EXCHANGE TRANSFUSION IN SEPTIC NEONATES WITH SCLEREMA: EF FECT ON IMMUNOGLOBULIN AND COMPLEMENT LEVELS

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Manuscript received: M arch 26, 1996; Initial review com pleted: May 24, 1996; Revision accepted : August 14, 1996

Objective: To study the ef fect of exchange transfusion (ET) on the level s of immunoglob ulins (Ig) and C, in neonatal sepsis with sclerenm. Design: Randomiz ed controlled trial in a referral neonatal unit of a teaching hospital. Su bjects: Consecutive culture positive septic neonates with sclerema were enrolled and were randomized to undergo ET (study group, n=20) or no ET (controls, n=20). Results: Mortality was 50% in the study group and 95% in controls. Gram negative organisms acc ounted for 85% in study group and 90% in controls. IgG, IgA and IgM levels rose significantly while C, levels did not show significant rise 12 -24 hours after ET. I g and C, levels did not change significantly in the controls. ***Conclusion:*** *ET with fresh whole blood in septicemic newborns with sclerema improves survival, particularly in the more premature group and significantly enha nces, IgG, IgA an d IgM levels.*

Key words: *Exchange transfusion, Immu noglobulin, Complement, Septicemia, Neonate.*

SEPTICE MIA is a freque nt and serious event which thre atens surviva l durin g the first four weeks of life(l-4). The newborn infant, especia lly pret erm, has markedly decreased serum levels of C_3, C_y properdin and factor B, all key elements in alternative pathway of complement(5,6). They have markedly decreased serum levels of IgM and IgA at birth. Although IgG may be normal in term infants, it is low in preterms(5-8). Because of low levels of antibody and complement, there is defective generation of chemotactic factors and abnormalities of opsonization leading to life threatening bacterial in fections(5).

Exchange transfusi on (ET) has been performed in cases of neonatal sepsis with sclerema(9-11), respiratory distress syn-Drome(11), disseminat ed intra vascular coagul ation(ll,12) and neutropenia(13). However, the efficacy of exchange transfusion in neonatal sepsis has not been thoroughly evaluated(14) and there is a paucity of controlled evaluation of the effects of ET(14) particularly on the levels of immunoglobuln and complement in severe neonatal septicem ia. This prompted us to undertake the present s tudy.

Subjects and Methods

This prospective study was done on neonates adm itted in the referr al neon atal unit of Lok Nayak Hospital, New Delhi which predom inantly serves the poorer strata of the s ociety. The neonates are mostly referred from hospitals with poor facili-

ties for neonatal care and are brought late in critically sick condition. The inclusion criteria were clinical features of sepsis with presence of sclerema, and a positive blood culture. Prior informed consent was obtained. The study was approved by the Institutional Research Committee. Consecutive cases of neonatal septicemia with sclerema were enrolled and randomized (random numbers) to undergo ET (Study group) or no ET (Control group) in addition to antibiotic and other supportive therapy. Blinding was not feasible. However, the investigator performing immunoglobulin and C_3 estimation was blinded to the randomization group. Therapy as per the randomized group was instituted immediately on hospitalization. Subjects in whom clinical impression of septicemia was not substantiated by microbiological culture were excluded from the study. A sample size of 20 in each group was predecided in view of the expensive tests involved.

A double volume ET with cross matched adult whole blood was done once in the study group. The anticoagulant used in donor blood was CPD Adeninie. The donor blood was tested for HBsAG and HIV. As a policy, the donor blood was taken only from the hospital blood bank, which accepts blood only from relative or voluntary donors. The rest of the management was essentially similar in both the groups. None of the babies in the control group required exchange transfusion for jaundice. Phototherapy or blood transfusion were given to neonates of both the groups whenever required.

Blood was drawn for immunoglobulin and complement levels twice from controls (at inclusion and 12-24 hours later), once from donors and before and 12-24 hours after ET in the study group. Blood for immunoglobulin and complement levels was collected and transferred to capped bottles and allowed to clot. The immunoglobulin and C_3 levels were quantified by single radial immunodiffusion technique using limit diffusion in agar gel. Tripartigen plates (Behring, Hoechst India, Bombay) were used for quantification of immunoglobulins. Complement was quantified using NOR Partigen C, plates (Behring, Hoechst India, Bombay). The control sera for immunoglobulin and complement (Behring, Hoechst India, Bombay) had a concentration of IgG 1250 mg/dl, IgA 23E mg/dl, IgM 96 mg/dl and C_3 0.9 g/1. Low concentrations of IgA and IgM undetectable by tripartigen plates were measured by counter immunoelectrophoresis (CIEP).

Statistical analyses included Pearson chi-square test, Fisher's exact test, Wilcoxon signed rank test and Mantel Haenszel's test for linear association.

Results

Twenty neonates with bacterial sepsis and sclerema underwent ET. Twenty septicemic neonates with sclerema served as controls.

Gram negative organisms accounted for 85% cases in the study group and 90% in controls. *Klebsilla* and E. *coli* contributed to 45% of cases in both the groups. The clinical profile in the study and control group were comparable ($p > 0.05$) with regard to age, mean weight, sex, gestational age, intrauterine growth, associated pneumonia, meningitis, hypoglycemia, mean base excess, shock, acidosis and baseline immunoglobulin and complement levels *(Table I)*. Mortality was 50% in the study group and 95% in controls. This difference was statistically significant ($p=0.0046$). There was no death related to exchange transfusion.

IgG, IgA and IgM levels rose significantly 12-24 hours after ET. Levels of C, did not rise significantly after ET. In the control group, the levels of immunglo-

TABLE I–*Population characteristic of study and control group.*

Parameter	Study group (n=20)	Contol group (n=20)
Home delivery	9	6
Age < 4 days	14	16
Male	12	15
Weight (mean ± SD)	1.56±0.58	1.64±0.46
Gestational age < 37 wks	15	15
Small for gestational age	7	8
Associated pneumonia	9	4
Associated meningitis	1	1
Blood sugar < 45 mg/dl	6	7
pH (mean ± SD)	7.126±0.133	7.164±0.099
Base excess (mean ± SD)	−14.49±5.33	−13.58±4.37
IPPV (No.)	8	4
IPPV (h)	36±21.98	22.50±18.57
Dopamine (No.)	11	7
Dopamine (h)	35.45±29.81	31.71±31.51

IPPV–Intermittent positive pressure ventilation.

bulins and C_3 did not change significantly over the next 12-24 hours *(Table II).* Blood transfusion was not required for any neonate during this period in the control group. Levels of immunoglobulins and C, in the donor blood (mean ± SD) were as follows: IgG-11.76 ± 4.37 g/1, IgA-2170.4 ± 728.2 mg/1, IgM-2041.2 ± 924.4 mg/1 and C_3-780± 200 mg/1.

Following exchange transfusion, the best survival in 28-32 weeks gestation group was 75% as compared to 43% and 20% in 33-36 weeks and >36 weeks gestation groups, respectively. No such difference was observed in the controls (*Table III).*

The effect of ET on immunoglobul in and C_3 levels was analyzed in different gestational age groups. The IgG levels rose significantly at 12-24 hours in 28-32 weeks group only. IgA and IgM levels rose significantly only in 32-36 weeks group. There was no significant increase in C, levels. *(Table IV).*

Discuss ion

Incomplete development of the host defence system of the neonate is largely responsible for the high mortality in neonatal sepsis. IgA, IgM and C_3 are not transferred transplacentally. Transfer of IgG occurs progressively, particularly after 20 weeks gestation and levels are low in premature infants. Several workers have attempted to compensate for these defects by performing ET (9-13,15-18). Improved survival following ET has been reported in neonatal septicemia with sclerema but immunological benefits associated with such improved survival have not been well documented.

In the present study, IgG, IgM and IgA levels rose significantly after ET. In one case, IgG level was 3 g/1 which rose to llg/1 12-24 hours after ET and the patient survived. In eight cases, pre exchange levels of IgG rose from <5 g/1 to a mean of 9.28 g/1 12-24 hours after ET and five out of these eight patients survived. Thus there was an overall significant increase in IgG levels following ET, and the increase was more marked in those with low baseline IgG levels. This may be attributed to the higher levels of immunoglobulins in the donor blood.

An earlier study(19) on 56 septicemic neonates documented improved survival (54% vs 18% in controls) and a definite rise

TABLE II–*Effect of Exchange Transfusion on Immunoglobulin and Complement Levels.*

Parameter	Study group		Wilcoxon signed rank test value	Control group		Wilcoxon signed rank test value
	Baseline	After 12-24 h		Baseline	After 12-24h	
IgG (g/l) Mean±SD (range)	8.753±5.175 (3.021-21.25)	11.396±4.195 (5.85-19.933)	<0.01	9.152±5.175 (2.505-18.021)	8.943±5.711 (1.88-20.588)	> 0.05
IgA (mg/l) Mean±SD (range)	185.9±319.1 (11.8-1189.0)	1101.5±756.4 (253-3384)	<0.01	244.2±402.4 (11.8-1689.0)	319.6±436.4 (118-1756)	=0.05
IgM (mg/l) Mean±SD (range)	666.3±1204.7 (19.2-4367.9)	1474.8±1204.7 (394.8-3231.6)	<0.01	419.43±652.2 (9.6-2674.2)	500.1±7094 (19.2-3135.6)	>0.05
C3 (mg/l) Mean±SD (range)	506±185 (164-900)	624±238 (246-1390)	>0.05	476±409 (105-1440)	542±345 (164-1290)	>0.05

TABLE III–*Mortality After Exchange Transfusion in Relation to Gestational Age.*

Gestational age (weeks)	Study group			Control group		
	Number	Survival (%)		Number	Survival (%)	
28-32	8	6	(75)	6	0	(0)
33-36	7	3	(43)	9	1	(11)
> 36	5	1	(20)	5	0	(0)

p <0.05 (Mantel-Haenszel's test for linear association).

in mean levels of IgG, IgA, IgM and C_3 levels after ET. Another study(10) on 10 septicemic neonates with sclerema showed improved survival after ET (70%). The immunoglobulin and complement levels were quantified before and after ET in 5 neonates. The IgA and IgM rose significantly but IgG did not change significantly while C_3, C_4 and CH_{50} showed a inconsistent and insignificant rise. Similarly, documented by another group (20). In the current study too, no significant change was evident in C_3 levels after ET.

An interesting observation in the present study was greater improvemen t in survival after ET in more premature group (28-32 wks gestation) compared to those with gestation >32 weeks. Probably providing immunological components through ET to the immunological ly immature preterm with sepsis assumes greater importance in their management. In septic neonates, administration of intravenous immunoglobulins proved more beneficial in the premature groups as compared to the term group(21). However, ET may provide other advantages like removal of bacteria and bacterial toxins, increase in the pool of normal neutrophils, improvement in perfusion and tissue oxygenation and decrease in hemorrhagic complications(22). Thus ET is

TABLE IV–*Effect of Exchange Transfusion on Immediate and 12-24 h Post Exchange Immunoglobulin and Complement Levels in Relation to Gestational Age.*

Parameter	Weeks of gestation (n)	Pre-exchange	12-24 h post exchange	Wilcoxon signed rank test value
IgG (g/l) Mean±SD (range)	28-32 (8)	5.949±2.321 (3.021-9.58)	9.064±3.259 (6.288-16.18)	<0.05
	33-36 (7)	9.803±5.876 (4.183-21.25)	11.586±4.26 (4.183-16.788)	>0.05
	> 36 (5)	11.769±6.079 (4.183-20.588)	13.997±4.769 (8.60-19.933)	>0.05
IgA (mg/l) Mean±SD (range)	28-32 (8)	324.8±428.4 (11.8-1189)	1231.9±1028 (302-3384)	>0.05
	33-36 (7)	110.2±239.7 (11.8-653)	927.3±636.6 (253-2251)	<0.05
	> 36 (5)	69.5±102.6 (23.6-253)	1136.9±413.6 (702-1605.5)	>0.05
IgM (mg/l) Mean±SD (range)	28-32 (8)	998.5±1711.9 (19.2-4368)	1301.3±945.2 (394.8-3131.6)	>0.05
	33-36 (7)	412.2±817.8 (48-2243.2)	1918±801.9 (884.4-3231.6)	<0.05
	> 36 (5)	490.7±624.2 (19.2-1402.8)	1130.6±425.7 (767.1-1864)	<0.05
C3 (mg/l) Mean±SD (range)	28-32 (8)	565±143 (427-859)	603±233 (246-982)	>0.05
	33-36 (7)	430.0±151.0 (164-595)	675.0±324.0 (459-1390)	>0.05
	> 36 (5)	516±274 (190-900)	584±91 (492-705)	>0.05

an inexpensive and simple mode of immunotherapy in neonatal sepsis, particularly useful for the developing world.

In conclusion, our study suggests that ET with fresh whole blood in septicemic newborn infants with sclerema improves survival, particularly in the more premature group and significantly IgG, IgA and enhances IgM levels.

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