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ORIGINAL ARTICLE

Double Volume Exchange Transfusion in Severe Neonatal Sepsis

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Abstract
Objectives To study the efficacy and safety of double volume exchange transfusion (DVET) in neonates>1000 g birth weight with severe sepsis.
Methods Eighty-three neonates weighing >1000 g with severe sepsis were randomly assigned to DVET or standard therapy (ST) group. Primary outcome was mortality by 14 d from enrollment.
Results A 21 % reduction in mortality, albeit non-significant, by 14 d from enrollment was observed in DVET group in comparison to ST group [RR: 0.79 (95 % C.I 0.45–1.3); *p* 0.4]. A similar trend in mortality reduction was observed with early mortality and mortality by discharge in DVET group. No difference was observed in normalization of dysfunctional organs by 14 d. Cardiovascular and hematological system benefitted the most, followed by renal dysfunction with DVET. A significant improvement in post DVET IgG, IgA, IgM, C3 and base deficit was observed. No serious adverse effects occurred following DVET.
Conclusions In neonates >1000 g with severe sepsis, DVET was associated with a trend towards decrease in mortality by 14 d from enrollment. A significant improvement in immunoglobulin and complement C3 levels and acid base status were observed following DVET. DVET is a safe procedure in severely sick and septic neonates.

Keywords Double volume exchange transfusion · Mortality · Neonate · Organ dysfunction · Severe sepsis

Introduction

Sepsis is an important cause of morbidity and mortality in the neonatal period. Early recognition, timely administration of appropriate antibiotics and good supportive care form the mainstay of management in neonatal sepsis [1, 2]. Various adjunctive therapies have been tried in neonatal sepsis without any proven benefit [3, 4]. Double volume exchange transfusion (DVET) removes bacterial toxins and pro-inflammatory cytokines from the blood and replaces with fresh and immunologically replete blood thereby leading to improvement in tissue perfusion and oxygenation. Despite these theoretical benefits, evidence for clinical efficacy and safety of DVET has not been rigorously evaluated. Out of 11 controlled trials (3 randomized and 8 non-randomized) done in 570 neonates, six have shown a significant improvement in survival in the DVET group in comparison to no DVET [5–14]. However, all studies were heterogeneous with regards to patient characteristics, eligibility criteria, stage and severity of sepsis at enrollment, study design and steps taken to minimize the bias, type of blood used and outcomes analyzed. Hence, this randomized, controlled trial was conducted to compare the efficacy of DVET with standard therapy (ST) in reducing mortality by 14 d from enrollment in neonates >1000 g with severe sepsis.

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Material and Methods

This study was conducted in the level III neonatal unit of a tertiary care referral hospital of Northern India between February 2012 and March 2014. Inborn neonates with birth weight>1000 g and with objective evidence of severe sepsis (clinical signs of infection plus biochemical/radiological/microbiological evidence of infection plus objective evidence of organ dysfunction) in the first 28 d period were considered eligible for enrollment. Evidence of infection was defined as presence of any one of the following: blood or cerebro-spinal fluid (CSF) culture positive for a microorganism, chest x-ray suggestive of pneumonia, CSF examination suggestive of meningitis or sepsis screen positive. Apart from the above stated parameters, neonates with sclerema and refractory metabolic acidosis (metabolic acidosis in two blood gases repeated 6 h apart) that were not explained by a non-infective pathology were also considered as having evidence of infection. Organ dysfunction was defined as per pre-defined published criteria, modified for neonates [15]. Neonates who were requiring more than two vasoactive drugs for stabilization of the shock, with a platelet count in the previous 24 h of <20, 000 per mm^3 and/or with significant non-mucosal clinical bleed (grade 3 or more intraventricular hemorrhage, pulmonary hemorrhage and intraperitoneal hemorrhage), those with major life threatening malformations and those who were terminally ill were excluded. An informed, written consent was obtained prior to enrollment from one of the parents and the Institute Ethics Committee approved the trial. This clinical trial was registered with the Clinical Trials Registry- India (CTRI number –CTRI/2012/09/003014).

The level of sickness at baseline was assessed using the Score for Neonatal Acute Physiology version II (SNAP-II). These neonates were then randomly allocated to DVET group or ST group using a web based random sequence generator [16]. Random allocations were concealed by placing the allocation sequence in serially numbered, tamper proof, opaque and sealed envelopes. Random allocation was done separately for two strata (Strata 1 – 1000 to 1999 g and Strata 2 – 2000 g and above) in a blocked fashion with blocks of varying size [4, 6, 8]. Masking the treating team and the investigators was not possible due to the nature of the intervention. However, the

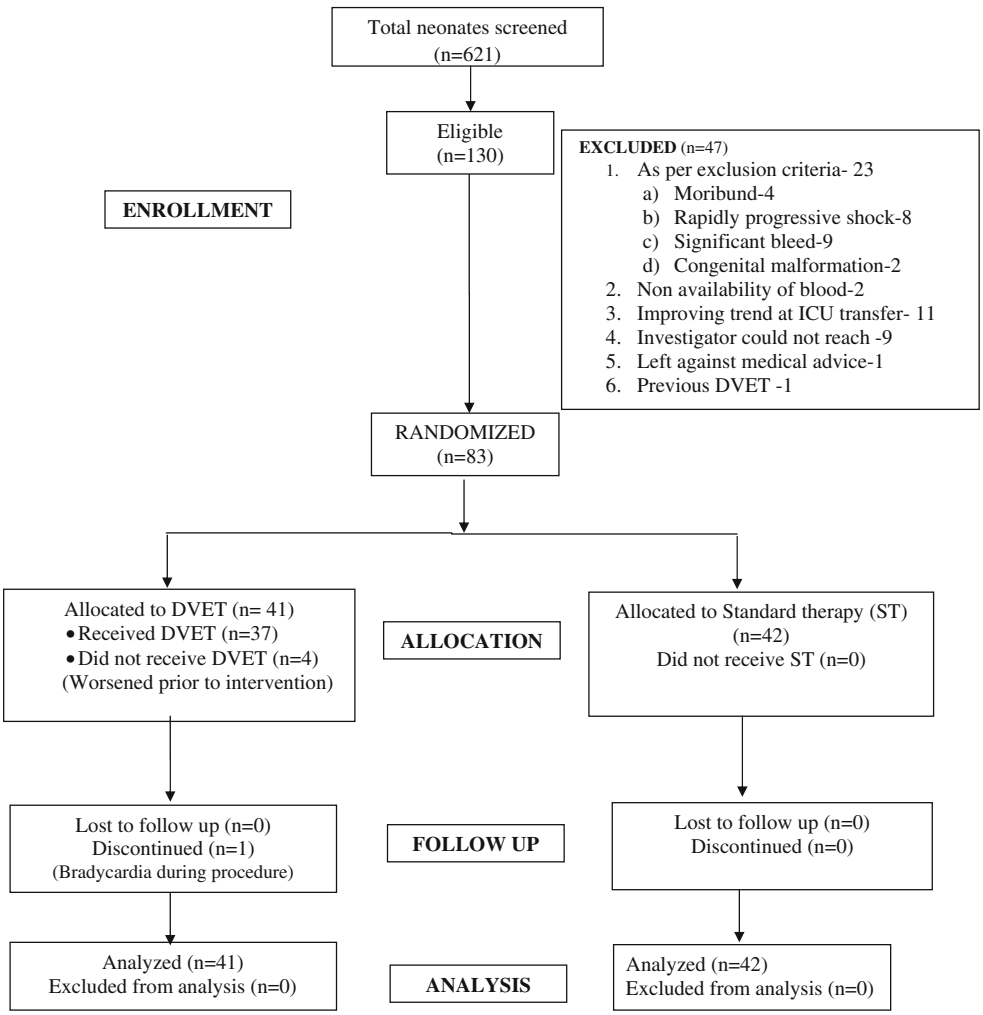

Fig. 1 Flow of patients in the trial

laboratory personnel who performed the analysis of metabolic, biochemical and immunologic parameters were masked by coding the vials that contained the sample.

The subjects in the experimental arm underwent DVET in addition to the standard treatment for severe sepsis. Exchange was done using reconstituted blood. Reconstitution was done with packed red blood cells and fresh frozen plasma in the blood bank under all aseptic precautions using sterile connecting device (Fresenius Hemocare, GmBH, Germany) to achieve a target hematocrit of≈50 %. Blood product older than 5 d was not used for the purpose of the trial and the procedure was completed in 45–60 min duration.

The control arm received all standard treatments for severe sepsis (except blood exchange transfusion) as per the unit protocol (ST group). This usually includes respiratory support with supplemental oxygen and ventilation and airway stabilization, cardiovascular support in the form of isotonic fluids administration and vasopressors / inotropes, renal support in the form of fluids, diuretics and peritoneal dialysis, and hematologic support using blood and blood products.

Non-standard therapies such as Intravenous immunoglobulins (IVIg) and Colony stimulating factors were avoided. Baseline biochemical, metabolic and immunological parameters were measured in both the groups and 12–24 h after DVET in the DVET group. Protocol violations were documented in the case record form.

The key outcome variable was mortality (all causes) by 14 d from enrollment. Secondary outcome variables were early mortality (mortality by 7 d from enrollment), mortality by discharge, time to mortality, organ dysfunction status (normalization/ persistence/ worsening/ any new organ involvement) by 14 d from enrollment, levels of immunoglobulins (IgG, IgA and IgM), complement 3 (C3), C-reactive protein (CRP) and absolute neutrophil count following DVET, complications associated with DVET (occurring within 48 h from the procedure), duration of hospital stay, duration of intensive care unit (ICU) stay and neurological status of survivors at discharge. All the enrolled infants were followed up daily till 14 d from enrollment or death (whichever was earlier). During the follow-up period, details of the organ function were monitored daily using the same standard criteria used during inclusion. Neurological examination at discharge was performed by the Amiel-Tison method [17]. Serum immunoglobulins IgG, IgA, IgM, C3 and CRP were estimated by end-point nephelometry using a semi-automated nephelometer (MININeph, The Binding Site, UK) and MININEPH kits were used for the specific analytes [18].

During the year prior to the start of the study (2010), there were 85 babies who were greater than 1000 g birth weight, and had developed severe sepsis (Annual data of the Newborn unit of the Dept. of Pediatrics; unpublished). Out of them, 41 babies died during the hospital stay (48 %). To identify a 40 % risk reduction in mortality (from 48 to 28 %) with an alpha error of 5 % and power of 80 %, 92 neonates per group with severe sepsis were required. However, due to slow recruitment, the study was aborted before it could reach the predecided sample size with a final sample size of 83 subjects. Descriptive statistics were used to describe the baseline variables. Categorical outcome variables were analyzed by Chi square test with continuity correction or Fisher's exact test depending on cell size. Normally distributed numerical variables were compared using Student 't' test and non-parametric variables were analyzed with Mann Whitney *U* test. Paired 't' test was used for the comparison of metabolic and immunological parameters before and after DVET. Effect size and strength of association were measured using relative risk and risk difference. Time to mortality was assessed by time series assessment by constructing a Kaplan-Meier survival curve. An intention to treat analysis (ITT) was done. *P* value of less than 0.05 was taken as significant. Analysis was done using statistical software packages IBM-SPSS 20 version (SPSS Inc. Chicago, IL, USA).

Results

Out of 130 neonates who had features of severe sepsis, 47 were excluded (Fig. 1). The remaining 83 neonates were randomly allocated to DVET group (n=41) or ST group (n=42). Four neonates in the DVET group did not receive DVET due to rapid worsening before availability of blood (n=2) or due to

Table 1 Demographic parameters and morbidities at baseline (n=83)

Characteristics	DVET (n=41) n (%)	ST (n=42) n (%)
Gestational age (in weeks); Mean±SD	31±2.8	31±3
Birth weight (in grams); Mean±SD	1387±367	1456±375
Male sex	30 (73)	27 (64)
Small for gestational age	15 (36)	16 (38)
Complete course of antenatal steroids	34 (83)	29 (69)
Pregnancy induced hypertension	11 (27)	17 (40)
Clinical chorioamnionitis	7 (17)	5 (12)
Intrapartum antibiotics	14 (34)	10 (24)
pPROM (>24 h)	14 (34)	13 (31)
Need for resuscitation at birth	2 (5)	5 (12)
Hyaline membrane disease	16 (39)	17 (40)
Patent Ductus Arteriosus	17 (41)	17 (40)
Intraventricular hemorrhage (Grade 1 & 2)[a]	9 (22)	13 (31)
Respiratory support (all forms)	30 (73)	31 (74)

DVET Double volume exchange transfusion; *ST* Standard therapy; *pPROM* Preterm premature rupture of membranes

[a] Grade 3 Intraventricular hemorrhage and intra-parenchymal extension of the bleed were excluded

difficulty in gaining a vascular access (n=2). The baseline demographic characteristics, maternal morbidities and major neonatal morbidities were comparable between the groups (Table 1). Forty-one (49 %) neonates had culture proven sepsis while half of them (n=22) grew multi-drug resistant organisms (Table 2). Level of sickness at baseline and median number of dysfunctional organs at enrollment was comparable between the study groups (Table 2). Cardiovascular dysfunction [71 (86 %)] was the most frequent organ involved followed by hematological [46 (55 %)], renal [22 (27 %)] and respiratory [6 (7 %)] systems. None of the enrolled neonates had hepatic dysfunction associated with severe sepsis.

The primary outcome of mortality by 14 d from enrollment was observed in 14 (34 %) neonates in the DVET group in comparison to 18 (42 %) in the ST group [RR: 0.79 (95 % C.I. 0.45, 1.13); p 0.4], Similarly, early mortality (mortality by 7 d) as well as mortality by discharge showed a trend towards reduction in the DVET group in comparison to the ST group (Table 3). No significant difference could be observed in the time to mortality (Fig. 2 and Table 3). On comparing the improvement in individual organ functions, a 29 % [(95 % C.I. 2–49 %) (p 0.04)] and 17 % [(95 % C.I. 5–29 %) (p 0.003)] improvement was observed with cardiovascular and hematological dysfunctions, respectively and a trend towards greater improvement was

Table 2 Details of sepsis, level of sickness and organ dysfunction status at baseline (n=83)

Characteristics	DVET group (n=41) n (%)	ST group (n=42) n (%)
Age at onset of sepsis (hours); median (IQR)	72 (48–120)	72 (48–123)
Culture positive sepsis	20 (48)	21 (50)
Gram negative bacilli	17 (41)	18 (43)
Multidrug resistant organism[a]	10 (24)	12 (28)
Sepsis Screen positive[b]	20 (49)	18 (43)
Chest X-ray suggestive of pneumonia	35 (85)	39 (93)
Meningitis	5 (12)	13 (31)
SNAP II; median (IQR)	9 (0–24)	10 (5–24)
Level of severity (based on SNAP II)		
• Mild <20	28 (68)	29 (69)
• Moderate 20–40	10 (24)	9 (21)
• Severe >40	3 (7)	4 (9)
No. of dysfunctional organs; median (IQR)	2 (1–3)	2 (1–2)
Cardiovascular dysfunction	36 (88)	35 (83)
Need for vasoactive support	25 (61)	23 (54)
Need for >1 vasoactive drug	17(41)	11 (26)
Refractory metabolic acidosis	27 (66)	24 (57)
Blood pH; mean±SD	7.2±0.13	7.2±0.15
Sclerema	20 (48)	21 (50)
Respiratory dysfunction	3 (7)	3 (7)
Hypoxemia (PaO_2<50 mmHg)	2 (5)	2 (5)
Hematological dysfunction	23 (56)	23 (54)
Thrombocytopenia	19 (46)	19 (45)
Neutropenia	9 (22)	8 (19)
Platelet count/mm^3; median (IQR)	59,000 (33,250–80,750)	38,000 (30,000–54,000)
ANC/mm^3; median (IQR)	1409 (970–5600)	1700 (224–4700)
Renal dysfunction	14 (34)	8 (19)
Ig G (g/L); mean±SD	5.7±1.9	5.73±1.75
Ig A (g/L); median (IQR)	0.184 (0.06 – 0.4)	0.07 (0.06–0.27)
Ig M (g/L); median (IQR)	0.17 (0.1 –0.27)	0.12 (0.95 – 0.2)
C3 (g/L); mean±SD	0.58±0.2	0.622±0.2

SNAP II Score for neonatal acute physiology II; *C3* Complement factor 3; *ANC* Absolute neutrophil count

[a] Bacteria resistant to>2 broad spectrum antibiotics

[b] Sepsis screen constituted of CRP, TLC, ANC, ITR, μESR

Table 3 Outcome variables (both primary and secondary)

	Characteristics	DVET Median (IQR) (n=41)	ST Median (IQR) (n=42)	RR (95 % C.I)	'p'
1	Mortality by 14 d; n (%) (Primary outcome)	14 (34)	18 (42)	0.79 (0.45–1.13)	0.4
2	Mortality by 7 d; n (%) (Early mortality)	12 (29)	17 (38)	0.7 (0.4–1.3)	0.3
3	Mortality by discharge; n (%)	14 (34)	19 (45)	0.7 (0.4–1.3)	0.3
4	Time to mortality (days); mean (95 % C.I)	10.7 (9–12)	9.4 (7.8–11)	-	0.3[a]
5	Organ dysfunction by day 14; n (%)	13 (31)	17 (40)	0.8 (0.43–1.4)	0.4
6	Duration of hospital stay (in days)	25 (11–37)	19.5 (7–32)	-	0.2[b]
7	Duration of ICU stay (in days)	10 (5–19)	8 (4–16)	-	0.1[b]
8	Abnormal neurological status at discharge amongst survivors; n(%)	1 (4)	2 (9)	0.5 (0.05–5.1)	0.5
Sensitivity analysis (after removing the mild illness subgroup)					
9	Mortality by 14 d; n (%)	10 (77)	11 (84)	0.9 (0.6–1.3)	1.0

DVET Double volume exchange transfusion; *ST* Standard therapy; *SNAP II* Score for neonatal acute physiology II; *ICU* Intensive care unit

[a] log rank test

[b] Mann Whitney

noted with renal dysfunction [0.78 (0.4,1.5) *vs.* 1.9 (0.9,3.9)] in the DVET group in comparison to the ST group. At baseline [median duration of 86 h IQR (60–132)] immunoglobulins and complement levels were comparable between both the groups. Following DVET, a statistically significant improvement in base deficit, IgG, IgM, IgA and C3 levels were observed (Table 4).

In those who underwent DVET, the donor blood had a mean (± SD) hematocrit (in %) of 55±6; pH of 6.75±0.07; base deficit of −21±5, potassium of 10±4 mEq/L and a median (IQR) HCO_3 of 11(7–18). None of the donor blood was deficient in Glucose-6-phosphate dehydrogenase enzyme. DVET was performed through the umbilical venous route (by push-pull technique) in 22 (59 %) neonates and through the peripheral artery-vein route (simultaneous exchange) in the remaining neonates. In the 6 h duration following DVET, 1 (2 %) neonate died from worsening sepsis; 12 (29 %) developed mild hypothermia (36.0 – 36.4 °C) during line placement for DVET; and 2 (5 %) had transient bradycardia that spontaneously recovered. Within 48 h from DVET, 2 (5 %) had serum potassium >6.5 mEq/L without any electrocardiography evidence of hyperkalemia and another 2(5 %) had serum sodium >145 mEq/L and both recovered spontaneously. In comparison to the ST group, significantly lesser neonates in the DVET group had progression of thrombocytopenia [ST *vs.* DVET: 30 (71) *vs.* 14 (37); RR (95 % C.I): 2.1 (1.3–3.3); p 0.005] and worsening of metabolic acidosis [ST *vs.* DVET: 12 (28) *vs.* 3 (7); RR (95 % C.I): 3.9 (1.2–13); p 0.02] following DVET.

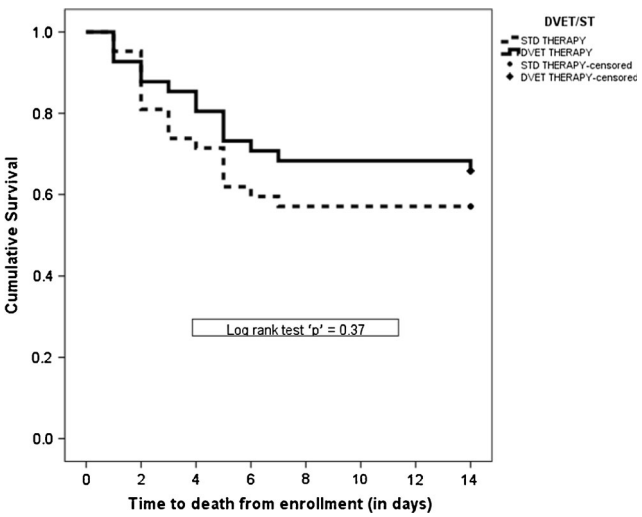

Fig. 2 Kaplan – Meier Survival curve demonstrating cumulative survival and time to death between both the groups

Discussion

DVET has long been proposed and has been practiced in many units as a therapeutic measure for severely septic neonates. Many units perform DVET as a last resort to rescue sick and severely septic neonates. However, its efficacy and safety as an adjunctive therapy has been inconclusive despite its theoretical benefits. The current study has shown a non-significant 21 % reduction in the risk of mortality by 14 d from enrollment in DVET group as compared to ST group. Similarly, early mortality (by 7 d from enrollment) and mortality by discharge also showed a trend towards decrease in the DVET group in comparison to the ST group. No difference was observed in the time to mortalitybetween the study groups. Amongst the individual organ dysfunctions, cardiovascular dysfunction and hematological dysfunction benefitted the most by DVET followed by renal dysfunction. However, no such benefit was observed with

Table 4 Effect of DVET on hematologic, metabolic and immunologic parameters

	Characteristics	Pre DVET Mean±SD	Post DVET Mean±SD	MD (95 % C.I.)	P^a
1	Hematocrit (in %)	45±7	49±6	− 4 (− 7 to −1.1)	0.002
2	Potassium (mEq/L)	4.9±1.1	4.6±1.1	0.12 (−0.1 to 0.7)	0.16
3	Blood pH	7.26 ±0.1	7.31±0.1	0.01 (−0.07 to −0.01)	0.002
4	Base deficit	−10±5	−7.4±5	0.7 (1.7 to 4.6)	<0.001
5	Platelets (per mm^3)	90,940±98,403	79,121±55,809	11,818 (−24,911 to 48,548)	0.5
6	ANC (per mm^3)	5585±9046	3531±3053	2053 (−2745 to 6851)	0.4
7	CRP (mg/L)	49±39	32±35	17.9 (3.3 to 32)	0.01
8	IgG (g/L)	5.7±2.2	8.1±1.5	− 2.5 (−3 to −1.4)	<0.001
9	IgA (g/L)	0.3±0.2	1.06±0.3	− 0.8 (− 0.95 to −0.65)	<0.001
10	IgM (g/L)	0.22±0.16	0.76±1.5	− 0.53 (− 1.04 to −0.004)	0.05
11	C3 (g/L)	0.6±0.18	0.83±0.2	− 0.22 (−0.32 to −0.12)	<0.001

DVET Double volume exchange transfusion; *ST* Standard therapy; *MD* Mean difference; *ANC* Absolute neutrophil count; *CRP* C-reactive protein; *Ig* Immunoglobulin; *C3* Complement factor 3

[a] Paired *T* test; all negative symbols indicate an increase following DVET

respiratory dysfunction. A significant improvement in the biochemical, immunological and acid base status was observed following DVET.

From the developing countries, Sadana et al. reported a significant improvement in survival in the DVET group in comparison to no DVET group (50 *vs.* 5 %) in neonates with sclerema [12]. Mathur et al. in an earlier study observed a 35 % absolute reduction in mortality in the DVET group in comparison to no DVET group (70 *vs.* 35 %) [11]. However, these two studies were done with a primary objective of analyzing the granulocyte function and immunoglobulin and complement levels; both had a very high baseline mortality risk (95 and 70 % respectively); had small numbers and suffered a high risk of bias. The current study had a baseline mortality rate of 42 %. A direct comparison of the current study with the above two may not be appropriate mainly due to the significant improvement in the understanding of supportive care of sick neonates over the last two decades and an increased awareness in effective and timely initiation of broad spectrum antibiotics. Similar to the present results, a later study done by Gunes et al. did not observe any significant change in mortality between these groups [13].

As DVET may act by repleting the immunological competence of a sick neonate, and to understand the biological pathway of DVET, the authors also measured immunoglobulin IgG, IgM and IgA along with complement factor 3 (C3), both at baseline as well as after DVET and could observe a significant improvement in all these parameters post-DVET. A similar increase in the immunoglobulin levels following DVET was observed by previous studies [7, 12, 13].

Instead of a clinician's perception of sickness being a deciding factor for inclusion in the trial, the current study used more objective criteria that mandated atleast one organ dysfunction to be present to classify sepsis as severe enough to be enrolled in the trial [15]. None of the previous studies have till now used such objective criteria for inclusion nor have reported the organ dysfunction status after the intervention. The level of sickness, as measured by SNAP II, was similar at baseline between both the groups. A large number of the study subjects [n=37 (45 %)] had SNAP II scores<20, indicating a milder illness severity. Antibiotics and supportive care formed the mainstay of standard therapy in severe sepsis. In this study, both the groups received similar care during the study period and the unit policy for starting and hiking up of antibiotics and the choice of antibiotics remained unchanged during the study period.

Considering the multitude of complications involved in more sick neonates, moribund neonates and those with severe bleeding as well as refractory shock requiring more than 2 drugs were not included in the current trial. Similarly, extreme low birth weight neonates were not included in this trial due to the perceived higher risk of procedure related complications in this population.

Safety of an elaborate procedure like DVET has been much debated in the past. The authors took 6 h for mortality and 48 h for other adverse effects as cut-offs to associate an event to DVET. The lone subject in the DVET group who died had a severe sickness level even at baseline (SNAP score of 35) and had a relentless progression of multi-organ dysfunction. Contrary to the belief, it was observed that the blood pH and base deficit improved from 7.26±0.1 to 7.31± 0.1 and −10±5 to −7±5 (p<0.001) respectively, following DVET. This improvement was observed despite the use of slightly older blood with a mean donor blood pH of 6.75. Previous studies had postulated that the transfused blood was acidic predominantly due to the citrate content of anticoagulant used [19, 20]. Tollner et al. [6] and Vain et al. [7] also observed a similar improvement in

metabolic acidosis, with the former postulating that improvement in metabolic acidosis and oxygen requirement might be associated with an overall improvement in the microcirculation. Similarly, only 2 (5 %) neonates in the DVET group had serum potassium>6.5 mEq/L despite a donor blood potassium of 10±4 mEq/L. This could be explained by the complex in-vivo metabolic changes that occur at the level of cell membrane of RBC in an environment of adequate ATP. Previous studies have also reported a similar donor blood potassium levels (5–27 mEq/L) [19, 20].

The current study has certain important strengths. First, this was a rigorously conducted largest randomized controlled trial with mortality as a primary outcome with a low risk of bias. Secondly, objective and reproducible inclusion criteria were applied to increase the generalizability of the results. Thirdly, the level of sickness at baseline was objectively scored and compared between the study groups with a validated severity score like SNAP II with an excellent psychometric property. Fourthly, serial assessment of improvement in organ dysfunction was done with objective criteria. Even though inability to blind the intervention from the treating team as well as the investigators was a limitation, mortality as an outcome would have been least affected by this limitation. Moreover, all other biochemical and immunological outcome variables were analyzed and reported in a blinded fashion.

To conclude, DVET showed a trend towards reduction in mortality of 21 % in comparison to ST in severely septic neonates of >1000 g birth weight. A significant improvement was observed in the cardiovascular and hematological organ functions following DVET. DVET was associated with a significant improvement in IgA, IgG, IgM, complement 3 and metabolic acidosis in comparison to the standard therapy. Thus, DVET is a safe procedure in severely septic neonates.

Contributions ASA: Conceptualized the study, collected the data and drafted the initial manuscript and approved the final manuscript; VS: Conceptualized and designed the trial, designed the data collection tool, supervised conduct of the trial, analyzed the data, critically reviewed the manuscript and approved the final manuscript; PK: Conceptualized the study idea, supervised the design and implementation of the trial, critically reviewed the data analysis and the manuscript and approved the final manuscript; SMG: Assisted in designing the trial and data collection, was involved in the study conduct, critically reviewed the manuscript and approved the final manuscript; AJ: Planned blood products administration, designed the data collection tool, planned the preparation and administration of blood products, critically revised the manuscript and approved the final manuscript; AR: Contributed to the study design, conducted the analysis of biochemical and immunological parameters, reviewed the manuscript and approved the final manuscript. PK will act as guarantor for this paper.

Conflict of Interest None.

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