Transfusion-associated necrotising enterocolitis in very low birth weight babies: transfusion and feeding practices in two neonatal units in Bloemfontein, Free State

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Background. Necrotising enterocolitis (NEC) is life-threatening with a rising incidence due to improved neonatal care. While researchers' focus has shifted to causes, risk factors and preventative clinical strategies, little is known about the exact aetiology of NEC. Risk factors include the relationship between red blood cell transfusions (RBCTs) and the development of transfusion-associated NEC (TANEC) and peri-transfusion feeding, increasing the risk of TANEC.

Objectives. Evaluate the relationship between RBCT and peri-transfusion feeding practices and the development of TANEC in very low birthweight (VLBW) neonates over 5 years.

Methods. This was a retrospective analytical record review of all VLBW neonates admitted to two tertiary hospitals' neonatal units in Bloemfontein, South Africa (SA), from 1 January 2012 - 31 December 2016.

Results. The study population (n=1 426) had a median birthweight of 1 260 g and a median gestation age of 30 weeks. RBCTs were given to 41.9%, and NEC developed in 7.4%, of whom 47.6% had an RBCT (TANEC). Half (47.2%) were kept nil per os (NPO) around the transfusion. No association was found between NPO status and TANEC development (8.9% NPO patients, 7.9% non-NPO patients, p=0.6826). No significant differences regarding Modified Bell's Staging were found between neonates who developed TANEC v. NEC.

Conclusion. Optimising the administration of RBCTs and evidence-based feeding protocols is crucial in reducing TANEC's impact on premature neonates.

Keywords. Red blood cell transfusions, transfusion-associated necrotising enterocolitis, transfusion protocol

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Contribution of the study

The study examines the link between red blood cell transfusion and transfusion-associated necrotising enterocolitis in very low birthweight neonates. It highlights the need for evidence-based feeding protocols to reduce transfusion-associated necrotising enterocolitis risk during transfusions. It calls for standardised clinical guidelines to improve neonatal outcomes and lower necrotising enterocolitis and transfusion-associated necrotising enterocolitis incidence.

Necrotising enterocolitis (NEC) refers to the inflammatory cellular death of the bowel in the neonatal period. Its pathogenesis is multifactorial, with various aetiological mechanisms causing progressive tissue inflammation and disruption of intestinal mucosal integrity, leading to the final disease phenotype.[1-4] NEC causes a considerable burden to the healthcare system[4] owing to its high mortality, accounting for 10% of neonatal intensive care unit (ICU) deaths.[5] In addition, NEC leads to numerous complications, such as sepsis, disseminated intravascular coagulation, shock, multi-organ dysfunction and failure, intestinal obstruction and fistulae, short bowel syndrome and a poor neurological outcome (e.g., deafness, cerebral palsy, visual impairment, developmental and psychomotor impairment).[4,5]

Approximately one-third of NEC cases are associated with a red blood cell transfusion (RBCT) in the preceding 48 hours, known as transfusion-associated necrotising enterocolitis (TANEC).[6,7] TANEC is caused by the change in circulation to the gut in response to anaemia. RBCT can cause tissue hypoxia and re-perfusion, stimulating bowel inflammation and mucosal barrier damage.[2,3] Multiple observational studies have investigated the association between NEC, RBCT and anaemia as contributing factors to the disease.[6-8] However, determining the exact relationship between these factors is challenging as a transfusion is often the treatment for anaemia. Also, a more liberal transfusion threshold has not indicated an increased risk for TANEC in observational and small randomised controlled trials (RCT).[9-12] Therefore, the *Transfusion of Prematures* (TOP)[9,13,] and the *Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-weight Infants* (ETTNO)[14,15] are two RCTs comparing restrictive v. liberal transfusion thresholds and will report on survival and two-year neurodevelopmental outcomes with NEC as a secondary outcome. An example of a transfusion guideline is shown in Table 1.[16]

The effect of enteral feeding during a transfusion is another proposed risk factor for TANEC development.[17-20] Some form of a standardised

Table 1. Red blood cell transfusion threshold for preterm neonates*[17]

Assisted ventilation			CPAP/HFNC		Low flow oxygen	
<28 days	≥28 days	≥28 days	<28 days	≥28 days	(<3 L/min)	Room air
FiO_2 ≥0.3	FiO_2 <0.3	-	-	-	FiO_2 ≥0.21	Well in air
Hb <12 g/dL	Hb <11 g/dL	Hb <10 g/dL	Hb <10g/dL	Hb <8 g/dL	Hb <7 g/dL	Hb <6 g/dL

CPAP = continuous positive airway pressure; HFNC = high-flow nasal cannula.
*Hb (g/dL) = haematocrit (HCT) / 3; RBCT may be considered at higher thresholds than the above for neonates requiring acute resuscitation; dose: 20 mL/kg RBCs over 4 hours; furosemide should not be routinely given; withhold enteral feeds for the duration of transfusion due to the possible risk of TANEC; additional intravenous fluids are not required.

feeding protocol during transfusions has been associated with a decreased risk of developing TANEC.[17-20] However, the most optimal protocol still needs to be determined.[20-27] One such feeding guideline advised that all enteral feeds and fluids should be withheld for 4 hours before, during and 4 hours after an RBCT.[28,29]

NEC is a crippling, life-threatening disease with a rising incidence owing to improved neonatal care. However, little is known about the exact aetiology of the disease. Researchers' focus has only recently shifted from the management of NEC to finding causes, risk factors and preventative clinical strategies. Therefore, this study aims to explore the possible causative relationship between RBCT, peri-transfusion feeding and the development of TANEC in very low birthweight (VLBW) neonates. Since no formal standardised RBCT and peri-transfusion feeding protocols have been implemented in the neonatal intensive care units (NICUs) at the two tertiary government hospitals in Bloemfontein, Free State, South Africa (SA), patients receive transfusions and feeds at various clinical stages at the discretion of the treating physician.

Aim and objectives

The study aimed to evaluate the relationship between RBCT and peri-transfusion feeding practices and the development of TANEC in VLBW neonates at Pelonomi Tertiary Hospital (PTH) and Universitas Academic Hospital (UAH) NICUs in Bloemfontein, over 5 years.

The objectives were to:

- determine the RBCT rates,
- determine whether enteral feeds were stopped around an RBCT,
- determine the incidence and severity of NEC and TANEC,
- determine the haematocrit (HCT) levels at which the RBCTs were given,
- determine the clinical state of neonates during RBCT; and
- identify any changes in RBCT practices over the five-year study period.

Evaluating RBCT practices in relation to NEC will aid researchers in determining whether an association exists between RBCT in neonates, the timing of enteral feeds relative to transfusions and the development and severity of TANEC. Evaluating these practices over 5 years and identifying potential shortcomings could improve the practice of RBCT.

Methods

Study context

The UAH neonatal unit includes intensive and high-care facilities with 12 ventilatory beds, while PTH has only a high-care neonatal unit with two ventilatory beds. If surgical intervention is needed, the patient must be transferred to UAH for paediatric surgical care unless already admitted there. At the time of the study and currently, no standardised RBCT or feeding protocol was implemented in these two hospitals; decisions are left to the treating physician's discretion. This study aligns with SDG 3 (Good Health and Well-being) by highlighting the need for improved neonatalcare facilities and standardised protocols to enhance health outcomes.[30]

Study sample and measurement

This study was an analytical retrospective review using data from PTH and UAH neonatal units. It reviewed all VLBW (1 000 - 1 499 g) neonates born at PTH and UAH and/or admitted to the respective neonatal units between 1 January 2012 and 31 December 2016. Neonates were excluded if they:

- were born in other hospitals and subsequently admitted after 48 hours of life
- had any significant congenital abnormalities
- died within 72 hours of life.

Data were collected by obtaining the Department of Paediatrics' admission statistics from the electronic Meditech database. To identify all VLBW neonates for the study period, the electronic notes of neonates were reviewed, and the following information was captured for neonates fulfilling the inclusion criteria:

- date of birth
- birthweight
- gestational age
- whether an RBCT was received.

The following information was captured for neonates who had received an RBCT:

- date of the RBCT
- pre-transfusion and post-transfusion HCT values (National Health Laboratory Services-LABTRAK database used)
- cessation of feeds around the RBCT
- clinical condition during the transfusion (absence of respiratory or cardiovascular dysfunction and need for support)[31]
- ventilator support during the transfusion.

Patients within the VLBW group who developed NEC were identified, and the following was recorded:

- whether the NEC developed within 48 hours following an RBCT (TANEC)
- the severity of the NEC/TANEC (≥Grade IIB) according to the Modified Bell's Staging. (Bell's Stages I and IIA represent largely non-specific clinical and radiological phenomena).[32]

Pilot study

A pilot study was conducted on the first 20 patients (10 from each unit) to evaluate the feasibility of data collection and the adequacy of the datasheet to document the study parameters. Pilot study results indicated that using the Department of Paediatrics statistics to identify VLBW neonates was not feasible because of gaps in their data. Therefore, the online Meditech system was used. These 20 patients were included in the final study data. Conducting this pilot study supports SDG 9 (Industry, Innovation, and Infrastructure) by emphasising the importance of reliable health information systems and infrastructure for effective healthcare delivery.[30]

Data analysis

Data were captured on an Excel spreadsheet and analysed by the

Department of Biostatistics, Faculty of Health Sciences, University of the Free State (UFS). Results were summarised by frequencies and percentages (categorical variables) and medians and interquartile ranges (IQR) (numerical variables). Subgroups were compared using the χ^2 or Fisher's exact tests (categorical variables) and Mann-Whitney or Kruskal-Wallis tests (numerical variables). The 95% confidence intervals (CI) were calculated for differences between medians of subgroups. This comprehensive data analysis approach contributes to SDG 3 (Good Health and Well-being) by ensuring accurate assessment of health outcomes and enabling evidence-based healthcare decisions.[30]

Ethical considerations

Approval of the study was obtained from the Health Sciences Research Ethics Committee of the UFS (UFS-HSD2017/0616) and the Free State Department of Health (FS_201805_003). Identifying patient details was not recorded on the data collection forms. The researchers maintained patient confidentiality by keeping data on a secure, password-protected computer. Upholding ethical standards aligns with SDG 16 (Peace, Justice, and Strong Institutions) by promoting justice, accountability and strong institutions in healthcare research.[30]

Results

During the study period, 1 426 VLBW neonates were admitted and treated in the neonatal units at PTH (n=1 044) and UAH (n=541). Fig. 1 outlines the reasons for and the number of exclusions at each hospital. The data of 950 patients from PTH and 476 patients from UAH were included in the study. The total study population had a median birthweight of 1 260 g (IQR 1 140 - 1 380) and a median gestation age of 30 weeks (IQR 29 - 32). The median birthweight of patients at PTH was 1 300 g (IQR 1 160 - 1 400), with a median gestation age of 30 weeks (IQR 29 - 32). The median birthweight of patients at UAH was 1 200 g (IQR 1 100 - 1 330), with a median gestation age of 29 weeks (IQR 28 - 31). Patients at UAH weighed significantly less (p<0.0001; 95% CI for median difference −80 - −40 g) and had a significantly shorter gestation age (95% CI −1 - −1 weeks, p<0.0001) than those at PTH.

Regarding RBCTs, 41.9% of the total study population were transfused (PTH 35.8%; UAH 54.0%, p<0.0001) over the study period. The transfusion percentages declined over time at both institutions (Table 2). Necrotising enterocolitis developed in 7.4% (n=105), of whom 47.6% (n=50) had an RBCT (TANEC). Of the 950 patients treated at PTH, 7.0% were recorded to have developed NEC. Of the 66, 32 (48.5%) developed TANEC. At UAH, 39 (8.2%) developed NEC, similar to PTH (p=0.3956). Of the 39, 18 (46.2%) developed TANEC. Approximately 8% of transfused patients at both hospitals developed TANEC, with the highest percentage recorded in 2012. There was a significant decrease in NEC from the earlier to the later years at PTH (p=0.0200), but no significant decreases were observed regarding TANEC. For the cessation of feeds around an RBCT, 47.2% were kept nil per os (NPO) during and at least 4 hours after the transfusion (Table 2) (PTH 50.6%; UAH 42.8%, p=0.0592). These percentages increased over time. In the total study population, no association was found between NPO status and TANEC development (8.9% of NPO patients; 7.9% of non-NPO patients, p=0.6826). At PTH, NPO patients were more likely (but not significantly) to develop TANEC (12.2% of NPO patients; 6.6% of non-NPO patients, p=0.0739). This overall pattern was also observed each year except 2016. In contrast, at UAH, NPO patients were less likely (but not significantly) to develop TANEC (3.6%) than non-NPO patients (9.5%, p=0.0764). This overall pattern at UAH was also observed for 2012, 2013 and 2014. Approximately 60% of the patients at both institutions were clinically stable during transfusion, with a decrease over time at PTH (Table 2). No significant difference was found

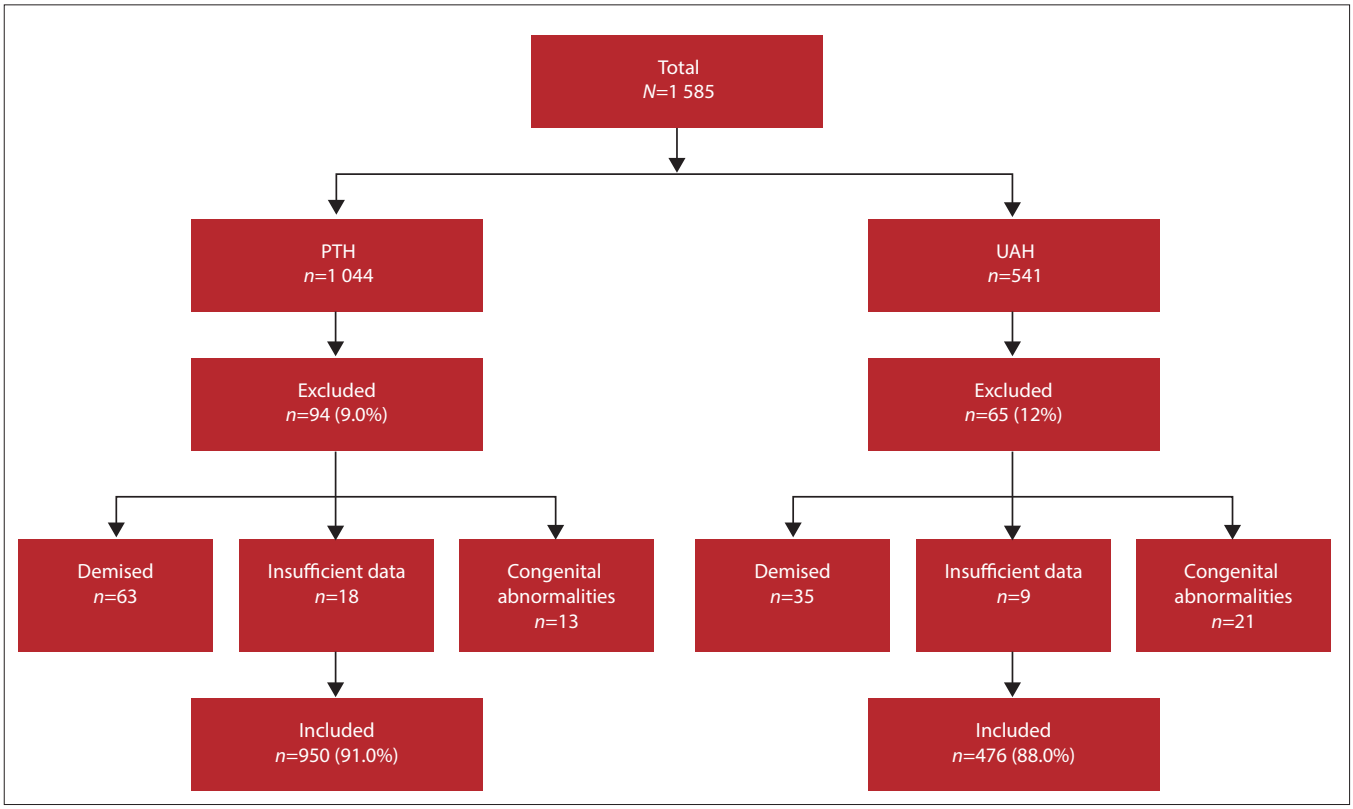

Fig. 1. Profile of very low birthweight neonates excluded from the study at each hospital (2012 - 2016). (PTH = Pellonomi Tertiary Hospital; UAH = Universitas Academic Hospital.)

between patients with a stable condition (8.7%) and those not in a stable state (8.0%) developing TANEC (p=0.7549). At PTH, 7.8% of patients in a stable condition developed TANEC compared with 11.7% not in a stable state (p=0.2463). In contrast, at UAH, those in a stable condition were significantly more likely to develop TANEC (9.7%) than those not in a stable state (2.9%, p=0.0384). This overall pattern for UAH was also observed for 2012, 2013 and 2014.

PTH's largest percentage of neonates who developed non-TANEC NEC were classified as Grade IIIB and UAH as Grade IIB according to the Modified Bell's Staging[32] (p=0.1178, Table 3). No significant differences regarding Modified Bell's Staging were found between neonates who developed TANEC v. non-TANEC NEC at either institution (Table 3, PTH p=0.3591; UAH p=0.4488).

For the total study population over the 5-year study period, the median pre-transfusion HCT was 0.33 L/L (IQR 0.3 - 0.36) and the median post-transfusion HCT 0.4 L/L (IQR 0.37 - 0.43). For PTH patients, pre-transfusion HCT values were available for 311 (91.5%) patients and post-transfusion values for 214 (62.9%) patients. The median pre-transfusion HCT was 0.34 L/L (IQR 0.30 - 0.36), with the median post-transfusion HCT 0.40 L/L (IQR 0.36 - 0.43). For UAH patients, pre-transfusion HCT values were available for 247 (96.1%) patients and post-transfusion values for 219 (85.6%) patients. The median pre-transfusion HCT was 0.33 L/L (IQR 0.30 - 0.36), with the median post-transfusion HCT 0.41 L/L (IQR 0.38 - 0.44). At both institutions, median pre-transfusion HCT values decreased over time. For the total study population over the 5-year study period, the pre-and post-transfusion HCT levels between the TANEC developers (median pre 0.34 L/L and post 0.41 L/L) and those who did not develop TANEC (median pre 0.33 L/L and post 0.40 L/L), did not differ significantly (95% CI for difference in pre 0 - 0.03 and post 0.01 - 0.03). Similar patterns were observed at both hospitals.

The clinical conditions of neonates during RBCTs are described in Table 4. Exchange transfusion was significantly more prevalent at PTH

Table 2. Transfusion practices over time at both institutions

	Pelonomi Tertiary Hospital		Universitas Academic Hospital		Total study population	
Year	***N***	***n* (%)**	***N***	***n* (%)**	***N***	***n* (%)**
		Transfused		Transfused		Transfused
2012	192	114 (59.4)	106	73 (68.9)	298	187 (62.8)
2013	211	90 (42.7)	101	44 (43.6)	312	134 (43.0)
2014	177	55 (31.1)	89	52 (58.4)	266	107 (40.2)
2015	189	44 (23.3)	92	56 (60.9)	281	100 (35.6)
2016	181	37 (20.4)	88	32 (36.4)	269	69 (25.7)
2012 - 2016	950	340 (35.8)	476	257 (54.0)	1426	597 (41.9)
		Kept NPO during transfusion		**Kept NPO during transfusion**		**Kept NPO during transfusion**
2012	114	45 (39.5)	73	21 (28.8)	187	66 (35.3)
2013	90	43 (47.8)	44	25 (56.8)	134	68 (50.8)
2014	55	35 (63.6)	52	24 (46.2)	107	59 (55.1)
2015	44	26 (59.1)	56	26 (46.4)	100	52 (52.0)
2016	37	23 (62.2)	32	14 (43.8)	69	37 (53.6)
2012 - 2016	340	172 (50.6)	257	110 (42.8)	597	282 (47.2)
		Clinical condition stable during transfusion		**Clinical condition stable during transfusion**		**Clinical condition stable during transfusion**
2012	90	63* (70.0)	73	51 (69.9)	163	114 (69.9)
2013	90	57 (63.3)	44	22 (50.0)	134	79 (59.0)
2014	55	23 (41.8)	52	33 (63.5)	107	56 (52.3)
2015	44	22 (50.0)	56	31 (55.4)	100	53 (53.0)
2016	37	14 (37.8)	32	18 (56.3)	69	32 (46.4)
2012 - 2016	316	179 (56.6)	257	155 (60.3)	573	334 (58.3)
		Developed NEC		**Developed NEC**		**Developed NEC**
2012	192	24 (12.5)	106	11 (10.4)	298	35 (11.7)
2013	211	18 (8.5)	101	8 (7.9)	312	26 (8.3)
2014	177	11 (6.2)	89	8 (9.0)	266	19 (7.1)
2015	189	7 (3.7)	92	6 (6.5)	281	13 (4.6)
2016	181	6 (3.31)	88	6 (6.8)	269	12 (4.5)
2012 - 2016	950	66 (7.0)	476	39 (8.2)	1426	105 (7.4)
		Developed NEC post-transfusion		**Developed NEC post-transfusion**		**Developed NEC post-transfusion**
2012	114	16 (14.0)	73	9 (12.3)	187	25 (13.4)
2013	90	9 (10.0)	44	4 (9.1)	134	13 (9.7)
2014	55	4 (7.3)	52	2 (3.9)	107	6 (5.6)
2015	44	1 (2.3)	56	2 (3.6)	100	3 (3.0)
2016	37	2 (5.4)	32	1 (3.1)	69	3 (4.4)
2012 - 2016	340	32 (9.4)	257	18 (7.0)	597	50 (8.4)

NEC = necrotising enterocolitis; NPO = nil per os.
**24 cases information not noted.*

than at UAH (p=0.0466). No other conditions differed significantly between the institutions. The most common reason for not being stable was the side effects of sepsis/septic shock overall and at both hospitals (PTH 12.7%; UAH 14.8%; total study population 13.6%).

The ventilatory support of the neonates who received RBCTs is shown in Table 5. Nasal continuous positive airway pressure was used more commonly at PTH than at UAH (p<0.0001).

Discussion

This study population's median birthweight and gestation age were 1 260 g and 30 weeks, respectively. These values align with a study from Thailand,[33] although they were slightly higher than those from studies from Atlanta[19] and Michigan[24] in the USA. One possible reason for this difference is that SA and Thailand are both lower-middle-income countries, with a patient population resembling those of the developing world. In contrast, the USA is a high-income country where smaller and more premature babies survive owing to advanced antenatal and neonatal care.

The overall incidence of NEC (≥Grade IIB) in this study was 7.4% (105/1 426), which is in line with the literature (SA[34] (8.2%, 173/2 111), Thailand[33] (13.1%, 58/444), Atlanta[19] (6.4%, 73/1 139) and Michigan[24] (15.2%, 19/125). There is a gradual increase in the incidence of NEC in high-income countries in premature neonates (<32 weeks, <1 000 g).[35] This increase may be due to a wide range of definitions or inconsistencies in definitions (clinical and radiological signs) used for NEC case ascertainment,[35] as well as differences in clinical practices, such as NICU admission criteria and feeding practices.[35,36] Future preventative and therapeutic investigations and research are needed to reduce the incidence and impact of NEC.

In this study population, 41.9% (597/1 426) of patients received RBCT. This transfusion rate aligns with literature indicating that ~60% of preterm infants born <32 weeks gestation receive RBCT during the neonatal period.[33,37] This finding indicates that RBCTs are a regular means of treatment in this patient population. Therefore, finding ways to limit its use and optimise the conditions under which

Table 3. Modified Bell's Staging of very low birthweight neonates who developed necrotising enterocolitis at Pelonomi Tertiary Hospital and Universitas Academic Hospital (2012 - 2016)

	Pelonomi Tertiary Hospital			Universitas Academic Hospital			Total study population		
Grade	NEC	TANEC	Non-TANEC NEC	NEC	TANEC	Non-TANEC NEC	NEC	TANEC	Non-TANEC NEC
IIB	30 (45.5)	15 (46.9)	15 (44.1)	22 (56.4)	12 (66.7)	10 (47.6)	52 (49.5)	27 (54.0)	25 (45.5)
IIIA	7 (10.6)	5 (15.6)	2 (5.9)	2 (5.1)	0 (0)	2 (9.5)	9 (8.6)	5 (10.0)	4 (7.3)
IIIB	29 (43.9)	12 (37.5)	17 (50.0)	15 (38.5)	6 (33.3)	9 (42.9)	44 (41.9)	18 (36.0)	26 (47.3)

NEC = necrotising enterocolitis; TANEC = transfusion-associated necrotising enterocolitis.

Table 4. Clinical condition of very low birthweight neonates at Pelonomi Tertiary Hospital and Universitas Academic Hospital during red blood cell transfusion (2012 - 2016)

Clinical condition	Pelonomi Tertiary Hospital *n* (%)	Universitas Academic Hospital *n* (%)	Total study population *n* (%)
Acidaemia	1 (0.3)	0 (0)	1 (0.2)
Apnoea	10 (3.2)	4 (1.6)	14 (2.4)
Exchange transfusion	8 (2.5)	1 (0.4)	9 (1.6)
Haemolysis	2 (0.6)	0 (0)	2 (0.4)
Hypovolemic shock	23 (7.3)	11 (4.3)	34 (5.9)
Pulmonary haemorrhage	4 (1.3)	0 (0)	4 (0.7)
Respiratory distress	23 (7.3)	15 (5.8)	38 (6.6)
Stable (no clinical abnormality)	179 (56.6)	155 (60.3)	334 (58.3)
Sepsis/septic shock	40 (12.7)	38 (14.8)	78 (13.6)
Tachycardia	23 (7.3)	29 (11.3)	52 (9.1)
Tachypnoea	1 (0.3)	2 (0.8)	3 (0.5)
Unstable (specific clinical signs not specified)	2 (0.6)	1 (0.4)	3 (0.5)
Upper gastrointestinal bleed	0 (0)	1 (0.4)	1 (0.2)

Table 5. Ventilatory support in very low birth weight neonates at Pelonomi Tertiary Hospital and Universitas Academic Hospital during red blood cell transfusion (2012 - 2016)

Ventilatory support	Pelonomi Tertiary Hospital *n* (%)	Universitas Academic Hospital *n* (%)	Total study population *n* (%)
High-frequency oscillatory ventilation	0* (0)	13 (5.1)	13 (2.2)
Intermittent positive pressure ventilation	30 (8.8)	18 (7.0)	48 (8.0)
Nasal continuous positive airway pressure	70 (20.6)	28 (10.9)	98 (16.4)
Nasal high-flow oxygen	97 (28.5)	73 (28.4)	170 (28.5)
Room air	143 (42.1)	125 (48.6)	268 (44.9)

*Not available at Pelonomi Tertiary Hospital at the time of the study.

it is administered is paramount to reducing costs and preventing side-effects.

Of the total study population who developed NEC (7.4%, 105/1 426), 47.6% (50/105) were associated with an RBCT (TANEC). The rate of TANEC varies widely in the literature from 20 - 74%, with additional contradicting studies challenging the association between RBCT and TANEC.[19,24,33,37] This may be due to the different study designs, sizes and patient and management variables. One key factor that might play a role is the patient's number of transfusions before developing TANEC[19] since receiving more than one transfusion might increase the risk for TANEC.[19] Therefore, it is recommended that the number of RBCTs for each patient be limited when deemed necessary.

Results showed no difference in grading between patients who developed TANEC and those who developed NEC without a preceding transfusion. This finding aligns with the literature indicating that the disease phenotype is the same and the management of TANEC and NEC is similar once the disease develops.[19,24,33] However, the challenge remains to reduce the risk and prevent the disease through ongoing research and optimising management protocols.

Enteral feeds were stopped around an RBCT for 47.2% (282/597) of transfused patients, but this did not significantly reduce the incidence of TANEC. This finding aligns with similar observations in the literature, including studies from Thailand,[33] Atlanta (48.1 - 58.3%),[19] and Michigan (22.2 - 40%).[24] There is limited evidence from RCTs on the effects of feeding practices during an RBCT on the development of TANEC.[17-20,38] Large, adequately powered RCTs are needed to provide high-quality evidence. Based on the systematic review of observational or case-control studies, stopping feeds around an RBCT can be considered, although the level of evidence is low.[36] Thus, implementing a practice of withholding feeds 4 hours before, during and 4 hours after an RBCT is still advised.[24]

The median HCT level of patients who developed TANEC (0.34 L/L) and those who did not (0.33 L/L) was very similar. This aligns with the ETTNO and TOP trials that compared liberal and restrictive RBCT thresholds and did not find an association between TANEC and low pre-transfusion HCT/Hb values.[9,15] The studies from Atlanta[19] and Michigan[24] also showed no difference in the HCT values pre-transfusion between TANEC and non-TANEC patients. These findings may suggest that it is not a single factor (such as HCT level) but a combination of patient and management factors that may lead to the development of TANEC. Therefore, more research on TANEC prevention and causes for development is needed.

Almost 60% of the patients who received an RBCT were clinically stable (58.3%) (absence of respiratory or cardiovascular dysfunction and need for support),[31] and those on room air comprised 44.9%. Regarding the total study population, no significant association was found between patients in a stable state (8.7%) developing TANEC and those not in a stable state (8.0%) (p=0.7549). This is contrary to what is noted in the literature.[9,13,15,31,39] The reason for this is uncertain, although limiting the amount of RBCT should be a goal with preventative strategies to avoid anaemia and reduce the need for RBCTs.

Neither PTH nor UAH had a formally implemented RBCT and feeding protocol, and decisions were made at the treating physician's discretion. Results from both hospitals showed a gradual decrease in the number of RBCTs administered, a incline in the number of patients' feeds stopped around a transfusion and a drop in the rate of TANEC over the 5-year study period. This may indicate a move in the right direction and supports the thinking of a causal effect between RBCTs, feeds and the development of TANEC. Subsequently, the protocol in Table 1 has been implemented and is being followed at the PTH and UAH neonatal units.[16]

Study limitations

This study experienced several limitations that warrant careful consideration. First, its retrospective nature and the lack of comprehensive patient electronic records may have led to incomplete data, potentially impacting the precision of our findings. Second, the study's single-centre design restricts the generalisability of the results to the experiences of just two units. Future research should consider a prospective multi-centre design to enhance the robustness of our conclusions and recommendations.

Furthermore, it is crucial to highlight that the study's patient population lacks adequate description. Studies on NEC should reflect the prevalence of risk factors, including small for gestational-age infants, as they are known to have a higher chance of developing the condition. Factors such as the proportion of infants fed preterm formula v. human milk and the incidence of maternal illnesses such as gestational hypertension (GPH) are highly pertinent but remain unreported in this study. Including these essential details in future investigations will enable a more comprehensive understanding of the factors influencing NEC outcomes and the potential impact of preventive measures.

Conclusion

In conclusion, this study sheds light on TANEC among premature neonates. It highlights the importance of limiting RBCTs and optimising their administration, along with the need for evidence-based feeding protocols during RBCTs. The study's findings support the notion that hospital-specific practices can impact TANEC rates, suggesting room for improvement in care. These insights underscore the ongoing need for research and collaboration to reduce TANEC's incidence and impact on premature neonates in diverse healthcare settings.

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