate metabolism stepped up and serum levels were stabilized or even fell marginally. This explains no further elevation or rather a subsequent marginal fall in the serum total calcium levels.

Phosphate: The mean pre-exchange serum phosphate concentration was 6.62 ± 1.69 mg% which showed a gradual fall during the course of the procedure. The mean mid-exchange value dropped to 6.46 ± 1.59 mg% and the mean post-exchange value showed a slight further fall (6.42 ± 1.59 mg%). All the values were, however, in the normal ranges only and were not clinically significant. There have been no previous reports of the effect of exchange transfusion on serum phosphate levels. The progressive fall observed in the present study is probably secondary to alterations in the serum calcium levels discussed above.

Glucose: In the donor's blood the plasma concentration was high due to use of citrate-phosphate-dextrose (CPD) as an anticoagulant and preservative.

This has a significant hyperglycaemic effect on the blood glucose levels of the recipient infants whose 87% blood is replaced by the CPD blood during course of exchange transfusion (13,21). In the present study it was observed that there was a progressive rise in the plasma glucose concentration and the mean mid-exchange (166.1 ± 59.96 mg%) and post-exchange values (189.62 ± 57.04 mg%) were significantly higher than the mean pre-exchange (123.63 ± 68.4 mg%) level. Hyperglycaemia brings about increased plasma insulin levels and gradual progressive fall in the plasma glucagon levels which may lead to rebound hypoglycaemia (20, 21, 22). In spite of hypoglycaemic effects of the above hormonal changes, a significant rise in the plasma glucose levels was brought about during the procedure without any incidence of rebound hypoglycaemia.

Urea: The mean pre-exchange blood urea level was (44.0 ± 15.53 mg%) which was not statistically different from that of donor's blood (32.29 ± 11.4 mg%). The exchange transfusion did not produce any significant change in the blood urea concentration in the infants at any point; the mid-exchange (39.88 ± 14.98 mg%) and post-exchange (41.88 ± 14.44 mg%) values not being significantly different from the initial pre-exchange value.

Osmolality: There was a progressive increase in the plasma osmolality from the pre-exchange value of 294.73 ± 10.84 m.osm/kg. The mean mid-exchange value (298.06 ± 11.00 m.osm/kg) showed a slight rise only, whereas the mean post exchange value (302.31 ± 8.36 m.osm/kg) rose significantly higher than the pre-exchange value ($p=0.0009$). Increase in the plasma osmolality was due to increase in plasma glucose and serum sodium concentration in the recipient's blood during the procedure. Moreover, infusion of a large volume of hyperosmolar donor blood (319.14 ± 11.42 m.osm/kg) also had a significant effect in raising the osmolality of the recipient's blood ($p=0.007$). Similar observations were made by Boda et al (10) who reported a transient but substantial rise in osmotic pressure.

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