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ORIGINAL RESEARCH

A prospective, multicentre, observational, cross-sectional study of the prevalence of blood transfusion associated with caesarean section in KwaZulu-Natal, South Africa

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Background: Maternal mortality following a caesarean section (CS) is 50-fold higher in Africa compared to high-income countries (HIC), and strongly associated with peripartum haemorrhage. Blood transfusion (BT) may be lifesaving and the identification of associated preoperative factors may improve outcomes, especially in resource-limited settings.

Methods: We conducted a prospective, multicentre cross-sectional study of all consecutive patients undergoing CS at three government-funded hospitals in KwaZulu-Natal. The primary outcome variable was the prevalence of BT. Multivariable binary logistic regression analysis was used to identify factors independently associated with BT. We hypothesised that there would be a higher prevalence of BT, but similar associated factors, compared to in HIC.

Results: We recruited 1 533 patients between January and May 2021. Most patients presented for urgent or emergency CS (72.4%; 1 104/1 524). Human immunodeficiency virus (HIV) infection (38.6%) and hypertensive disorders of pregnancy (23.4%) were the most common comorbidities. In total, 71 patients received a BT, a prevalence of 4.6% (95% confidence interval [CI] 3.6–5.7%). The prevalence of preoperative anaemia was 36.7% (558/1 520; 95% CI 34.3–39.1%), while 6% (92/1 533; 95% CI 4.8–7.2%) of patients had bleeding during or after CS (BDACS). Factors independently associated with BT were 'major bleeding risk' (a composite of placenta praevia, abruptio placentae and antepartum haemorrhage) (adjusted odds ratio [aOR] 5.34; 95% CI 2.11–13.52%); preoperative anaemia both mild (2.39; 1.10–5.22%) and moderate/severe (28.37; 12.39–64.97%); platelet count < 100 000 cells/mm^3 (5.02; 1.41–17.83%), previous CS (two or more) (2.52; 1.21–5.25%) and BDACS > 1 500 ml (27.86; 6.72–115.54%).

Conclusion: We confirmed that there was a higher prevalence of BT in the hospitals studied than in HIC. Major bleeding risks and BDACS should be identified early to allow appropriate perioperative planning and mobilisation of blood resources. Antenatal anaemia is a preventable and treatable condition. Therefore, earlier diagnosis and treatment should be prioritised. We also showed that even moderate thrombocytopaenia may be associated with BT.

Keywords: blood transfusion, caesarean section, risk factors, maternal outcome, perioperative anaemia

Introduction

Obstetric haemorrhage remains one of the leading, but preventable, causes of maternal mortality worldwide,[1] with low- and middle-income countries (LMICs) disproportionately affected.[2] Bishop et al.[3] identified a 50-fold increased mortality rate in Africa following caesarean section (CS) compared to high-income countries (HIC), which is strongly associated with peripartum haemorrhage. In South Africa, the risk of a woman dying after CS was three times higher than that for vaginal delivery, and bleeding during or after CS contributed to 15.7% of maternal mortality.[4] Transfusion of blood products can be lifesaving. Identifying factors associated with blood transfusion (BT) may allow for appropriate preparation in the individual case and prompt mobilisation of limited blood resources, especially in limited-resource environments where lack of blood and blood products contributed to one-quarter of maternal deaths.[5]

There is a paucity of prospective data from LMICs on BT in CS. A recent meta-analysis identified placental abnormalities (i.e. placenta praevia [PP], abruptio placentae [AP]), general anaesthesia, preterm labour, unbooked pregnancy, fibroid uterus, emergency CS, hypertensive disorders of pregnancy, prolonged labour, multiple gestation and antenatal low haemoglobin (Hb) levels/anaemia as risks independently associated with BT.[6] Although countries across income categories were included, most of the data were retrospective. Coagulation abnormalities, antepartum haemorrhage (APH), severe blood loss at CS and history of previous CS have also been identified as risks for BT.[7-15] In a South African study, Bloch et al.[16] identified two potentially novel risks for peripartum BT, namely human immunodeficiency virus (HIV) infection and thrombocytopaenia (TCP). TCP was also identified as a risk during CS by Isikalan et al.[17] The primary aim of this prospective observational cross-sectional study was to establish the prevalence of BT associated with CS in KwaZulu-Natal, South Africa. We hypothesised a higher prevalence of BT in the hospitals studied than in HIC, but similar associated factors.

Methods

Study design, setting and participants

We performed a prospective, multicentre, observational, cross-sectional study of obstetric patients undergoing CS at three public sector hospitals in KwaZulu-Natal, South Africa: King Edward VIII Hospital (regional/tertiary level; recruitment dates 22/01/2021 to 07/04/2021), Greys Hospital (tertiary level; recruitment dates 24/02/2021 to 11/05/2021) and Harry Gwala Regional Hospital (regional level; recruitment dates 16/02/2021 to 22/04/2021).

We included all obstetric patients with a gestational age greater than 26 weeks undergoing elective and emergency CS, and aimed to consecutively recruit all eligible patients to address selection bias. Recruitment of all eligible patients was verified by local study coordinators against a study log of all CS performed during the respective recruitment periods. Primary ethics approval was received from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (UKZN), South Africa (BE082/19). Owing to the observational nature of the study, a waiver of individual patient consent was granted by the UKZN BREC. We also obtained approval from participating hospital sites and the KwaZulu-Natal Department of Health.

The primary outcome of the study was the prevalence of BT associated with CS. The secondary outcomes were the factors associated with BT, the prevalence of preoperative anaemia and postpartum haemorrhage (PPH), defined as bleeding during or immediately after CS (BDACS) of > 1 000 ml blood loss, and the indications for BT.

Variables and data collection

Data were collected prospectively using a case report form (CRF) completed by the attending anaesthetist. Patients were pseudonymised by allocating a unique patient identifier. Data were verified by study investigators and entered into a password-protected electronic database (Microsoft Excel spreadsheet, Microsoft Corporation, Redmond, WA, USA). Study reporting was in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

The primary outcome variable was the occurrence of a blood transfusion, defined as the transfusion of red cell concentrate or whole blood that occurred at any time from admission to the labour ward, or in the 24 hours preceding the CS, during the CS, and within 24 hours after CS. BT was clinician-dependent and not standardised between hospitals.

We also recorded the following variables: the number of blood products transfused (red cell concentrate, pooled platelets, cryoprecipitate, plasma); timing of transfusion (preoperatively, intraoperatively, postoperatively); indication for BT (Hb level, haemodynamic instability as judged by the attending anaesthetist, ongoing blood loss, or 'other'); and pretransfusion Hb. Postoperative and/or post-transfusion Hb was obtained through chart follow-up or from the National Health Laboratory Service (NHLS). All patients were followed up for 24 hours after delivery for postoperative BT and cross-referenced with data provided by the South Africa National Blood Transfusion Service (SANBS) to prevent omission of any transfusions.

Variables describing the cohort included patient age, gestation, gravidity, parity, number of previous CS, American Society of Anesthesiologists (ASA) physical status, maternal medical conditions (hypertensive disorder, coagulation disorder or history of anticoagulant use, HIV status, SARS-CoV-2 virus infection (COVID-19) status, and 'other' comorbidities, as well as any placental pathology that was recorded preoperatively (PP, AP). The indication for CS, urgency of CS (category 1 – immediately life-threatening to mother or fetus; category 2 – urgent but no immediate threat to life of mother or fetus; category 3 – scheduled, requires early delivery; and category 4 – elective),[18] timing, duration of surgery, mode of anaesthesia (spinal, epidural, combined spinal-epidural [CSE], general anaesthesia [GA]) and documented estimated blood loss (EBL in ml < 1 000, 1 000–1 499, > 1 500) during or immediately after CS (BDACS). If available, the laboratory investigations such as Hb level at antenatal clinic booking, preoperative Hb, platelet count, international normalised ratio (INR) and activated partial thromboplastin time (aPTT), were also recorded. Entry of free text by investigators was possible for the indication for CS, any 'other' comorbidity, and indication for transfusion not on the predefined list.

Statistical methods

We estimated the prevalence of BT to be 5% based on preliminary data from the hospital sites and South African studies with a similar study population and category of hospital.[16,19] We used calculator.net (https://www.calculator.net/sample-size-calculator.html) to calculate the required sample size for the cross-sectional study. For a desired 5% margin of error with a 95% confidence interval (CI) and a pre-specified estimate of 5% for BT in patients undergoing CS, the required sample size was 73 subjects, without correction for population size. As we also aimed to assess up to seven variables as factors associated with BT, we required an additional calculation for sample size. To avoid model overfitting, it is suggested to have a minimum of 10 events per variable (EPV) tested in a regression model, although 5–10 EPV may be used.[20] We therefore required a minimum of 70 events and 1 400 patients for 10 EPV (for seven variables tested). We elected to enrol 1 500 participants to allow for a lower-than-expected rate of transfusion.

Baseline patient characteristics were reported as mean and standard deviation (SD) for normally distributed data, continuous non-normally distributed data were reported as median and range, and differences were compared using student's t-test or Wilcoxon Mann–Whitney tests, respectively. The prevalence of categorical variables, including the primary outcome, was calculated and reported as number (percentage) and 95% CI.

To assess the association between several exposure variables and BT, we performed univariable analyses followed by a

multivariable binary logistic regression analysis, and presented results as unadjusted odds ratios (OR) and adjusted odds ratios (aOR) with 95% CI, respectively. As novel peripartum transfusion associations not previously explored in CS had been identified in a South African peripartum BT study,[16] a decision was made to construct the model in two steps. This would allow for the exploration of candidate variables not initially anticipated, while retaining the 5 to 10 EPV rule-of-thumb.[20]

We first analysed exposure variables previously identified in the literature and of clinical utility for their univariable performance.[6-15] We computed a composite variable 'major bleeding risk' by combining 'placental abnormalities' and 'antepartum haemorrhage'. This would allow us to compare our data with the African Surgical Outcomes Study (ASOS) obstetrics dataset where a similar composite variable was computed.[3] The variables tested for univariable performance were the following: major bleeding risk; preterm labour; multiple gestation; hypertensive disorders of pregnancy; urgency of CS (category 1 and 2); previous CS (two or more); preoperative Hb (divided into three groups in g/dL: > 10.9, 9.0–10.9 and < 9.0); early PPH (BDACS) (three groups in ml: < 1 000, 1 000–1 499 and > 1 500); and these were included in the multivariable model if significant ($p < 0.05$). We also performed univariable analyses on two novel risks, platelet count (divided into three groups in cells/mm^3: > 150 000, 100 000–150 000, < 100 000) and HIV status, and aimed to include these if significant. Categories for Hb (and anaemia),[21] platelet count[16] and PPH[22] were defined a priori based on defined obstetric thresholds, but due to low numbers of patients in the lower ranges for Hb and platelet count, these were combined to allow for analysis.

In the next step, a multivariable binary logistic regression analysis was performed for the following seven exposure variables found significant in the univariable analysis: (i) major bleeding risk (PA, AP, APH), (ii) preterm labour, (iii) urgency of CS (category 1 and 2), (iv) previous CS (two or more), (v) preoperative anaemia (three groups), (vi) preoperative platelet count (three groups), and (vii) PPH (BDACS in three groups). Factors were tested for collinearity and one or more variables would have been excluded if the variance inflation factor (VIF) was greater than two and the model would then be retested. As < 5% of data were missing for the primary outcome, a complete case analysis was used.[23] Statistical analyses were performed using SPSS statistics, version 27 (IBM Corp., Chicago, IL, USA). The level of significance was a p-value of < 0.05 for all analyses.

Results

The patient recruitment process is illustrated in Figure 1. The final analysis included 1 533 patients, all of whom were followed up for 24 hours postoperatively for an event of BT. One patient was excluded from the database as she had received an incorrect postoperative BT that was intended for another patient. The patient required overnight treatment in the high care unit due to blood incompatibility and made a full recovery.

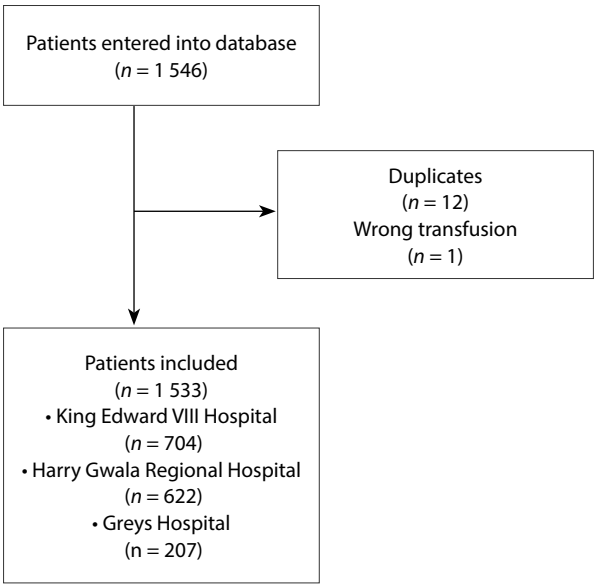

Figure 1: Patient selection flow diagram

Cohort characteristics

Characteristics of the cohort are displayed in Table I. The mean (SD) patient age was 28.4 (6.7) years. The median (range) gestational age was 38.0 weeks (26–43) and 23.7% (360/1 516) of parturients underwent preterm CS. The mean (SD; range) gravidity was 2.46 (1.25; 1–8). Of the patients, 52.3% (792/1 531) had no previous CS, while 17.9% (271/1 513) had a history of two or more previous CS. HIV infection was the most common comorbidity present in 38.6% (591/1 533) of patients, followed by hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, eclampsia and haemolysis elevated liver enzymes low platelets (HELLP) syndrome) in 23.4% (358/1 533) of patients.

Table II shows procedure-related data. Of the patients, 72.4% (1 104/1 524) presented for emergency CS (category 1 and 2). The indications for CS were 'obstetric' in 46.6% (708/1 518) of cases, and 'fetal' in 31.3% (475/1 518). APH occurred in 5.1% (77/1 518) of parturients. A placental abnormality (PP and/or AP) was present in 5.2% (80/1 533) of patients. Median (range) estimated blood loss was 500 ml (100–4 500). We identified 95 patients (6.2%; CI 5.0–7.4) as having a 'major bleeding risk' (see methods), with 33 (2.2%) patients having one risk and 62 (4%) having two or more major bleeding risks.

Table III indicates the perioperative blood investigations. The antenatal booking Hb was known in 15% (230/1 533) of patients, and 27.8% (64/230) of these patients had anaemia (Hb < 11 g/dL as defined by the World Health Organization).[21] In comparison, a preoperative Hb was known in 99.2% (1 520/1 533) of patients. The mean (SD; range) preoperative Hb level was 11.5 g/dL (1.64; 5.0–18.0).

BT-related data are displayed in Table IV. The indication for BT was the Hb level in 46.5% of patients, ongoing blood loss in 23.9% and haemodynamic instability in 12.6%. The mean (SD; range) Hb trigger for transfusion was 7.1 g/dL (0.93; 5–9). Patients were transfused in all perioperative phases.

Table I: Description of cohort

Variable	All patients (*n* = 1 533) *n/N* (%)	Patients receiving blood transfusion (*n* = 71) *n/N* (%)	Patients not receiving blood transfusion (*n* = 1 462) *n/N* (%)	Univariate odds ratio (95% CI)	*p*-value
Age	*N* = 1 531				
Mean (SD)	28.4 (6.7)	27.7 (6.1)	28.5 (6.7)	0.98 (0.95–1.02)	0.356
< 18 years	72 (4.7)	4 (5.6)	68 (94.4)	Reference	0.405
18–34 years	1 148 (75.0)	57 (5.0)	1 091 (95.0)	0.89 (0.31–2.52)	0.824
≥ 35 years	311 (20.3)	10 (3.2)	301 (96.8)	0.57 (0.17–1.86)	0.346
Gestation	*N* = 1 516				< 0.001
Median (IQR; range) weeks	38.0 (37.0–39.0; 26–43)	37.0 (33.0–39.0)	38.0 (37.0–39.0)	0.87 (0.82–0.93)	< 0.001
Preterm (26–36 weeks)	360 (23.7)	32 (8.9)	328 (91.1)	2.87 (1.77–4.67)	< 0.001
Term (37–42 weeks)	1 152 (76.0)	38 (3.3)	1 114 (96.7)	Reference	
Post-dates (> 42 weeks)	4 (0.3)	0 (0)	4 (100)	-	-
Gravidity	*N* = 1 530				
Mean (SD; range)	2.46 (1.25; 1–8)	2.68 (1.26)	2.45 (1.25)	1.15 (0.96–1.37)	0.143
1	396 (25.9)	16 (4.0)	380 (96.0)	Reference	0.076
2	457 (29.9)	14 (3.1)	443 (96.9)	0.75 (0.36–1.56)	0.441
3	381 (24.9)	26 (6.8)	355 (93.2)	1.74 (0.92–3.30)	0.090
4 or more	296 (19.3)	15 (5.1)	281 (94.9)	1.27 (0.62–2.61)	0.519
Singleton vs multiple	*N* = 1 529				
Singleton	1 471 (96.2)	67 (4.6)	1 404 (95.4)	Reference	
Multiple	58 (3.8)	4 (6.9)	54 (93.1)	1.55 (0.55–4.41)	0.409
Previous caesarean section (CS)	*N* = 1 513				
0	792 (52.3)	33 (4.2)	759 (95.8)	Reference	0.002
1	450 (29.7)	13 (2.9)	437 (97.1)	0.68 (0.36–1.31)	0.254
2 or more	271 (17.9)	23 (8.5)	248 (91.5)	2.13 (1.23–3.70)	0.007
Comorbidities	*N* = 1 533				
COVID					
Negative	1 065 (69.5)	48 (4.5)	1 017 (95.5)	Reference	0.507
Unknown	461 (30.1)	22 (4.8)	439 (95.2)	1.06 (0.63–1.78)	0.820
Positive	7 (0.5%)	1 (14.3)	6 (85.7)	3.53 (0.42–29.92)	0.247
HIV status	*N* = 1 533				
Negative	924 (60.3)	37 (4.0)	887 (96.0)	Reference	0.358
Positive	591 (38.6)	33 (5.6)	558 (94.4)	1.42 (0.88–2.30)	0.155
Unknown	18 (1.2)	1 (5.6)	17 (94.4)	1.41 (0.18–10.88)	0.742
Hypertensive disorders	*N* = 1 533				
None	1 127 (73.5)	52 (4.6)	1 075 (95.4)	Reference	0.287
Chronic HPT	48 (3.1)	3 (6.3)	45 (93.8)	1.38 (0.42–4.58)	0.601
Gestational HPT	91 (5.9)	2 (2.2)	89 (97.8)	0.47 (0.11–1.94)	0.293
Eclampsia/preeclampsia	245 (16.0)	11 (4.5)	234 (95.5)	0.97 (0.50–1.89)	0.933
HELLP syndrome	22 (1.4)	3 (13.6)	19 (86.4)	3.26 (0.94–11.38)	0.063
Categories compared	*N* = 1 533				
No HPT disorder	1 127 (73.5)	52 (4.6)	1 075 (95.4)	Reference	0.859
Chronic HPT	48 (3.1)	3 (6.3)	45 (93.8)	1.38 (0.42–4.59)	0.601
HPT disorder of pregnancy	358 (23.4)	15 (4.5)	342 (95.5)	0.97 (0.55–1.71)	0.909

n – number; data are *n/N* (%), denominators vary with the completeness of the data, SD – standard deviation, IQR – interquartile range, CI – confidence interval, CS – caesarean section, COVID – severe acute respiratory syndrome coronavirus, HIV – human immunodeficiency virus, HPT – hypertension, HELLP – haemolysis, elevated liver enzymes, low platelet count

Table II: Procedure-related information

Variable	All patients (*n* = 1 533) *n/N* (%)	Patients receiving blood transfusion (*n* = 71) *n/N* (%)	Patients not receiving blood transfusion (*n* = 1 462) *n/N* (%)	Univariate odds ratio (95% CI)	*p*-value
ASA PS	*N* = 1 531				< 0.001
ASA II	1 349 (88.1)	47 (3.5)	1 302 (96.5)	Reference	
ASA III–IV	182 (11.9)	24 (13.2)	158 (86.8)	4.21 (2.51–7.07)	< 0.001
Urgency of surgery (Category of CS)	*N* = 1 524				0.001
Emergency/urgent (Category 1 + 2)	1 104 (72.4)	64 (5.8)	1 040 (94.2)	3.63 (1.65–7.99)	0.001
Scheduled/elective (Category 3 + 4)	420 (27.6)	7 (1.7)	413 (98.3)	Reference	< 0.001
Primary indication for CS	*N* = 1 518				*P* < 0.001
APH	77 (5.1)	19 (24.7)	58 (75.3)	9.11 (3.25–25.55)	< 0.001
Fetal	475 (31.3)	18 (3.8)	457 (96.2)	1.10 (0.40–3.00)	0.860
Maternal	114 (7.5)	6 (5.3)	108 (94.7)	1.54 (0.46–5.20)	0.483
Obstetric	708 (46.6)	23 (3.2)	685 (96.8)	0.93 (0.35–2.50)	0.891
Multiple (excluding APH)	144 (9.5)	5 (3.5)	139 (96.5)	Reference	
Time of surgery	*N* = 1 528				
Day (07:00–16:59)	890 (58.2)	34 (3.8)	856 (96.2)	Reference	
Afterhours (17:00–06:59)	638 (41.8)	37 (5.8)	601 (94.2)	1.55 (0.96–2.50)	0.072
Hospital	*N* = 1 533				*P* = 0.003
Harry Gwala Regional (regional)	622 (40.6)	15 (2.4)	607 (97.6)	Reference	0.004
King Edward VIII (regional/tertiary)	704 (45.9)	42 (6.0)	662 (94.0)	2.57 (1.41–4.68)	0.002
Greys (tertiary)	207 (13.5)	14 (6.8)	193 (93.2)	2.94 (1.40–6.19)	0.005
Mode of anaesthesia	*N* = 1 516				< 0.001
Regional (spinal/CSE/epidural)	1 374 (90.6)	44 (3.2)	1 330 (96.8)	Reference	< 0.001
General (GA or converted)	142 (9.4)	27 (19.0)	115 (81.0)	7.10 (4.24–11.89)	< 0.001
Placental abnormalities	*N* = 1 533				
Placenta praevia (PP)	19 (1.2)	7 (36.8)	12 (63.2)	13.22 (5.03–34.70)	< 0.001
Abruptio placentae (AP)	62 (4.0)	13 (21.0)	49 (79.0)	6.46 (3.32–12.57)	< 0.001
Placental abnormalities	*N* = 1 533				
No abnormality	1 453 (94.8)	52 (3.6)	1 401 (96.4)	Reference	< 0.001
Placental abnormality (PP + AP)	80 (5.2)	19 (23.8)	61 (76.3)	8.39 (4.68–15.06)	< 0.001
Intraoperative blood loss	*N* = 1 498				
Median (range) in ml	500 (100–4 500)	650 (200–4 500)	500 (100–2 000)	-	< 0.001
Estimated blood loss (PPH)	*N* = 1 498				
No PPH (< 1 000 ml)	1 406 (93.9)	54 (3.8)	1 352 (96.2)	Reference	
PPH (1 000–1 499 ml)	74 (4.9)	5 (6.8)	69 (93.2)	1.81 (0.70–4.68)	0.218
Severe PPH (> 1 500 ml)	18 (1.2)	11 (61.1)	7 (38.9)	39.34 (14.68–105.45)	< 0.001
Major bleeding risk*	*N* = 1 533				
No risk	1 438 (93.8)	51 (3.5)	1 387 (96.5)	-	
Major bleeding risk	95 (6.2)	20 (21.1)	75 (78.9)	7.25 (4.11–12.78)	< 0.001

n – number; data are *n/N* (%), denominators vary with the completeness of the data, ASA PS – American Society of Anesthesiologists physical status, CS – caesarean section, APH – antepartum haemorrhage, CSE – combined spinal-epidural, GA – general anaesthesia, PP – placenta praevia, AP – abruptio placentae, PPH – postpartum haemorrhage
*Major bleeding risk is defined as a composite of placenta praevia, abruptio placentae and antepartum haemorrhage

Table III: Blood investigations

Variable	All patients (*n* = 1 533) *n/N* (%)	Patients receiving blood transfusion (*n* = 71) *n/N* (%)	Patients not receiving blood transfusion (*n* = 1 462) *n/N* (%)	Univariate odds ratio (95% CI)	*p*-value
Preoperative haemoglobin (g/dL)	*N* = 1 520				
Mean (SD; range)	11.5 (1.64; 5.0–18.4)	11.6 (1.54)	9.5 (2.14)	-	0.001*
Hb categories by severity	*N* = 1 520				
< 8.9 (moderate, severe)	87 (5.7)	31 (35.6)	56 (64.4)	32.73 (16.90–63.38)	< 0.001
9–10.9 (mild)	471 (31.0)	24 (5.1)	447 (94.9)	3.17 (1.67–6.04)	< 0.001
> 11.0 (normal/high)	962 (63.3)	16 (1.7)	946 (98.3)	Reference	
Platelet count (cells/mm³)	*N* = 1 169 (76.3%)				
Mean (SD; range)	230.19 (179.0; 18–602)	230.52 (75.69)	224.18 (99.72)	-	0.006*
Platelet count by severity (cells/mm³)	*N* = 1 169				
< 100 (severe, moderate)	33 (2.8)	8 (24.2)	25 (75.8)	6.74 (2.88–15.76)	< 0.001
101–150 (mild)	121 (10.4)	7 (5.8)	114 (94.2)	1.30 (0.57–2.93)	0.538
> 151 (normal)	1 015 (86.8)	46 (4.5)	969 (95.5)	Reference	

n – number; data are *n/N* (%), denominators vary with the completeness of the data, CI – confidence interval, SD – standard deviation, Hb – haemoglobin in g/dL, BT – blood transfusion
*Independent samples t-test

Table IV: Transfusion-related data

Variable	Number of transfusion events *n – n/N* (%)
Timing of BT	*N* = 76
Preoperative only	17 (22.4)
Intraoperative only	11 (14.5)
Postoperative only	36 (47.4)
Multiple (pre/intra/post)	12 (15.8)
Indication for BT	*N* = 71
Haemodynamic instability	9 (12.6)
Haemoglobin level	33 (46.5)
Ongoing blood loss	17 (23.9)
Multiple/other	11 (15.5)
Hb trigger for BT	
Mean (SD; range)	7.1 (0.93; 5–9)
Transfusion of blood products	*N* = 1 533
Platelets concentrate	13 (0.8%)
FDP (FFP)	15 (1%)
Cryoprecipitate	1 (0.1%)

n – number; data are *n/N* (%), BT – blood transfusion, Hb – haemoglobin in g/dL, FDP – freeze dried plasma, FFP – fresh frozen plasma

A platelet count was available for 76.3% (1 169/1 553) of patients. Thrombocytopaenia, platelet count < 100 000 cells/mm³, was present in 2.8% (33/1 169) of patients, 10% (121/1 169) had counts from 100 000–150 000 cells/mm³ and 13 (0.8%) had a platelet transfusion.

Outcome data

Of the patients, 71/1 533 received a BT, which is an overall prevalence of 4.6% (95% CI 3.6–5.7). The prevalence of pre-operative anaemia was 36.7% (558/1 520; 34.3–39.1) and the prevalence of PPH (BDACS) of > 1 000 ml was 6.1% (92/1 498; 4.8–7.2).

Of the exposure variables identified from the literature (as described in the methods section), seven were identified as significant in univariable analyses and were entered into the multivariable model, namely: major bleeding risk (PP, AP and APH), preterm delivery, preoperative anaemia, previous CS, emergency CS, preoperative platelet count and PPH (BDACS). Hypertensive disorders of pregnancy, multiple gestation and HIV-infection status were found not significant in univariable analyses. Table V displays the multivariable analysis. Of the seven variables entered into the multivariable model, five were found independently predictive of BT, namely: (i) major bleeding risk (PP, AP and APH) aOR 5.34 (95% CI 2.11–13.52; $p < 0.001$; VIF 1.061); (ii) preoperative anaemia both mild (Hb 9–10.9 g/dL) 2.39 (1.10–5.22; $p = 0.029$; VIF 1.022) and moderate/severe (Hb < 9 g/dL) 28.37 (12.39–64.97; $p < 0.001$; VIF 1.022); (iii) previous CS (two or more) 2.52 (1.21–5.25; $p = 0.014$; VIF 1.090); (iv) platelet count < 100 000 cell/mm³ 5.02 (1.41–17.83; $p = 0.013$; VIF 1.019); and (v) PPH > 1 500 ml 27.86 (6.72–115.54; $p < 0.001$; VIF 1.033). While urgency of CS and preterm delivery were significantly associated with BT in the univariable analyses, this association was not demonstrated in the multivariable analyses.

Discussion

The principal finding of this prospective observational study was that the prevalence of BT associated with CS in KwaZulu-Natal is twice that in HIC, with one in twenty women requiring a BT.[7,14] More than one in three women had preoperative anaemia, and one in sixteen experienced a PPH. Five variables independently associated with BT were major bleeding risk (PP, AP and APH), preoperative anaemia, platelet count < 100 000 cells/mm³, a history of two or more previous CSs, and PPH > 1 500 ml (BDACS).

Table V: Multivariable analysis of candidate variables for blood transfusion

Risk factors	Univariate analysis		Multivariable analysis			
	OR (95% CI)	*p*-value	ß weight	SE	OR (95% CI)	*p*-value
Major bleeding risk*	7.25 (4.11–12.78)	< 0.001	1.68	0.47	5.34 (2.11–13.52)	< 0.001
Emergency CS	3.63 (1.65–7.99)	0.001	0.71	0.46	2.03 (0.82–5.01)	0.126
Preterm labour	2.87 (1.77–4.67)	< 0.001	0.26	0.35	1.30 (0.66–2.56)	0.457
Preoperative anaemia						
Hb < 8.9 g/dL	32.73 (16.90–63.38)	< 0.001	3.35	0.42	28.37 (12.39–64.97)	< 0.001
Hb 9.0–10.9 g/dL	3.17 (1.67–6.04)	< 0.001	0.88	0.40	2.39 (1.10–5.22)	0.029
Hb > 11.0 g/dL	Reference				Reference	
Previous CS (two or more)	2.41 (1.44–4.05)	0.001	0.92	0.38	2.52 (1.21–5.25)	0.014
Platelet count (cells/mm³)						
< 100	6.74 (2.88–15.76)	< 0.001	1.61	0.65	5.02 (1.41–17.83)	0.013
100–150	1.30 (0.57–2.93)	0.538	0.53	0.50	1.70 (0.64–4.53)	0.288
> 150	Reference				Reference	
Postpartum haemorrhage – bleeding during or after CS						
< 1 000 ml	Reference				Reference	
1 000–1 499 ml	1.81 (0.70–4.68)	0.218	-0.30	0.79	0.74 (0.16–3.48)	0.702
> 1 500 ml	39.34 (14.68–105.45)	< 0.001	3.32	0.73	27.86 (6.72–115.54)	< 0.001
Constant	-	-	-5.25	0.52	0.005	< 0.001

OR – odds ratio, CI – confidence interval, ß weight – ß coefficient, SE – standard error, CS – caesarean section, Hb – haemoglobin
*Major bleeding risk is defined as a composite of placenta praevia, abruptio placentae and antepartum haemorrhage

It is not unexpected that our study confirms that the prevalence of BT associated with CS is higher than in HIC, but lower than in low-income countries (LICs), where one in ten to as many as one in four women require BT.[7,12,13,15] In HIC, BT averages 2.5% but may be as low as 0.63%.[9,14,24] Our transfusion rate was similar to that in other middle-income countries,[17,25] although higher than in China, where a retrospective study found a BT rate of only 0.53%.[7] The prevalence of PPH (6.1%) in our study was within the estimated worldwide prevalence of 5–10%. However, PPH or BDACS is commonly underestimated due to reporting error even in HIC, and when blood loss is measured more accurately, PPH may be as high as 13–20%.[26] PPH is not only a significant determinant of mortality in CS,[3,4] but is also considered a 'near-miss' for potential mortality and may result in devastating events such as cardiopulmonary resuscitation, emergency hysterectomy and repeat laparotomy, and require transfer to higher levels of care, postoperative intensive care, acute dialysis and need for large volume BT.[27]

Reasons for the higher prevalence of BT and PPH in LMICs are multifactorial and may include quality of antenatal, peripartum and perioperative care.[3,21] Despite this higher prevalence, access to blood is limited and compounds the risks associated with CS.[3-5] Our finding that estimated blood loss during and after CS of > 1 500 ml increased the odds of transfusion 27-fold, highlights the importance of early recognition of complications at CS, accurate estimation of blood loss, and staff training and drills on recognition and management of PPH.[4,27] Two of the hospitals in our study had onsite blood banks and the third had ready access to blood and blood products. However, this is not the case at all South African hospitals. Lack of access to blood and blood products was not only identified in 54% of rural district hospitals performing CS in KwaZulu-Natal, but also in 40% of urban regional hospitals.[28]

Placental abnormalities and APH are consistently identified as high risk for BT,[6,7,9] and as a composite, preoperative 'major bleeding risk' is not only associated with increased maternal mortality[3] but also a fivefold increased risk of BT as identified in our study. PP must be screened for in pregnancy, and patients need to be referred to a higher level of care. Early recognition of AP and APH must similarly alert clinicians to an increased risk of BT, and blood resources must be mobilised early to allow appropriate perioperative planning.

Our study identified a twofold increased risk for BT for patients with mild preoperative anaemia, and 28-fold increased risk for moderate/severe anaemia, and confirmed findings from previous studies.[6] One in three patients in this study had anaemia, a similar finding to that in other South African studies[29] but far higher compared to HIC.[30] We were concerned about the low rate of antenatal booking blood results from the referral centres in our patients' charts, and postulate this was due to poor integration of patient records from clinics to hospitals. The high prevalence of preoperative anaemia indicates that antenatal management of anaemia is suboptimal in our CS population and requires attention. This represents a missed opportunity for timely diagnosis and management of antenatal anaemia, which may reduce the need for BT. In addition, repeated blood tests at CS become necessary, which has cost implications.

Our study also showed that a platelet count of < 100 000 cells/mm³ was associated with a fivefold increased risk for BT. To our

knowledge, only one other retrospective study has identified thrombocytopaenia to be associated with BT at CS.[17] In the recently updated practice guidelines for obstetric anaesthesia by the ASA, a routine preoperative platelet count in a healthy parturient is not recommended.[31] This view is supported by other authors from HICs who reserve full blood count (FBC) for patients with identified risks for BT; however, this is in a context where the BT rate was < 0.6% and the prevalence of antenatal anaemia was low or appropriately treated.[9] As both anaemia and thrombocytopaenia independently increased the odds for BT, the necessity for a routine preoperative FBC (or at least Hb and platelet count), although not currently a standard of care, should be further studied in the South African CS population to identify those patients who require preoperative platelet count testing.[32] We postulate that this may be the case in patients with an identified major bleeding risk or preeclampsia/eclampsia.[33]

Our study did not identify preterm delivery or emergency CS as risks for BT,[6] although we did find that a history of two or more previous CSs is associated with a 2.5-fold increased odds for BT. Data on previous CS as a factor predicting BT are contradictory,[9,34-36] although pooled data from the recent meta-analysis by Iqbal et al.[6] did not find such an association. Differences in findings may be due to study populations, complexity, surgical experience and the referral category of the hospitals studied.[15] In our population, patients with two or more previous CSs should be considered at risk for BT and additional measures undertaken, such as screening for anaemia, ensuring availability of blood and referral to a higher level of care.

Hypertensive disorders of pregnancy have previously been identified as associated with an increased prevalence of BT at CS.[6] However, we did not confirm this finding. It is possible that the presence of hypertensive disorders per se may not result in an increased need for BT, but rather the associated thrombocytopaenia. However, this is speculative and the lack of association between hypertensive disorder of pregnancy and BT should be further explored in future studies.

The prevalence of HIV infection in our study was 38.6%, more than double that of the ASOS obstetrics data set.[3] A South African study published in 2018 indicated that HIV infection was associated with peripartum BT.[16] However, as in a study in Nigeria,[15] we did not confirm this finding. Since 2018, significant changes in testing and treatment regimens were issued in South Africa and all HIV-positive pregnant women are now treated regardless of their CD4 count, improving their overall health status, including anaemia.[37] Although speculative, this may explain our findings.

Study limitations and strengths

There were several limitations in our study. To ensure completeness of data collection, we limited the variables collected to those most commonly described in the literature, and may therefore have missed important information regarding associations with BT. The hospitals which were studied are relatively well resourced and manage more complex obstetric cases compared to other units, and therefore do not represent the same obstetric population, staffing or resources available at all KwaZulu-Natal hospitals. This may limit the generalisability of the findings. The details of transfusion protocols at the hospitals studied were not investigated, therefore indications for BT may have differed among the three hospitals.

A strength of our study is that this was a large prospective study of associations with BT specifically in the setting of CS in South Africa, and the factors identified can be easily disseminated and used in our obstetric population to pre-empt the need for BT or referral to higher levels of care. The study has also identified missed opportunities to improve care of pregnant women (e.g. treatment of antenatal anaemia) which may reduce the prevalence of BT. Our dataset could also be used as a derivation population to develop a predictive score for the likelihood of BT, which could be validated in a larger cohort.

Conclusion

We confirmed a higher prevalence of BT in the setting of CS than in HIC. Major bleeding risks (a composite of PP, AP and APH) and BDACS should be identified early to allow appropriate perioperative planning and mobilisation of blood resources. Antenatal anaemia is a preventable and treatable condition, and earlier diagnosis and treatment should be prioritised. We have also shown that even moderate thrombocytopaenia increases the risk of BT.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

Primary ethics approval was obtained from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (UKZN), South Africa (BE082/19).

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