An audit of the practice of red packed cell transfusion in neonatal surgery in an academic hospital

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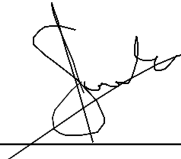
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

Johannesburg, 2022

Declaration

I, Kushal Govender declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



08 August 2022

Dedication

I dedicate this body of work to my family, who have always made unconditional sacrifices to support me in my endeavours. Thank you dearly.

Abstract

Background

Neonates undergoing surgery are at greater risk of requiring red packed cells transfusion. Paediatric transfusion practices vary widely between countries and institutions, especially in the management of neonates.

Aims

The aim of this study was to describe the practice of intraoperative red packed cells transfusion primarily, and blood products and fluid transfusion secondarily in neonates presenting for surgery.

Methods

A retrospective contextual and descriptive study was conducted at Chris Hani Baragwanath Academic Hospital. A total of 1077 anaesthetic records of neonates who underwent surgery from 1 January 2015 to 31 December 2019 were reviewed. Descriptive and inferential statistics were used to analyse the data.

Results

Three hundred and twenty seven (30%) neonates received intraoperative red packed cells transfusion. The median (IQR) volume of red packed cells, fresh frozen plasma, platelets and clear fluid administered was 15 (10 - 21.8) ml/kg, 12.3 (10 - 23.5) ml/kg, 13.6 (10 - 20.5) ml/kg and 19 (9.1 - 28.8) ml/kg respectively. Very low weight, low preoperative haemoglobin, long total anaesthetic time, emergency surgery and major surgery were independently associated with blood product transfusion. Post-conceptional age, low and very low weight, blood product transfusion and major surgery were independently associated with the composite adverse outcomes.

Conclusions

Intraoperative blood product transfusion occurred up to three times more frequently in our study than in comparative studies. Weight-based dosing of red packed cells, blood products and clear fluids were in keeping with current

recommendations. Further prospective cohort studies are recommended to inform an institution specific patient blood management programme.

Clinical Implications

Neonatal patient blood management programmes are informed by limited scientific data. Current evidence based guidelines do not address the perioperative period. An audit of transfusion practice is the first step in developing evidence based institutional perioperative neonatal transfusion guidelines.

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List of abbreviations

ABG	Arterial blood gas
CHBAH	Chris Hani Baragwanath Academic Hospital
FFP	Fresh frozen plasma
Hb	Haemoglobin
ICU	Intensive care unit
PBM	Patient blood management
RPC	Red packed cell
SANBS	South African National Blood Service

Statement

The Research Report consists of a draft article and appendices. A literature review and the study proposal is included as appendices for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the Research Report in order to comply with the author guidelines of Pediatric Anesthesia, the journal to which it is intended to be submitted.

Draft article

An audit of the practice of red packed cell transfusion in neonatal surgery in an academic hospital

Running title: Transfusion practices and outcomes during neonatal surgery: a 5 year retrospective review

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Data availability statement: The data that supports the finding of this study are available on request from the corresponding author. The data are not publically available due to privacy or ethical restrictions.

Abstract

Background

Neonates undergoing surgery are at greater risk of requiring red packed cells transfusion. Pediatric transfusion practices vary widely between countries and institutions, especially in the management of neonates.

Aims

The aim of this study was to describe the practice of intraoperative red packed cells transfusion primarily, and blood products and fluid transfusion secondarily in neonates presenting for surgery.

Methods

A retrospective contextual and descriptive study was conducted at Chris Hani Baragwanath Academic Hospital. A total of 1077 anesthetic records of neonates who underwent surgery from 1 January 2015 to 31 December 2019 were reviewed. Descriptive and inferential statistics were used to analyze the data.

Results

Three hundred and twenty seven (30%) neonates received intraoperative red packed cells transfusion. The median (IQR) volume of red packed cells, fresh frozen plasma, platelets and clear fluid administered was 15 (10 - 21.8) ml/kg, 12.3 (10 - 23.5) ml/kg, 13.6 (10 - 20.5) ml/kg and 19 (9.1 - 28.8) ml/kg respectively. Very low weight, low preoperative hemoglobin, long total anesthetic time, emergency surgery and major surgery were independently associated with blood product transfusion. Post-conceptional age, low and very low weight, blood product transfusion and major surgery were independently associated with the composite adverse outcomes.

Conclusions

Intraoperative blood product transfusion occurred up to three times more frequently in our study than in comparative studies. Weight-based dosing of red packed cells, blood products and clear fluids were in keeping with current recommendations. Further prospective cohort studies are recommended to inform an institution specific patient blood management program.

Key words: blood transfusion; infant; newborn; surgery

Clinical Implications

Neonatal patient blood management programs are informed by limited scientific data. Current evidence based guidelines do not address the perioperative period. An audit of transfusion practice is the first step in developing evidence based institutional perioperative neonatal transfusion guidelines.

Introduction

The Pediatric Perioperative Cardiac Arrest (POCA) registry identified hypovolaemia resulting from blood loss as the most common cause of anesthesia related cardiac arrests.[1] Red packed cell (RPC) transfusion is a life-saving intervention for neonates and children undergoing surgery. While perioperative transfusion is uncommon in adults and older children, neonates tend to require RPC transfusion more frequently.[2] In the face of "anemia of infancy" simultaneous non-physiologic processes, such as bleeding, hemolysis, and impaired red cell production, may contribute to a clinically significant anemia, requiring intervention.[3]

Neonates undergoing surgery are at risk of requiring RPC transfusion owing to their small circulatory volumes, relatively high metabolic needs and inability to compensate for tissue oxygen demands in the face of anemia.[4] The relationship between preoperative anemia and perioperative mortality in patients undergoing non-cardiac surgery has been described in adult[5], pediatric[6] and neonatal patient subpopulations.[7]

Following RPC's, platelet concentrate, the second most commonly administered blood component in neonates[8], may be indicated in thrombocytopenia affecting up to 70% of extremely low birth weight neonates.[9] Most platelet transfusions are administered to neonates with severe thrombocytopenia in the face of active hemorrhage.[10] Neonates at risk of surgical hemorrhage amounting to more than 40% of the circulating blood volume may require both platelet and plasma transfusions.[4]

Evidence based Perioperative Blood Management (PBM) programs aim to optimize patient care by avoiding unnecessary transfusions and limiting adverse effects.[11] Currently, there is a paucity of literature specific to PBM in children with limited evidence based guidelines.[12] Various national and institutional pediatric transfusion guidelines vary in their recommendations regarding safe restrictive transfusion thresholds, particularly in the neonatal subgroup.[13] While neonates undergo surgery and receive RPC transfusion at Chris Hani Baragwanath Academic Hospital (CHBAH), no departmental or institutional guidelines exist to guide intraoperative RPC transfusion practice.

We therefore embarked on a 5-year retrospective review of blood product transfusion practice and outcomes in neonatal patients presenting for surgery at CHBAH. The aim of this study was to describe the practice of intraoperative RPC transfusion primarily, and blood products and fluid transfusion secondarily in neonates presenting for surgery; to describe the association between patient factors, blood product transfusion and the composite of adverse outcomes and mortality. The composite of adverse outcomes was defined as the presence of any of the following outcomes: postoperative ICU admission, postoperative intubation/ventilation, and postoperative inotrope/vasopressor administration.

Methods

A retrospective, contextual and descriptive study was conducted in the theatre complex of CHBAH in Johannesburg, South Africa, for neonates who underwent surgery from 1 January 2015 to 31 December 2019. A consecutive, convenience sampling method was used. Each available record was assigned a study number and the reviewed variables were captured using Microsoft® Office Excel® 2007 software (Copyright 2006 Microsoft Corporation, One Microsoft Way, Redmond, Washington 98052 - 7329). The variables included are in Supplementary Table 1. Missing, illegible and incomplete records were excluded. All data was collected by one author (KG).

The hospital is the largest in Southern Africa with 2888 beds and is affiliated to the Faculty of Health Sciences of the University of the Witwatersrand. The hospital has 25 operating rooms of which one is used for neonatal surgery and

on average 120 neonatal surgeries are performed annually. Approval to conduct this study was obtained from the Human Research Ethics Committee (Medical) (M210419) and the Graduate Studies Committee of the University of the Witwatersrand as well as the Medical Advisory Committee of CHBAH.

Stata/SE 16 statistical software (Copyright 1985-2019 Stata Corp LLC, Stata Corp, 4905 Lakeway Drive College Station, Texas 77845) was used to analyze the data. Demographic data were reported as frequencies and percentages for categorical data, means and standard deviations for normally distributed data and medians and interquartile ranges for non-parametric data. Patient characteristics, blood product and fluid profiles, and postoperative blood gas parameters of patients who were transfused were compared to those who were not using independent t-tests when data was normally distributed, and Mann-Whitney tests when data was not normally distributed. A regression analysis was used to analyze associations between blood product transfusion, demographic factors and the composite of adverse outcomes and mortality. A p-value of <0.05 was considered statistically significant.

Results

A total of 1078 neonates had surgery in the institution during the study period (Figure 1). The mean (SD) gestational age at birth was 34.9 (4.6) weeks and 648 (60%) were male (Table 1). The median (IQR) chronological age was 21.4 (12 - 28) days, whilst the mean (SD) post-conceptional age was 34.4 (11.6) weeks. The mean (SD) weight was 2479.3 (844.3) grams. Five hundred and

fifty-one (51%) patients had emergency surgery and 697 (65%) had major surgery, predominantly intra-abdominal. Of the total, 374 (35%) had blood product transfusion, with 327 (30%) receiving RPC transfusion (Figure 1).

Neonates who were transfused had a significantly lower median (IQR) gestational age at birth, median (IQR) post-conceptional age, and median (IQR) weight, than those who were not transfused ($p<0.001$). The median (IQR) chronological age of both transfused and non-transfused neonates were comparable at 12 (6 - 25.5) days and 12 (4 - 29) days respectively ($p=0.307$).

The median (IQR) preoperative Hb in neonates who received intraoperative transfusion was significantly lower than those who did not [11.6 (9.8 - 13.6) g/dl vs. 14.2 (11.5 - 16.7) g/dl, ($p<0.001$)]. A significantly larger proportion of neonates who received intraoperative transfusion underwent emergency surgery (65%), major surgery (92%) and had a longer median (IQR) total anesthetic time, 155 (115 - 205) minutes, ($p<0.001$).

Amongst the patients who were transfused, the median (IQR) volume of RPC, fresh frozen plasma (FFP) and platelets transfused were 15 (10 - 23.5) ml/kg, 12.3 (10 - 23.5) ml/kg and 13.6 (10 - 20.5) ml/kg respectively (Table 2). The total median (IQR) volume of fluid (clear and blood products) per kg, administered to neonates who received intraoperative transfusion was approximately twice as much as that to neonates who were not transfused, 37.8 (25 - 57.5) ml/kg vs. 18.5 (10.2 - 30.3) ml/kg respectively ($p<0.01$). The total

median (IQR) volume of clear fluid administered per hour was however comparable between groups, [19 (9.1 - 28.8) ml/kg and 18.5 (10.2 - 30.3) ml/kg respectively, (p=0.352)].

The postoperative median (IQR) Hb 11.8 (10.5 - 13.7) g/dl in neonates who were transfused was significantly lower compared to 13.2 (11 - 15.3) g/dl in those who were not transfused (p=0.001) (Table 2). The postoperative median (IQR) pH, pCO_2, pO_2 and BE were 7.32 (7.234 - 7.384), 43 (34.3 - 51.05) mmHg, 49.1 (39.1 - 79.9) mmHg and -4.1 (-7.6 - -0.9) respectively in those transfused. The median (IQR) postoperative lactate were higher amongst transfused neonates [2.5 (1.7 - 4.45) vs. (1.7 - 3.6) respectively, (p=0.02)].

The composite of adverse outcome occurred in 712/1078 (66%) neonates in total. Seven hundred and eight (65%) neonates were admitted to the ICU postoperatively. A total of 618 (57%) were intubated and ventilated while 117 (11%) required vasopressor/inotropic support (Table 3). The rate of ICU admission, postoperative intubation/ventilation and vasopressor administration were significantly higher in those who were transfused, (p<0.001).

Very low weight (aOR 4.02, 95% CI 1.77 - 9.12, p=0.001), preoperative Hb (aOR 0.68, 95% CI 0.63 - 0.74, p<0.001), total anesthetic time (aOR 1.01, 95% CI 1.01 - 1.01, p<0.001), emergency surgery (aOR 1.68, 95% CI 1.12 - 2.50, p=0.012) and major surgery (aOR 11.32, 95% CI 6.22 - 20.63, p<0.001) were independently associated with blood product transfusion (Table 4). Blood

product transfusion (aOR 4.27, 95% CI 2.55 - 7.16, p<0.001), post-conceptional age in weeks (aOR 0.889, 95% CI 0.919 - 0.965, p=0.005), low weight (aOR 3.60, 95% CI 2.27 - 5.72, p<0.001), very low weight (aOR 6.41, 95% CI 2.23 - 18.40, p=0.001), and major surgery (aOR 5.61, 95% CI 3.58 - 8.78, p<0.001) were independently associated with the composite adverse outcome (Table 5).

Discussion

The major findings of this study show that patients who received red packed cells and blood product transfusion were predominantly premature with lower weight at time of surgery. Their surgeries were mostly major emergency surgery characterized by intra-abdominal surgery. They experienced prolonged surgical times and received a large total volume of fluid and blood product transfusion combined. They had presented with lower preoperative Hb and continued to have lower Hb postoperatively. Very low weight, preoperative low Hb and prolonged major surgery predisposed patients to blood product transfusion. Blood product transfusion in turn, together with post-conceptional age, low weight, very low weight and major surgery, were independently associated with the composite of adverse outcome.

The basis of well-informed PBM programs is robust clinical evidence. There is, however, a paucity of strong scientific data to support such programs and guidelines in the pediatric population.[11, 13] Current international guidelines are heterogeneous as they are informed by limited scientific data and are hence based more on expert opinion. Therefore pediatric transfusion practices vary

widely between countries and institutions, especially in the management of neonates.[14]

Overall, our study found an increased frequency of intraopertive RPC transfusion (30%) in neonates who underwent surgery during the study period compared to reports of between 9.9% and 23.8% in previous studies.[2, 15-17] Quinn et al[16] and Keung et al[2] had found a relationship between low weight and laparotomy in neonates with increased risk of receiving perioperative RPC transfusion. Galvez et al[17] found that lengthy procedures put patients at risk of perioperative blood product transfusion. The factors associated with transfusion in our study were comparable to those reported by Quinn et al[16] and Keung et al.[2] A frequency of perioperative transfusion of between 27% and 30% has been reported amongst premature neonates with post-conceptional age less than 45 weeks.[17] The proportion of neonates in our study with post-conceptional age less than 45 weeks may account for the increased frequency of transfusion observed.

Our institution does not have a prescribed transfusion trigger, however, the mean Hb preoperatively and postoperatively was maintained at approximately 11 g/dl. Several international societies recommend transfusion triggers of between 8.5 - 11 g/dl in neonates requiring mechanical ventilation.[13, 18, 19]

The current South African National Blood Service (SANBS) Clinical Guidelines for the Use of Blood Products in South Africa recommends transfusion in an

acutely bleeding neonate when more than 10% of the blood volume is lost.[20] A transfusion trigger of 12 g/dl is recommended for neonates on mechanical ventilation while a more restrictive threshold of 8 - 11 g/dl is recommended for non-ventilated neonates still requiring supplementary oxygen support.[20] The guidelines do not address the perioperative conditions.

FFP and platelet transfusion seemed to follow the transfusion of RPC in our study at median (IQR) volumes of 12 (10 - 20) ml/kg and 13.6 (10 - 20.5) ml/kg respectively. They are indicated in dilutional coagulopathy following massive blood transfusion[5] with a recommended dose of FFP of 10 - 20 ml/kg[18-20] and 10 - 20 ml/kg platelets transfusions[4, 18-20] at a suggested threshold platelet count of $50x10^9$/L or lower.[19] The intraoperative administration of blood products serve to replace ongoing losses with the aim of maintaining normovolaemia in the bleeding neonate. Amongst the neonates who were not transfused in our study, the intraoperative losses were replaced with clear fluid the volume of which was comparable to the clear fluid administered to transfused neonates.

Studies have demonstrated an association between RPC transfusion in preterm infants and significant morbidity including the development of necrotizing enterocolitis[21, 22], intraventricular haemorrhage[23], retinopathy of prematurity[24], circulatory and iron overload and bronchopulmonary dysplasia[22]. While a restrictive transfusion strategy has been shown to be safe in hemodynamically stable pediatric patients in the ICU setting[25], evidence of safety in the neonatal subpopulation in the face of ongoing surgical hemorrhage is still lacking.

Limitations

Despite limitations of this study, the findings approximated the recommendations of existing national and international guidelines for blood management practice in neonates. The study was limited by its retrospective nature. The cross-sectional design of this retrospective study is limited in its ability to investigate the cause and effect relationship between co-variates in this study, including preoperative Hb, RPC transfusion, and the composite of adverse outcome. Further prospective study may be required to differentiate between association and causality in this regard. The results of this study are contextual and can therefore not be generalized.

Conclusions

Intraoperative RPC and blood product transfusion occurred up to three times more frequently in our study than in comparative studies which may be subsequent to the lack of a strict institutional PBM program. However, despite the absence of an institutional PBM program to guide neonatal intraoperative RPC transfusion practice at CHBAH, this study found that RPC transfusion practice during neonatal surgery at CHBAH is closely adherent to both local and international recommendations. Weight-based dosing of RPCs, blood products and clear fluids were in keeping with current recommendations. Further prospective cohort studies are recommended in order to determine the cause and effect relationship between patient co-variates, blood product transfusion and morbidity outcomes in a stepwise approach to defining appropriate and

safe intraoperative transfusion triggers which in turn will aid in the development of an institution specific PBM program at CHBAH.

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This research was done in partial fulfilment of a Master of Medicine degree.

Conflict of interest

The authors declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

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Table 1. Baseline characteristics.

Parameter	Transfused		Not Transfused		P Value
	n	median (IQR) / (%)	n	median (IQR) / (%)	
Gestation at birth (weeks)	349	33 (30 – 37)	619	36 (32 – 40)	<0.001
Chronological age (days)	372	12 (6 – 25.5)	702	12 (4 – 29)	0.307
Post-conceptional age (weeks)	374	35.5 (32.4 – 39.6)	704	39.5 (35 – 41.3)	<0.001
Weight (g)	371	1960 (1410 – 2500)	691	2700 (2100 – 3250)	<0.001
Preoperative hemoglobin (g/dl)	351	11.6 (9.8 – 13.6)	550	14.2 (11.5 – 16.7)	<0.001
Anesthetic time (minutes)	374	155 (115 – 205)	704	115 (85 – 155)	<0.001
Gender-Male	203	55	431	62	0.027
Emergency surgery	245	65.5	306	43.5	<0.001
Major surgery	344	92	353	50.2	<0.001

Table 2. Fluid and blood product transfusion profiles.

Parameter	Transfused		Not Transfused		P Value
	n	median (IQR)	n	median (IQR)	
RPC vol (ml)	326	30 (20 – 42)	0	-	-
RPC vol (ml/kg)	325	15 (10 – 21.8)	0	-	-
RPC vol rate (ml/kg/hr)	325	5.6 (3.6 – 9.3)	0	-	-
FFP vol (ml)	85	20 (15 – 30)	0	-	-
FFP vol (ml/kg)	85	12.3 (10 – 20.5)	0	-	-
FFP vol rate (ml/kg/hr)	85	5.6 (4 – 8.1)	0	-	-
Platelets vol (ml)	133	25 (15 – 32)	0	-	-
Platelets vol (ml/kg)	133	13.6 (10 – 20.5)	0	-	-
Platelets vol rate (ml/kg/hr)	133	6.9 (4.4 – 11.1)	0	-	-
Clear fluid vol (ml)	316	35 (18.5 – 60)	635	50 (29 – 80)	<0.001
Clear fluid vol (ml/kg)	314	19 (9.1 – 28.8)	626	18.5 (10.2 – 30.3)	0.352
Clear fluid vol rate (ml/kg/hr)	314	6.6 (3.9 – 10.4)	626	9 (5.6 – 14.4)	<0.001
Total fluid and blood product (ml)	374	71 (48 – 110)	635	50 (29 – 80)	<0.001
Total fluid and blood product (ml/kg)	372	37.8 (25 – 57.5)	626	18.5 (10.2 – 30.3)	<0.001
Total fluid and blood product rate (ml/kg/hr)	372	15 (9.5 – 22.5)	626	9 (5.6 – 14.4)	<0.001
Postoperative hemoglobin (g/dl)	206	11.8 (10.5 – 13.7)	161	13.2 (11 – 15.3)	0.001
Postoperative lactate	156	2.5 (1.7 – 4.45)	113	2.5 (1.7 – 3.6)	0.020
Postoperative pCO_2 (mmHg)	216	43 (34.3 – 51.05)	169	40.4 (34.8 – 47.4)	0.118
Postoperative pH	217	7.32 (7.234 – 7.384)	173	7.335 (7.263 -7.416)	0.111
Postoperative pO_2 (mmHg)	212	49.1 (39.1 – 79.9)	171	50.5 (38.3 – 113)	0.323
Postoperative base excess	207	-4.1 (-7.6 – -0.9)	170	-3.8 (-6.6 – -1.3)	0.548

* RPC - red packed cells, FFP - fresh frozen plasma, vol - volume, pCO_2 - partial pressure of carbon dioxide, pO_2 - partial pressure of oxygen.

Table 3. Morbidity outcomes.

Outcome Parameter		Transfused	Not Transfused	All	P Value
		n (%)	n (%)	n (%)	
Postoperative Intensive Care Unit	Yes	345 (94)	363 (52)	708 (66)	<0.001
	No	23 (6)	335 (48)	358 (34)	
Postoperative Intubation/Ventilation	Yes	331 (90)	287 (41)	618 (58)	<0.001
	No	37 (10)	411 (59)	448 (42)	
Vasopressor/Inotrope	Yes	90 (24)	27 (4)	117 (11)	<0.001
	No	279 (76)	673 (96)	952 (89)	

Table 4. Factors associated with blood product transfusion.

Parameter		uOR (95% CI)	P Value	aOR (95% CI)	P Value
Gestation at birth weeks		0.89 (0.86 - 0.91)	<0.001	0.93 (0.87 - 1.00)	0.051
Chronological age days		1.00 (0.99 - 1.00)	0.106	1.00 (0.98 - 1.01)	0.504
Post-conceptional age weeks		0.99 (0.98 - 1.01)	0.329	-	-
Gender:-Males		0.75 (0.58 - 0.97)	0.027	0.93 (0.63 - 1.36)	0.692
Weight (g)		1.00 (1.00 - 1.00)	<0.001	-	-
Birth weight categories	Macrosomia	0.54 (0.23 - 1.31)	0.175	0.87 (0.21 - 3.52)	0.844
	Normal	1 (Base)	-	1 (base)	-
	Low	3.16 (2.33 - 4.27)	<0.001	1.58 (0.97 - 2.57)	0.064
	Very low	11.45 (7.20 - 18.23)	<0.001	4.02 (1.77 - 9.12)	0.001
	Extremely low	15.27 (4.17 - 55.86)	<0.001	3.93 (0.67 - 23.11)	0.130
Preoperative hemoglobin (g/dl)		0.79 (0.75 - 0.83)	<0.001	0.68 (0.63 - 0.74)	<0.001
Anesthetic time		1.01 (1.01 - 1.01)	<0.001	1.01 (1.01 - 1.01)	<0.001
Emergency surgery		2.5 (1.9 - 3.2)	<0.001	1.68 (1.12 - 2.50)	0.012
Major surgery		11.4 (7.61 - 17.00)	<0.001	11.32 (6.22 - 20.63)	<0.001

Table 5. Factors associated with the composite of adverse outcomes.

Parameter	uOR (95% CI)	P Value	aOR (95% CI)	P Value
Gestation at birth	0.931 (0.903 - 0.960)	<0.001	1.045 (0.983 -1.110)	0.158
Post-conceptional age	0.986 (0.974 - 0.997)	0.017	0.889 (0.919 -0.965)	0.005
Weight	0.9985 (0.9983 - 0.9987)	<0.001	-	-
Macrosomia	0.23 (0.11 - 0.48)	<0.001	0.42 (0.16 - 1.13)	0.087
Normal weight	1 (Base)	-	1 (Base)	-
Low weight	5.82 (4.21 - 8.03)	<0.001	3.60 (2.27 - 5.72)	<0.001
Very low weight	15.24 (7.28 - 31.94)	<0.01	6.41 (2.23 - 18.40)	0.001
Extremely low weight	-	-	-	-
Gender (Male)	0.65 (0.50 - 0.85)	0.002	1.02 (0.70 - 1.48)	0.934
Blood product transfusion	11.94 (7.85 - 18.14)	<0.001	4.27 (2.55 - 7.16)	<0.001
Anesthetic time	1.01 (1.01 - 1.01)	<0.001	1.00 (1.00 - 1.00)	0.615
Emergency surgery	3.38 (2.59 - 4.42)	<0.001	1.21 (0.82 - 1.81)	0.339
Major surgery	14.44 (10.63 - 19.62)	<0.001	5.61 (3.58 - 8.78)	<0.001

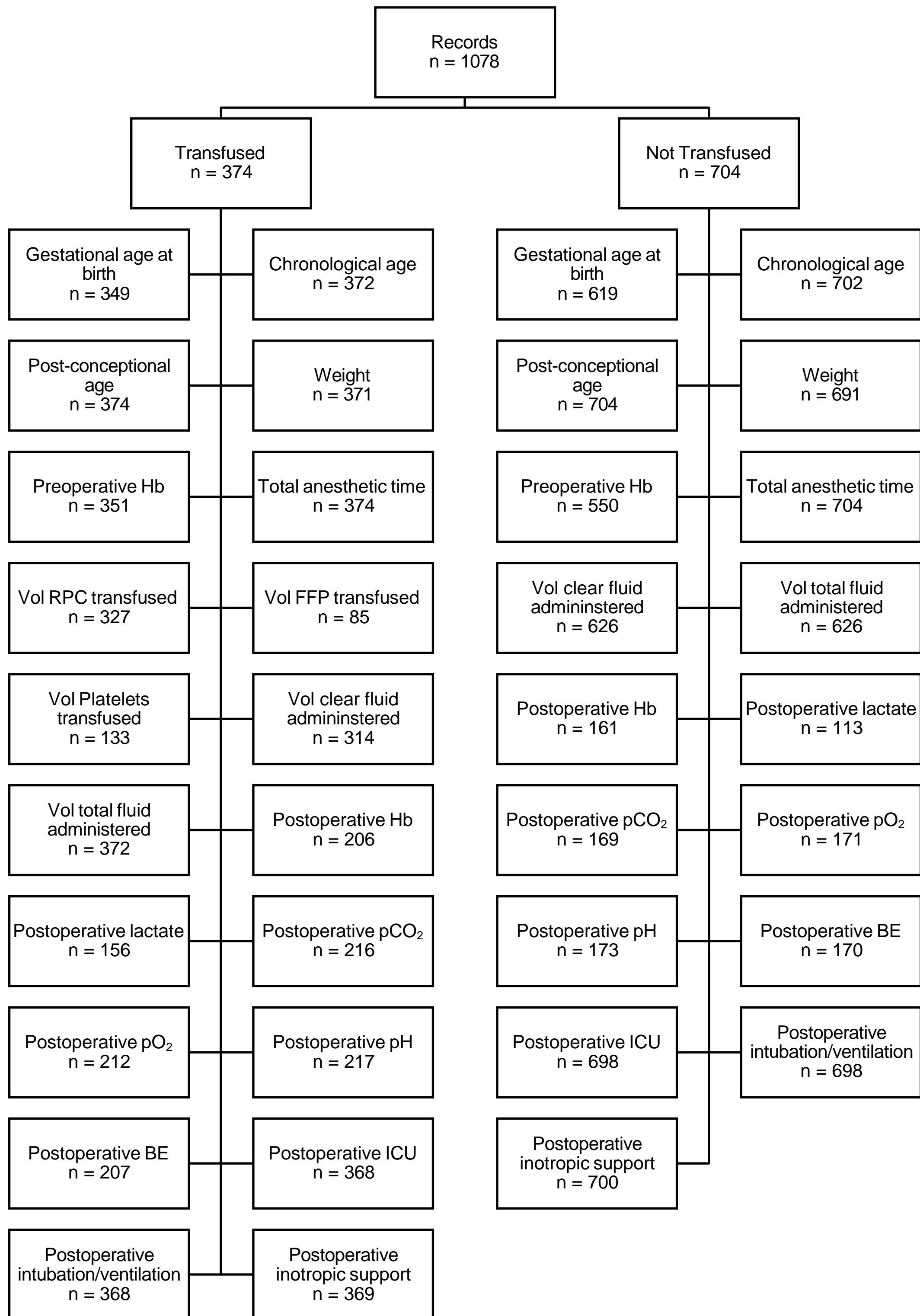

Figure 1. Flow diagram of records included in the study.

Supplementary Table 1. Patient variables.

Variable
Gestational age at birth
Chronological age
Post-conceptional age
Gender
Weight
Co-morbidities
Indication for surgery
Surgical procedure performed
Total anesthetic time
Preoperative hemoglobin
Volume of RPC transfused intraoperatively
Volume of clear fluids administered intraoperatively
Postoperative hemoglobin
Postoperative ICU admission
Postoperative intubation and ventilation
Postoperative inotrope/vasopressor administration

* RPC - red packed cells, ICU - Intensive Care Unit

Appendices

Appendix 1: Journal guideline to authors

Journal: Pediatric Anesthesia

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Appendix 2: Literature review

Literature review

1. Introduction

This literature review will begin with a brief discussion of neonatal physiology with respect to anaemia. The benefits and risks associated with red packed cell (RPC) transfusion in neonates, current transfusion practice recommendations, evidence based transfusion triggers and the role of patient blood management programmes will be then be reviewed.

2. Neonatal physiology

Neonatal surgery may result in major blood loss (1), requiring blood transfusion in order to correct the resulting acute anaemia (2). The Paediatric Perioperative Cardiac Arrest Registry identified hypovolaemia resulting from blood loss as the most common cause of anaesthesia-related cardiac arrests (3). RPC transfusion is a common life-saving intervention for neonates and children undergoing surgery. While perioperative transfusion is uncommon in adults and older children, neonates tend to require RPC transfusion more frequently (4).

Normal haemoglobin (Hb) levels have a wide range in neonates at birth. Normal levels range from 14 – 22 g/dl and progressively decrease to a nadir of 10 – 12 g/dl in term infants by 2 - 3 months (5). This decline is physiological and attributable to changes that occur during birth and transition to extrauterine life. The factors contributing to this change include: a shorter neonatal red blood cell lifespan; a progressive change in affinity of haemoglobin (Hb) for oxygen as foetal Hb transitions to adult Hb; an increase in neonatal red blood cell 2,3-diphosphoglycerate levels; neonatal cardiovascular compensatory mechanisms; and a decrease in plasma erythropoietin levels (6). The resulting "anaemia of infancy" is usually well tolerated and generally requires no intervention (7). Preterm and very low birth weight neonates are at increased risk of a more profound decline in Hb levels resulting in a nadir of 7 - 8 g/dl (6). Simultaneous non-physiologic processes, such as bleeding, haemolysis, and impaired red cell

production, may contribute to a clinically significant anaemia, requiring intervention (6, 8).

3. Benefits of RPC transfusion in neonates

RPC transfusion is indicated in cases of clinically significant anaemia, the most frequent of which is anaemia resulting from surgical or perinatal haemorrhagic shock and anaemia of prematurity (9). Venkatesh et al. (5) reports that "red cell transfusion remains the only treatment for the majority of cases of neonatal anaemia". When Hb levels drop below a critical threshold, a neonate will be unable to increase oxygen delivery to tissues despite compensatory increases in cardiac output (10). Following RPC transfusion, Hb levels increase and improve oxygen carrying capacity of blood. In so doing, oxygen delivery to tissues is improved. Numerous studies have shown that decreases in heart rate, cardiac output and fractional oxygen extraction occurs following transfusion of RPCs to infants with anaemia, hence reducing myocardial workload (11-13). Further benefits of RPC transfusion in neonates include a reduction in the incidence of apnoeic episodes (14) and a reduction in the need for intermittent positive pressure ventilation (15). Data from a study by Zagol et al. (16) showed that apnoeic episodes were less frequent in neonates with higher haematocrit levels (16). However, while RPC transfusion may be beneficial to replace blood loss during neonatal surgery, its utility has to be balanced against the potential risks.

4. Risks associated with RPC transfusion in neonates

RPC transfusion is associated with potential infectious and non-infectious risks, to which children are more vulnerable (17). Children, and in particular infants, have a higher incidence of adverse effects following transfusion than their adult counterparts as documented by the Serious Hazards of Transfusion (SHOT) Report (18). Out of 1867 cases reported in the SHOT report, 7.1% were in paediatric patients. Of these, 37.9% were in infants and 44% of this subgroup were neonates. The majority of paediatric reports were related to human error in either, the transfusion of incorrect blood products, avoidable transfusions, under transfusion, over transfusion, or lack of knowledge of specific requirements in blood products ordered (18, 19).

The three main causes of mortality following transfusion reported were transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO) and haemolytic transfusion reactions (20). Neonates are further at risk of necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), circulatory and iron overload, and bronchopulmonary dysplasia (BPD) following transfusion (21). Transfusion associated necrotizing enterocolitis (TANEC) is defined as an enterocolitis occurring within 48 hours of a transfusion (21). While retrospective studies (22, 23) debate whether NEC is in fact associated with recent blood transfusion, a study by Patel et al. (24) confirmed that NEC occurred twice as often in transfused neonates than in those who did not receive a transfusion.

Studies by Christensen et al. (25) and Bear et al. (26) confirmed that transfusions were associated with an increased risk of severe IVH particularly during the first week of life. A study by Yu-Cheng Wang indicated an association between transfusion and ROP (27), while another study by Dani et al. (28) implicated iron overload resulting from RPC transfusion with ROP most likely through oxidative injury from free radical formation (28). The oxidative stress resulting from iron overload may be implicated in the development of further disease such as BPD and the aforementioned NEC and ROP. With mounting evidence that transfusion during the neonatal period is not without associated risk, guidelines are necessary in order to direct appropriate transfusion practice.

5. Current transfusion practice recommendations

Guidelines by the South African National Blood Service (SANBS) (29), British Committee for Standards in Haematology (30), the Australian National Blood Authority (31) and the Canadian Blood Services (32) all recommend a small volume transfusion of 10 - 20 ml/kg of RPC for transfusion in a neonate in order to correct anaemia. However, the number of studies informing this consensus is extremely limited. A small study by Paul et al. (33) compared 10 versus 20 ml/kg RPC volume in very low birth weight infants and reported that 20 ml/kg volume resulted in a higher post transfusion Hb without any detrimental effects on pulmonary function.

A further study by Wong et al. (34) compared outcomes in infants receiving 15 versus 20 ml/kg RPC volume and found that fewer transfusions were necessary in the 20 ml/kg group without adverse effects. An observational study compared 15 versus 20 ml/kg RPC volume and found a reduction in the number of transfusions required when 20 ml/kg was used (35). Only one study investigated the optimal rate at which RPCs should be transfused and found that while slower rates of transfusion were associated with less haemodynamic disturbances, more rapid transfusion increased ejection fraction (36). The optimal transfusion volume in preterm neonates remains unknown. Whilst the guidelines may agree upon the recommended volume to be transfused, there is less consensus about the transfusion threshold at which a neonate should be transfused.

6. Evidence based transfusion triggers

Robust evidence supports a restrictive transfusion strategy in adult patients without adverse impact on clinical outcomes (37). This forms the basis of successful and well-informed patient blood management (PBM) programmes in this patient subgroup. There is, however, a paucity of strong scientific data to support such programmes and guidelines in the paediatric population (38-40). Only one large multicentre trial, the Transfusion Requirements in Paediatric Intensive Care Units (TRIPICU) trial (41), supports a restrictive transfusion strategy in children. The study compared transfusion at a liberal threshold of 9.5g/dl to a restrictive threshold of 7g/dl and found no benefits in using a liberal threshold (41). The study fell short in informing guidelines in neonatal patients undergoing surgery because the results could not be applied to patients with active bleeding or haemodynamic instability and the recommendation could not be extrapolated to premature infants.

Furthermore, studies comparing liberal versus restrictive thresholds in neonates need to account for differing thresholds according to gestation, postnatal age and comorbidity, as neonatal physiology is dynamic during this period. Three systematic reviews have evaluated the results of trials comparing restrictive versus liberal transfusion thresholds in preterm infants admitted to intensive care units. All three reviews found no significant difference in short term morbidity and mortality between neonates transfused at restrictive or liberal thresholds. However, the

studies included were underpowered to investigate long term outcomes of neonates transfused at restrictive thresholds, and again, were not in actively bleeding patients (42-44).

Conflicting data from studies have resulted in uncertainty surrounding neurological outcomes in neonates transfused at more restrictive thresholds (45-47). Some literature suggests that extremely low-birth-weight infants may be more susceptible to neurocognitive sequlae following transfusion at restrictive thresholds(45). However, a large multicenter trial, The Effects of Transfusion Thresholds on Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants (ETTNO) trial (48), found no difference in neurological outcomes at a corrected gestational age of 24 months in extremely low-birth-weight neonates transfused at a restrictive threshold and those transfused at a liberal threshold (48). The results of the ongoing trial, the Transfusion of Prematures (TOP) trial (49), may soon add to the growing knowledge base and address this disparity.

7. The role of patient blood management programmes

Current international guidelines are heterogenous as they are informed by limited scientific data and are hence based more on expert opinion. Therefore paediatric transfusion practices vary widely between countries and institutions, especially in the management of neonates (50). The SANBS Clinical Guidelines for the Use of Blood Products in South Africa recommends transfusion in an acutely bleeding infant, less than four months old, when more than 10% of the blood volume is lost (29). Recommended transfusion triggers for anaemia or in infants receiving mechanical ventilation are Hb levels less than or equal to 12 g/dl (29). The transfusion trigger in infants not requiring mechanical ventilation is stated as a Hb level less than or equal to 8 - 11 g/dl (51).

An overview of other international transfusion thresholds is shown in Table 1 below. The University of Kwazulu-Natal School of Clinical Medicine has published guidelines for neonatal and paediatric transfusion that are in agreement with the SANBS guidelines (51) as shown in Table 2 below. However, the University of the Witwatersrand as well as Chris Hani Baragwanath Academic Hospital (CHBAH) currently have no institutional guidelines to inform practice in this regard. In order

to optimise the care of patients requiring transfusion, a PBM programme should be developed. This will provide an opportunity to optimise care by avoiding unnecessary transfusions and limiting the potential for adverse effects (39). In order to develop a robust PBM programme, current institutional transfusion practice needs to be audited.

Table 1: Overview of international guidelines and triggers for RPC transfusion in neonates - Adapted from Updates in Red Blood Cell and Platelet Transfusions in Preterm Neonates (38).

	British Committee for Standards in Haematology (2016)		**Australian National Blood Authority (2016)**		**Canadian Blood Service (2017)**		**Dutch Guidelines Quality Council (2019)**	
Postnatal age	**Resp support**	**No resp support**	**Resp support**	**No Resp support**	**Resp support**	**No Resp support**	**Resp support**	**No resp support**
Week 1	10-12 g/dl	10 g/dl	11-13 g/dl	10-12 g/dl	11.5 g/dl	10 g/dl	11.5 g/dl	10 g/dl
Week 2	9.5-10 g/dl	7.5 g/dl	10-12.5 g/dl	8.5-11 g/dl	10 g/dl	8.5 g/dl	10 g/dl	8.5 g/dl
Week 3	8.5-10 g/dl	7.5 g/dl	8.5-11 g/dl	7-10 g/dl	8.5 g/dl	7.5 g/dl	8.5 g/dl	7.5 g/dl

Table 2: Overview of local guidelines and triggers for RPC transfusion in infants < 4months of age - Adapted from SANBS Clinical Guidelines for the Use of Blood Products in South Africa (29) and University of Kwazulu-Natal School of Clinical Medicine Guidelines for Neonatal & Paediatric Transfusion (51).

South African National Blood Services (2014)		**University of Kwazulu-Natal School of Clinical Medicine (2016)**	
Clinical condition	**Trigger**	**Clinical condition**	**Trigger**
Anaemia in the first 24 hours	< 12 g/dl	Preterm/term born anaemic	12 g/dl
Mechanical ventilation	< 12 g/dl	Severe pulmonary disease	12-14 g/dl
Acute blood loss	> 10% blood volume lost	Acute blood loss > 10% estimated blood volume	12 g/dl
Oxygen dependant (not ventilated)	< 8-11 g/dl	Chronic oxygen dependency	11 g/dl
Late anaemia, stable patient (off oxygen)	> 7 g/dl	Late anaemia stable patient	7 g/dl

8. Summary

In this review, neonatal physiology with respect to anaemia, the benefits and risks of RPC transfusion in neonates, current transfusion practice recommendations, evidence based transfusion triggers and the role of patient blood management programmes was discussed.

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Appendix 3: Study proposal

An audit of the practice of red packed cell transfusion in neonatal surgery in an academic hospital

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1. Introduction

1.1. Neonatal physiology

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The three main causes of mortality following transfusion reported were transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO) and haemolytic transfusion reactions (20). Neonates are further at risk of necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), circulatory and iron overload, and bronchopulmonary dysplasia (BPD) following transfusion (21). Transfusion associated necrotizing enterocolitis (TANEC) is defined as an enterocolitis occurring within 48 hours of a transfusion (21). While retrospective studies (22, 23) debate whether NEC is in fact associated with recent blood transfusion, a study by Patel et al. (24) confirmed that NEC

occurred twice as often in transfused neonates than in those who did not receive a transfusion.

Studies by Christensen et al. (25) and Bear et al. (26) confirmed that transfusions were associated with an increased risk of severe IVH particularly during the first week of life. A study by Yu-Cheng Wang indicated an association between transfusion and ROP (27), while another study by Dani et al. (28) implicated iron overload resulting from RPC transfusion with ROP most likely through oxidative injury from free radical formation (28). The oxidative stress resulting from iron overload may be implicated in the development of further disease such as BPD and the aforementioned NEC and ROP. With mounting evidence that transfusion during the neonatal period is not without associated risk, guidelines are necessary in order to direct appropriate transfusion practice.

1.4. Current transfusion practice recommendations

Guidelines by the South African National Blood Service (SANBS) (29), British Committee for Standards in Haematology (30), the Australian National Blood Authority (31) and the Canadian Blood Services (32) all recommend a small volume transfusion of 10 - 20 ml/kg of RPC for transfusion in a neonate in order to correct anaemia. However, the number of studies informing this consensus is extremely limited. A small study by Paul et al. (33) compared 10 versus 20 ml/kg RPC volume in very low birth weight infants and reported that 20 ml/kg volume resulted in a higher post transfusion Hb without any detrimental effects on pulmonary function.

A further study by Wong et al. (34) compared outcomes in infants receiving 15 versus 20 ml/kg RPC volume and found that fewer transfusions were necessary in the 20 ml/kg group without adverse effects. An observational study compared 15 versus 20 ml/kg RPC volume and found a reduction in the number of transfusions required when 20 ml/kg was used (35). Only one study investigated the optimal rate at which RPCs should be transfused and found that while slower rates of transfusion were associated with less haemodynamic disturbances, more rapid transfusion increased ejection fraction (36). The optimal transfusion volume in preterm neonates remains unknown. Whilst the guidelines may agree upon the

recommended volume to be transfused, there is less consensus about the transfusion threshold at which a neonate should be transfused.

1.5 Evidence based transfusion triggers

Robust evidence supports a restrictive transfusion strategy in adult patients without adverse impact on clinical outcomes (37). This forms the basis of successful and well-informed patient blood management (PBM) programmes in this patient subgroup. There is, however, a paucity of strong scientific data to support such programmes and guidelines in the paediatric population (38-40). Only one large multicentre trial, the Transfusion Requirements in Paediatric Intensive Care Units (TRIPICU) trial (41), supports a restrictive transfusion strategy in children. The study compared transfusion at a liberal threshold of 9.5g/dl to a restrictive threshold of 7g/dl and found no benefits in using a liberal threshold (41). The study fell short in informing guidelines in neonatal patients undergoing surgery because the results could not be applied to patients with active bleeding or haemodynamic instability and the recommendation could not be extrapolated to premature infants.

Furthermore, studies comparing liberal versus restrictive thresholds in neonates need to account for differing thresholds according to gestation, postnatal age and comorbidity, as neonatal physiology is dynamic during this period. Three systematic reviews have evaluated the results of trials comparing restrictive versus liberal transfusion thresholds in preterm infants admitted to intensive care units. All three reviews found no significant difference in short term morbidity and mortality between neonates transfused at restrictive or liberal thresholds. However, the studies included were underpowered to investigate long term outcomes of neonates transfused at restrictive thresholds, and again, were not in actively bleeding patients (42-44).

Conflicting data from studies have resulted in uncertainty surrounding neurological outcomes in neonates transfused at more restrictive thresholds (45-47). The results of two ongoing trials, the Transfusion of Prematures (TOP) trial (48) and the Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely

Low Birth Weight Infants trial (ETTNO) trial (49) may soon add to the growing knowledge base and address this disparity.

1.6. The role of patient blood management programmes

Current international guidelines are heterogenous as they are informed by limited scientific data and are hence based more on expert opinion. Therefore paediatric transfusion practices vary widely between countries and institutions, especially in the management of neonates (50). The SANBS Clinical Guidelines for the Use of Blood Products in South Africa recommends transfusion in an acutely bleeding infant, less than four months old, when more than 10% of the blood volume is lost (29). Recommended transfusion triggers for anaemia or in infants receiving mechanical ventilation are Hb levels less than or equal to 12 g/dl (29). The transfusion trigger in infants not requiring mechanical ventilation is stated as a Hb level less than or equal to 8 - 11 g/dl (51).

An overview of other international transfusion thresholds is shown in Table 1 below. The University of Kwazulu-Natal School of Clinical Medicine has published guidelines for neonatal and paediatric transfusion that are in agreement with the SANBS guidelines (51) as shown in Table 2 below. However, the University of the Witwatersrand as well as Chris Hani Baragwanath Academic Hospital (CHBAH) currently have no institutional guidelines to inform practice in this regard. In order to optimise the care of patients requiring transfusion, a PBM programme should be developed. This will provide an opportunity to optimise care by avoiding unnecessary transfusions and limiting the potential for adverse effects (39). In order to develop a robust PBM programme, current institutional transfusion practice needs to be audited.

Table 1: Overview of international guidelines and triggers for RPC transfusion in neonates - Adapted from Updates in Red Blood Cell and Platelet Transfusions in Preterm Neonates (38).

	British Committee for Standards in Haematology (2016)		**Australian National Blood Authority (2016)**		**Canadian Blood Service (2017)**		**Dutch Guidelines Quality Council (2019)**	
Postnatal age	**Resp support**	**No resp support**	**Resp support**	**No Resp support**	**Resp support**	**No Resp support**	**Resp support**	**No resp support**
Week 1	10-12 g/dl	10 g/dl	11-13 g/dl	10-12 g/dl	11.5 g/dl	10 g/dl	11.5 g/dl	10 g/dl
Week 2	9.5-10 g/dl	7.5 g/dl	10-12.5 g/dl	8.5-11 g/dl	10 g/dl	8.5 g/dl	10 g/dl	8.5 g/dl
Week 3	8.5-10 g/dl	7.5 g/dl	8.5-11 g/dl	7-10 g/dl	8.5 g/dl	7.5 g/dl	8.5 g/dl	7.5 g/dl

Table 2: Overview of local guidelines and triggers for RPC transfusion in infants < 4months of age - Adapted from SANBS Clinical Guidelines for the Use of Blood Products in South Africa (29) and University of Kwazulu-Natal School of Clinical Medicine Guidelines for Neonatal & Paediatric Transfusion (51).

South African National Blood Services (2014)		**University of Kwazulu-Natal School of Clinical Medicine (2016)**	
Clinical condition	**Trigger**	**Clinical condition**	**Trigger**
Anaemia in the first 24 hours	< 12 g/dl	Preterm/term born anaemic	12 g/dl
Mechanical ventilation	< 12 g/dl	Severe pulmonary disease	12-14 g/dl
Acute blood loss	> 10% blood volume lost	Acute blood loss > 10% estimated blood volume	12 g/dl
Oxygen dependant (not ventilated)	< 8-11 g/dl	Chronic oxygen dependency	11 g/dl
Late anaemia, stable patient (off oxygen)	> 7 g/dl	Late anaemia stable patient	7 g/dl

2. Problem statement

Neonates undergoing surgery are at risk of requiring RPC transfusion owing to their relatively high metabolic needs, small circulatory volumes and inability to compensate for tissue oxygen demands in the face of anaemia (10). RPC transfusion may reduce myocardial workload (11-13), the incidence of postoperative apnoeic episodes (14) and the need for intermittent positive pressure ventilation (15). Transfusion is also associated with an increased risk of morbidity and mortality in this patient subgroup. Evidence based PBM programs aim to optimise patient care by avoiding unnecessary transfusions and limiting adverse effects (39).

Currently, there is a paucity of literature specific to PBM in children with limited evidence based guidelines (52). Various national and institutional paediatric transfusion guidelines vary in their recommendations regarding safe restrictive transfusion thresholds, particularly in the neonatal subgroup (38). While neonates undergo surgery and receive RPC transfusion at CHBAH, no departmental or institutional guidelines exist to guide intraoperative RPC transfusion practice. Intraoperative RPC transfusion practice in neonatal surgery has not been audited at CHBAH before. In order to improve patient care and avoid unnecessary transfusions, current practice needs to be audited and compared to current evidence based national and international guidelines.

3. Aim

The aim of this study is to audit the practice of intraoperative RPC transfusion in neonates presenting for surgery at CHBAH.

4. Objectives

The primary objectives of this study are to:

- describe the frequency of RPC transfusion in neonatal surgery at CHBAH
- describe the patients' Hb level before surgery
- describe the volume of RPCs transfused intraoperatively
- describe the patients' Hb level after RPC transfusion at re-admission to ICU

- describe the volume of RPCs transfused according to the patients' weight

5. Research assumptions

The following definitions will be used in this study.

Neonate: is a paediatric patient from birth until one month old.

Premature neonate: is a neonate born before 37 completed weeks of gestation.

Anaesthetist: is any qualified doctor working in the Department of Anaesthesiology including medical officers, registrars and consultants.

Patient records: will include the patient's anaesthetic chart surgical notes and ICU charts.

6. Demarcation of study field

The study will be conducted in the theatre complex of CHBAH affiliated to the Department of Anaesthesiology at the University of the Witwatersrand. CHBAH is a 2888 bed central hospital. The hospital has 25 theatres, of which one is for neonatal surgery.

7. Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand. Permission to conduct the study will be requested from the Medical Advisory Committee of Chris Hani Baragwanath Academic Hospital (Appendix A). Permission will be requested from the Head of the Department of Anaesthesiology to access anaesthetic records (Appendix B).

The study is a retrospective review of patient records and no consent will be requested from the patients. The following steps will be taken to ensure anonymity of the data collected.

- A list of patients included in the study will be generated.
- Each patient will be allocated a study number.

- Patient's study numbers will be recorded on the data collection sheet.
- Patient names and hospital numbers will not be recorded on the data collection sheet.
- The list of patient names, hospital numbers and study numbers will be kept separately from the data collection sheet.

The following steps will be taken to ensure confidentiality of the data collected.

- Only the researcher and supervisors will have access to the raw data.
- Data will be stored securely on a password protected electronic database for six years after completion of the study.
  The study will be conducted according to the principles of the Declaration of Helsinki (53) and the South African Guidelines for Good Clinical Practice (54).

8. Research methodology

8.1. Research design

A retrospective, contextual, descriptive research design will be followed in this study.

Retrospective study designs “measure variables that have occurred in the past." (55) This is a retrospective study because historical intraoperative transfusion practices will be audited from patient records from 1 January 2015 to 31 December 2019.

This is a contextual study because it focuses on a specific group of patients within a specific location (56). The context of this study is neonates presenting for surgery at CHBAH.

A descriptive study is one in which data is gathered from a representative sample population in order to describe a phenomenon that occurs naturally in the population (55). None of the variables are manipulated by the researcher. This is a descriptive study because intraoperative RPC transfusion practice will be described by data gathered from records of neonates that presented for surgery at CHBAH.

8.2. Study population

The study population consists of all neonates who underwent surgery at CHBAH from 1 January 2015 to 31 December 2019.

8.3. Study sample

Sample method

In this study, a consecutive, convenience sampling method will be used. Endacott (57) describes convenience sampling as "The use of the most readily accessible individuals or units in a study." Consecutive sampling is a type of non-random convenience sampling which includes all available individuals or events within an accessible population (57). This study will utilise consecutive, convenience sampling because patient records for each neonate that underwent surgery at CHBAH during the period from 1 January 2015 to 31 December 2019 will be audited and included in the study. A list of available patient records will be cross checked against the neonatal theatre surgical register to ensure that all available records are included in the study sample.

Sample size

Data from patients' records in the period between 1 January 2015 to 31 December 2019 will be collected. An estimated sample size of 500 is envisaged from preliminary scoping performed where it was established that approximately 20 neonatal surgeries are performed per two-month period.

Inclusion and exclusion criteria

The inclusion criteria for this study will be:

- Records of all neonates that underwent surgery at CHBAH from 1 January 2015 until 31 December 2019.

The exclusion criteria for this study will be:

- Missing patient records
- Patient records missing important and significant data

- Illegible patient records

8.4. Collection of data

The data collection process will begin only after approval from the Ethics Committee has been granted, together with institutional and departmental permissions to access patient records. The researcher will review all records and exclude those that do not satisfy the study inclusion criteria. Study numbers will be assigned to each of the patient records to be included. Only the relevant data will be collected and entered onto a Microsoft Excel® spreadsheet (Appendix C). The following data will be collected:

- demographics (chronological age, post-conceptional age, gender, weight)
- comorbidity
- preoperative Hb
- volume of PRC transfused by the anaesthetist intraoperatively
- post-transfusion Hb

9. Data analysis

The data will be analysed with the aid of a biostatistician, using descriptive and inferential statistics. Data analysis will be performed using Stata/SE 16 statistical software (Copyright 1985 - 2019 Stata Corp LLC, Stata Corp, 4905 Lakeway Drive College Station, Texas 77845). Means and standard deviations will be used to describe the continuous variables when the data is normally distributed. Medians and interquartile ranges will be used to describe the continuous variables when the data is not normally distributed. Categorical data will be described with frequencies and percentages. Inferential statistics will be used to analyse study subsets where feasible. Student's t-test will be used to analyse parametric data while Mann-Whitney U test will be used to analyse nonparametric data. Categorical data will be analysed using the Chi-squared test. A p-value of less than 0.05 will be considered as statistically significant.

10. Significance of the study

Current intraoperative RPC transfusion practice varies. With blood being a scarce resource and the potential for causing harm from adverse outcomes related to blood transfusion, RPC should only be transfused when appropriate. PBM programmes serve to aid the clinician in appropriate transfusion and standardise transfusion practice (39). Integral to developing a PBM programme, blood utilisation needs to be reviewed and audited. Furthermore, current practice needs to be assessed to ensure adherence to recommendations (39).

This study aims to describe intraoperative utilisation of RPC in neonatal surgery at CHBAH. In so doing, it will draw attention to current transfusion practices at the institution. A comparison of the study findings to current recommendations may reveal areas for improvement in intraoperative transfusion practice in neonatal surgery with potential reduction in the number of unnecessary transfusions. Together with further study, the audit may form the basis for the future development of an institutional PBM programme.

11. Validity and reliability of the study

A valid study is one in which the measurements and conclusion are justifiable based on the study design and its interpretation (58). Furthermore, the validity of a study is indicated by whether the study measured what was intended to be measured. The lower the nonrandom or systematic errors in the study process, the greater the validity (59). Reliability refers to how consistently a measure was achieved (58). The fewer the random errors in the study process, the greater the reliability (59).

The following measures will ensure validity and reliability of the study.

- An appropriate study design will be used.
- A single researcher will collect all of the study data.
- A standardised electronic data collection sheet will be used.
- Every 10th data entry point will be checked.
- The data will be analysed in conjunction with a biostatistician.

In order to improve the validity and reliability of this study, a scoping study was performed. To assess whether the required patient data would be obtainable from patient records, the anaesthetic charts of all neonates that underwent surgery at CHBAH, over a two month period, were reviewed. A record number was assigned to each of anaesthetic charts. Data fields for patient age, weight, procedure, preoperative Hb level, estimated blood loss, volume of blood transfused, post-transfusion blood gas Hb level and post-transfusion formal Hb level were noted to be either, complete or incomplete and entered as such onto a Microsoft Excel® spreadsheet (Appendix D). No patient names, hospital numbers or data was recorded. Of the significant data needed, approximately 90% was obtained.

12. Potential limitations of the study

The study is limited by the availability of complete, legible and accurate patient records. Incomplete, illegible or missing records may result in patient exclusion from the study. Furthermore, the study will be conducted within the context of neonatal surgery at CHBAH. Hence, the study findings may not be applicable to other paediatric patients or neonates undergoing surgery at other institutions.

13. Project outline

Table 3: Overview of projected project timeline

Activity	Jan-Feb 2021	Mar 2021	Apr 2021	May 2021	Jun 2021	Jul 2021	Aug 2021	Sep 2021	Oct 2021	Nov 2021
Proposal preparation	X									
Literature review	X									
Proposal submission	X									
Ethics approval		X	X							
Postgraduate approval		X	X							
Data collection				X	X					
Data analysis						X	X			
Draft article								X	X	
Submission										X

14. Financial plan

The Department of Anaesthesiology will bear the cost of printing and paper.

Table 4: Overview of projected cost

Item	Price per page	Number of pages	Copies	Total
Proposal	R1	25	10	R250
Ethics	R1	10	25	R250
Post graduate form	R1	2	6	R12
Complete report	R1	100	4	R400
Grand total				**R912**

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16. Appendices

Appendix A: Letter to Medical Advisory Committee of Chris Hani Baragwanath Academic Hospital

Attention: Medical Advisory Committee

Chris Hani Baragwanath Academic Hospital

26 Chris Hani Road

Johannesburg

1864

11 March 2021

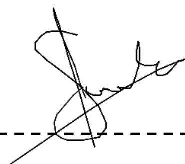
Re: Permission to conduct an audit of intraoperative red packed cell transfusion practice on neonates who underwent surgery at Chris Hani Baragwanath Academic Hospital.

Dear Sir/Madam,

My name is Kushal Govender. I am a registrar in the Department of Anaesthesiology and currently registered for a Masters in Medicine (MMed) with the University of the Witwatersrand. My research project is a retrospective audit of intraoperative red packed cell transfusion practices in neonates who underwent surgery at Chris Hani Baragwanath Academic Hospital from 1 January 2015 to 31 December 2019.

I hereby request permission to conduct my research at Chris Hani Baragwanath Hospital. There will be no additional cost to the hospital, and anonymity and confidentiality will be maintained throughout the process. The study has been approved by the Postgraduate Committee and the Human Research Ethics Committee (Medical).

Regards,



Dr Kushal Govender (Registrar)

Email: lahsuk@gmail.com

Cell: 0835425295

Appendix B: Letter to Head of Department of Anaesthesiology at Chris Hani Baragwanath Academic Hospital

Attention: Head of the Department of Anaesthesiology

Chris Hani Baragwanath Academic Hospital

26 Chris Hani Road

Johannesburg

1864

11 March 2021

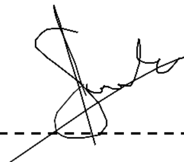
Re: Permission to access anaesthetic records.

Dear Dr Palesa Mogane,

My name is Kushal Govender. I am a registrar in the Department of Anaesthesiology and currently registered for a Masters in Medicine (MMed) with the University of the Witwatersrand. My research project is a retrospective audit of intraoperative red packed cell transfusion practices in neonates who underwent surgery at Chris Hani Baragwanath Academic Hospital from 1 January 2015 to 31 December 2019. The research will only be conducted after approval by the Postgraduate Committee and the Human Research Ethics Committee (Medical).

I hereby request permission to access the anaesthetic charts of neonates who underwent surgery at Chris Hani Baragwanath Hospital from 1 January 2015 to 31 December 2019, in order to proceed with my study. Anaesthetic charts will be reviewed on the premises. Anonymity and confidentiality will be maintained as both patient and clinician identity will not be included in the study.

Regards,



Dr Kushal Govender (Registrar)

Email: lahsuk@gmail.com

Cell: 0835425295

Appendix C: Example of data collection sheet

Patient Number		
Demographics		
Gestational age at birth (weeks)		
Chronological age (days)		
Gender		
Weight (grams)		
Preoperative		
Comorbidity/ies		
Preoperative Hb (g/dl)		
Intraoperative		
Indication for surgery		
Surgical procedure		
Total anaesthesia time		
Est volume of RPC transfused (ml)		
Est volume of clear fluid (ml)		
Post-transfusion ABG Hb (g/dl)		
Post-transfusion ABG Haematocrit		
Postoperative ABG Lactate		
Postoperative ABG pH		
Postoperative ABG CO2		
Postoperative ABG O2		
Postoperative ABG Base Excess		
Postoperative Destination (ICU)	Yes	No
Intubation and ventilation	Yes	No
Inotrope/Vasopressor support	Yes	No

Appendix D: Data collection sheet for the review of patient records over a two-month period

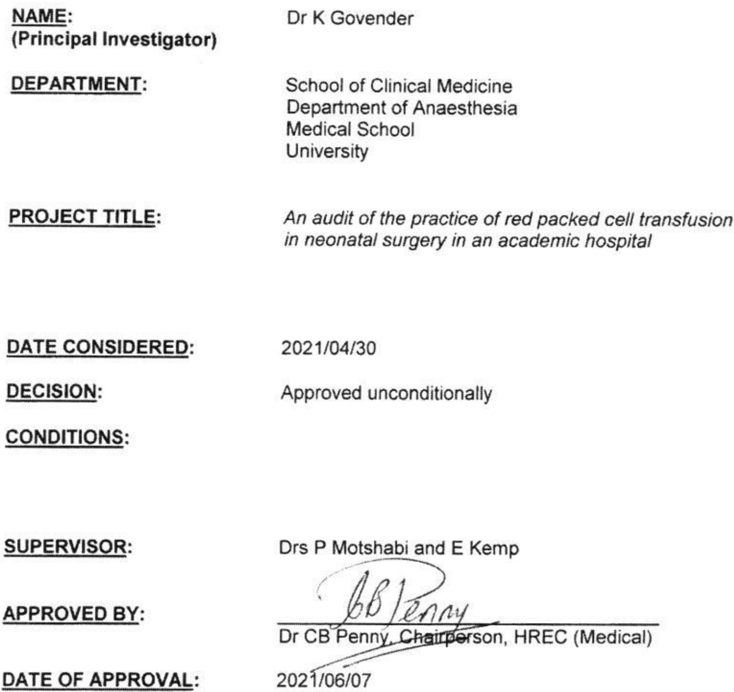
	Record number	Complete data field?						If transfused		
		Age	Weight	Procedure	Preoperative Hb	Estimated blood loss	Transfused	Volume	Post-transfusion Hb	
									Blood gas	Formal
	1	Yes	Yes	Yes	Yes	No	No			
	2	Yes	Yes	Yes	Yes	No	yes	Yes	Yes	No
	3	Yes	Yes	Yes	Yes	No	No			
	4	Yes	Yes	Yes	No	No	No			
	5	Yes	Yes	Yes	Yes	Yes	No			
	6	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
	7	Yes	Yes	Yes	Yes	No	No			
	8	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
	9	Yes	Yes	Yes	No	No	Yes	No	Yes	No
	10	Yes	Yes	Yes	No	No	No			
	11	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
	12	Yes	Yes	Yes	Yes	No	No			
	13	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
	14	Yes	Yes	Yes	Yes	Yes	No			
	15	Yes	Yes	Yes	Yes	No	No			
	16	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
	17	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	18	Yes	Yes	Yes	Yes	No	No			
	19	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	20	Yes	Yes	Yes	Yes	No	No			
	21	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
	22	Yes	No	Yes	Yes	No	No			
Total	**22**	**22**	**21**	**22**	**19**	**4**	**10**	**9**	**10**	**0**

There were 22 records of neonates that underwent surgery at CHBAH during the two month period. 10 of the 22 patients (45%) were transfused RPC's during the surgery. All 22 records (100%) contained data reflecting patient's age and procedure. 21 records (95%) contained data reflecting patient's weight while 19 records (86%) contained data reflecting patient's preoperative Hb level. Only 4 records (18%), however, contained data detailing estimated blood loss. 9 of the 10 records (90%) of patients that underwent transfusion contained data reflecting the volumes of RPC transfused while all 10 of the records (100%) contained post-transfusion Hb levels from a blood gas.

Appendix 4: Clearance from Human Research Ethics Committee

R49 Dr K Govender

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210419



NAME: (Principal Investigator) — Dr K Govender

DEPARTMENT: — School of Clinical Medicine
Department of Anaesthesia
Medical School
University

PROJECT TITLE: — *An audit of the practice of red packed cell transfusion in neonatal surgery in an academic hospital*

DATE CONSIDERED: — 2021/04/30

DECISION: — Approved unconditionally

CONDITIONS:

SUPERVISOR: — Drs P Motshabi and E Kemp

APPROVED BY: — Dr CB Penny, Chairperson, HREC (Medical)

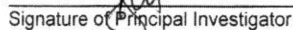
DATE OF APPROVAL: — 2021/06/07

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **April** and therefore reports and re-certification will be due in the month of **April** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).



Signature of Principal Investigator — Date: 2021/06/08

Appendix 5: Approval from Graduate Studies Committee

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

11 May 2021
Person No: 0604091X
PAG

Dr K Govender
6 Kelly Krest
13 Kelly Road
Bedfordview
2007
South Africa

Dear Dr Kushal Govender

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *An Audit of the practice of red packed cell transfusion in neonatal; surgery in an academic hospital.* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 6: Permission from Medical Advisory Committee

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 16th March 2021

TITLE OF PROJECT:

An Audit of the practice of packed red cell transfusion in neonatal surgery in an academic hospital.

UNIVERSITY: Witswatersrand

Principal Investigator: Dr K. Govender

Department: Anaesthesia

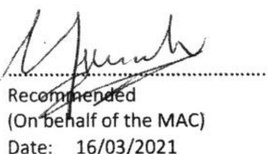
Supervisor : Dr E Kemp

Permission Head Department (where research conducted): Yes

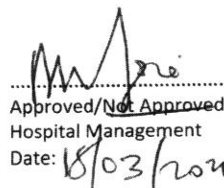
NHRD No.

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.



Recommended
(On behalf of the MAC)
Date: 16/03/2021



Approved/Not Approved
Hospital Management
Date: 18/03/2021

Appendix 7: Permission from Department of Anaesthesiology

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
DIRECTORATE - ANAESTHESIA
Enquiries: Dr P. Mogane
Tel. number: (011) 933-9334
Email: Palesa.Mogane@wits.ac.za

Department of Anaesthesiology
Chris Hani Baragwanath Academic Hospital
PO Bertsham
2013
11th March 2021

To whom it may concern

RE: PERMISSION TO CONDUCT RESEARCH

This serves to confirm that I grant permission for Dr Kushal Govender i to conduct research involving the Department of Anaesthesia at the Chris Hani Baragwanath Academic Hospital. The research topic is titled: **An audit of the practice of red packed cell transfusion in neonatal surgery in an academic hospital.**

I'd like to wish him luck in this endeavor and I am happy to support him wherever possible.

Kind regards.

Dr Palesa Mogane
Chief specialist and Head of Department
Department of Anaesthesiology
Chris Hani Baragwanath Academic Hospital
University of Witwatersrand
Email: Palesa.Mogane@wits.ac.za

Appendix 8: Permission from Department of Paediatric Surgery

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Directorate: Paediatric Surgery
Enquiries: Prof. J.A. Loveland
Tel. number: (011)933 8138; Email: Loveland@wol.co.za

17 May 2021

Dear Dr Kushal Govender,

RE: PROVISIONAL PERMISSION TO CONDUCT A STUDY

Your request to conduct a case report titled **"An audit of the practice of red packed cell transfusion in neonatal surgery in an academic hospital"**, intended for your Ethics application, on a Paediatric Surgery Patient at Chris Hani Baragwanath Academic Hospital is provisionally granted pending full ethics clearance from Wits HREC and CHBAH CEO. You therefore can obtain relevant information from patient's files once full Ethics clearance is obtained. Please be advised that you are to submit a full copy of your final protocol and final Ethics Clearance Certificate from Wits HREC before you are to commence data collection.

While it is recognised that research projects should comprise the researcher's work only and that publication of such work is encouraged, in the event that the information used comprises the diagnosis and management from anaesthetics, then joint authorship from a member of staff from the Department of Paediatric Surgery would not be required. However, should additional information such as management by Paediatric surgery (such as operative intervention, management and follow-up as conducted by the Department of Paediatric Surgery) be extracted from the report, it would be expected that this would be done in conjunction with a member of staff in the Department of Paediatric surgery and that joint authorship would follow in resulting publications. It is requested that you communicate your requirements with the Department of Paediatric Surgery in this regard.

Wishing you the best in your research endeavour and assuring you our assistance in this research project.

Kind regards,

Dr A. Withers

Operational Head of Research
Department of Paediatric Surgery,
Chris Hani Baragwanath Academic Hospital
University of the Witwatersrand

Professor JA Loveland

Academic Head
Department of Paediatric Surgery
School of Clinical Medicine
University of the Witwatersrand

Appendix 9: Turnitin report

K Govender - An audit of the practice of red packed cell transfusion in neonatal surgery in an academic hospital-3.pdf

ORIGINALITY REPORT

13%	11%	9%	2%
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