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Non-invasive haemoglobin measurement in patients undergoing elective Caesarean section

A. Butwick*, G. Hilton and B. Carvalho

Department of Anaesthesia (MC: 5640), Stanford University School of Medicine, 300 Pasteur Drive, Stanford CA 94305, USA

* Corresponding author. E-mail: ajbut@stanford.edu

Editor's key points

- This study evaluated a new non-invasive co-oximeter in patients undergoing Caesarean section (CS) under regional anaesthesia.
- There were variable bias and wide limits of agreement between co-oximeter and laboratory haemoglobin (Hb) values.
- Haemoglobin from Pulse CO-Oximeter measurements tended to be higher than laboratory Hb values with the greatest differences at 24 h after CS.

Background. The ability to measure haemoglobin (Hb) real-time and non-invasively offers important clinical value in the assessment of acute changes in maternal Hb during the peripartum period. This study evaluates the Masimo Rainbow SET® Radical-7 Pulse CO-Oximeter in a pregnant population undergoing Caesarean section (CS).

Methods. Fifty patients undergoing elective CS were enrolled in this prospective, controlled study and followed for 48 h after surgery. Non-invasive Masimo Hb (SpHb) values were compared with laboratory Hb values from venous blood samples drawn at baseline, immediately post-CS, and 24 h post-CS using the Bland–Altman plots. Longitudinal analysis of SpHb changes over time was performed using mixed-effects regression modelling.

Results. For the comparison between SpHb and laboratory Hb, SpHb displayed a significant positive bias at baseline {1.22 g dl^{-1} [95% confidence interval (CI): 0.89–1.54]} and at 24 h post-CS [1.36 g dl^{-1} (95% CI: 1.04–1.68)]. The bias immediately post-CS was 0.14 g dl^{-1} (95% CI: −0.18 to 0.46). The limits of agreement at baseline, immediately post-CS, and at 24 h post-CS were: −0.9 and 3.33, −2.35 and 2.56, and −0.55 and 3.27 g dl^{-1}, respectively. The mean decrease in SpHb from baseline to 48 h post-CS was ∼1 g dl^{-1}.

Conclusions. The variability in bias and limits of agreements of the Rainbow SET® Radical-7 Pulse CO-Oximeter SpHb may limit its clinical utility for assessing Hb concentration in patients undergoing elective CS. Modifications are needed in the calibration of the device to improve accuracy and precision in an obstetric setting.

The study was registered at clinicaltrials.gov (NCT01108471) before participant enrolment: URL=http://clinicaltrials.gov/ct2/show/NCT01108471?term=butwick&rank=1.

Keywords: blood loss, surgical; Caesarean section; haemoglobin; haemoglobinometry; haemorrhage; haemorrhage, postpartum; transcutaneous oximetry

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Recent evidence indicates that the incidence of postpartum haemorrhage in well-resourced countries is increasing.[1] Although rates of maternal death due to postpartum haemorrhage are decreasing in the USA[2] and UK,[3] severe haemorrhage is a major contributory factor towards severe obstetric morbidity (such as peripartum hysterectomy, postpartum intensive care support).[4–7] Transfusion therapy is an important component in the management of postpartum haemorrhage. However, there is marked variability among obstetricians and anaesthetists in attitudes towards transfusion therapy for obstetric patients,[8] and concern regarding the use of inappropriate transfusions in obstetric patients.[9 10]

The introduction of a device for measuring real-time, continuous non-invasive haemoglobin (Hb) measurement offers the potential to monitor acute changes in maternal Hb concentrations during the peripartum period, and to improve physician decision-making for the timing of transfusion therapy in patients experiencing postpartum haemorrhage. Recent technological advances in the field of multi-wavelength pulse oximetry have led to the commercial release of the Masimo Rainbow SET® Radical-7 Pulse CO-Oximeter (Masimo Corp., Irvine, CA, USA) that continuously and non-invasively estimates total Hb (SpHb). A recent study in human volunteers undergoing haemodilution reported that the Pulse CO-Oximetry assessment was accurate to 1 g dl^{-1} (at 1 SD).[11] However, variable absolute differences between SpHb and laboratory Hb values have also been reported (<1.5 g dl^{-1} for 61% of observations,

between 1.6 and 2.0 g dl^{-1} for 16% observations, and >2.0 g dl^{-1} for 22% of the observations) in patients undergoing spinal surgery.[12]

To our knowledge, there have been no published studies investigating SpHb measurement in pregnant patients. The aims of this study were to test the accuracy and reliability of SpHb measurement compared with Hb measurement using standard laboratory CO-Oximetry among obstetric patients undergoing elective Caesarean section (CS). The secondary aims were to assess the relationships between SpHb and laboratory Hb values with total estimated blood loss (EBL) values and to assess temporal changes in SpHb values up to 48 h post-CS.

Methods

After obtaining Institutional Review Board approval and written informed consent, 50 healthy term patients (≥37 weeks gestation) undergoing elective CS were enrolled in this prospective controlled study. Inclusion criteria were ASA I or II status, age between 18 and 40 yr, singleton pregnancies, and elective CS with a Pfannenstiel incision. Patients were excluded from study participation if they met any of the following criteria: abnormal Hb disorders, hyperbilirubinaemia, smokers, peripheral vascular disease or conditions affecting vascularity of the digits, significant medical condition, and multiple pregnancy. The study was conducted at Lucile Packard Children's Hospital (Stanford, CA, USA), and patients were enrolled between April 2010 and September 2010.

Before surgery, all patients received premedication with i.v. ranitidine 50 mg and metoclopramide 10 mg. All patients received 500 ml of 6% hetastarch (Hespan®; B. Braun Medical Inc., Irvine, CA, USA) as a fluid preload i.v. ~30 min before neuraxial anaesthesia. Spinal or combined spinal–epidural anaesthesia was performed at the L3–4 interspace with the patient in the sitting position by an anaesthetist not involved in the study. Spinal anaesthesia comprised hyperbaric bupivacaine 1.6 ml 0.75%, fentanyl 10 μg, and morphine 100 μg. Each patient was then moved to the supine position with left lateral uterine displacement. Surgery was allowed to proceed after achieving a minimum T5 sensory level to pinprick. Crystalloid solution (lactated Ringer's solution) was infused during the intraoperative period, with the aim of keeping total crystalloid volume to ≤2 litre. Intraoperative fluid management was at the discretion of the supervising anaesthetist who was not involved in the study.

For the treatment of intraoperative hypotension (defined as any decrease in systolic arterial pressure >10% below baseline), an i.v. bolus of phenylephrine 50–100 μg was used as the primary vasopressor and an i.v. bolus of ephedrine 5–10 mg was reserved as a second-line agent. After delivery of the fetus, the supervising obstetrician manually removed the placenta and performed uterine massage. Uterine exteriorization was performed at the discretion of the obstetrician. All patients received i.v. oxytocin prophylaxis which comprised a 1 unit bolus followed by an infusion (30 units oxytocin diluted in 1000 ml lactated Ringer's solution at an infusion rate determined by the supervising anaesthetist).

The primary study endpoints were SpHb and laboratory Hb values, which were measured at specific time points defined *a priori*: baseline (before preload in the preoperative period), in the immediate postoperative period (within 10 min of arrival in recovery), and 24 h after completion of surgery. SpHb measurements were also obtained at other pre-defined time points: immediately before anaesthesia; after confirming adequate neuraxial blockade height for surgery; at the time of uterine incision; after adequate uterine tone had been confirmed by manual assessment by the supervising obstetrician; and at 1, 4, and 48 h after CS.

SpHb values were recorded using the Masimo Rainbow SET® Radical-7 Pulse CO-Oximeter (software version 7.6.0.4; Masimo Corp.), and data were extracted using Trendcom™ software (provided by Masimo Corp.). The device applies multiple visible and infrared wavelengths of light to the measurement site (finger) from light-emitting diodes. This light is then received by a photodetector that generates electrical signals, and advanced algorithms process these digital signals to provide an output of predicted Hb density. For this study, the SpHb probe (version Rev E) was attached to the index or middle finger of the non-dominant hand. An approved plastic shield was used to cover the sensor to avoid optical interference. The Pulse CO-Oximeter also provides a pulsatile index value, which is the pulsatile signal indexed against the non-pulsatile signal and is an indication of localized perfusion; these values were also recorded at the same time points for SpHb measurement. Laboratory Hb measurement was performed in the Stanford University Medical Center Clinical Laboratories using one of the following instruments: Coulter LH 750 or LH 780 haematology analysers (Beckman Coulter, Inc., Brea, CA, USA); CELL-DYN Sapphire® or CELL-DYN 1800 haematology analysers (Abbott Laboratories, Abbott Park, IL, USA).

Maternal venous blood samples were used for the measurement of laboratory Hb concentrations. Blood samples were collected by trained study investigators who were not involved in patient care during the study period. In the preoperative period, an 18 G peripheral i.v. cannula was inserted into a forearm vein and the baseline blood sample was obtained. The post-CS blood samples were obtained from a peripheral vein using a 22 G butterfly needle from the arm not containing the i.v. cannula. SpHb values were recorded at the same time as the venous blood sampling. The supervising anaesthetist was blinded to SpHb measurements, and no clinical decisions were based on the recorded SpHb values during the study period.

The measurement of total EBL was performed at the end of surgery. Total EBL was calculated as the sum total of the following measurements: (i) the weight of blood on surgical swabs using electronic scales; (ii) estimation of the volume of blood in the suction chamber; and (iii) blood loss around the surgical field not accounted for by suction and surgical swabs. I.V. fluid volume administered was recorded at the end of the intraoperative period and 24 h post-CS. Other

data recorded included: time from uterine incision to delivery of the fetus (min) and time from delivery of the fetus to delivery of the placenta (min).

Statistical analysis

Patient characteristics and outcome data are summarized with descriptive statistics. Results are expressed as the mean (SD), the median [inter-quartile range (IQR)], or number (%) as appropriate. Data were assessed for normal distribution of variance using normality plots and the Kolmogorov–Smirnov test.

We used linear mixed-effects modelling (SAS PROC MIXED) to assess the method of Hb measurement (laboratory and SpHb) at baseline, immediately post-CS, and 24 h post-CS. The model utilized the Kenward–Roger method and a subject-level random effect to account for within-individual correlations.[13] As we observed time-dependent effects on the method of Hb measurement, the level of agreement between the two measurement techniques was assessed, using the method described by Bland and Altman,[14] at baseline, immediately after CS, and 24 h post-CS. Using this approach, the bias was calculated as the mean difference between the two measures, and the limits of agreement as the interval defined by the bias (2 SD) from the observed differences. We used linear mixed-effects modelling to assess the standard error estimate of the least square mean to provide 95% confidence limits of the bias.

Secondary analyses included an assessment of the magnitudes of differences between SpHb and laboratory Hb. The differences between these two measurements were calculated and subdivided into five categories: <0.5, 0.5–1.0, 1.1–1.5, 1.6–2.0, and >2.0 g dl^{-1}. We analysed the distribution of magnitude of differences into these five categories at baseline, immediately post-CS, and at 24 h post-CS using a model for multinomial data using SAS PROC GENMOD based on a generalized estimated equation approach. We used a cumulative logit model using the distributed data at 24 h post-CS as the response and distributed data at baseline and immediately post-CS as covariates.

Longitudinal analysis of SpHb changes over time was performed using linear mixed-effects regression modelling. In this model, SpHb was the response variable with time as the repeated effect and patient as a random effect. Other covariates included in this model as time-independent variables were total EBL and total i.v. fluids given at 24 h post-CS. We also investigated whether associations existed between percentage change in SpHb and that in laboratory Hb (using baseline and 24 h post-CS values, respectively) with total EBL using Pearson's correlation and linear regression analyses.

The primary sample size calculation was based on the expected difference in laboratory Hb and SpHb values and the confidence interval (CI) for the 95% limits of agreement as described by Bland and Altman.[14] Based on a previously reported SD of the difference between measurements of 0.92 g dl^{-1}, we calculated that a sample size of 45 patients would provide a 95% CI for the limits of agreement equal to ± 0.47 g dl^{-1}. Based on an estimated 10% patient dropout rate, we aimed to recruit 50 patients for our study. Statistical analysis was performed with Microsoft Excel 2004® (Microsoft Corp., Redmond, WA, USA), SPSS 17.0 statistical package for Windows (Chicago, IL, USA), and SAS 9.2 statistical package (Cary, NC, USA) at a $P<0.05$ significance level.

Results

All 50 patients enrolled completed the study, and no patients were lost to follow-up or non-compliance (Fig. 1, Table 1). Before surgical incision, the median (IQR) upper dermatomal level to cold and pinprick was T3 (T2–T4) and T4 (T3–T4), respectively. The median (IQR) duration of the intraoperative period was 51 (39–67) min. The perfusion index values were $>0.75\%$, the threshold value recommended by the

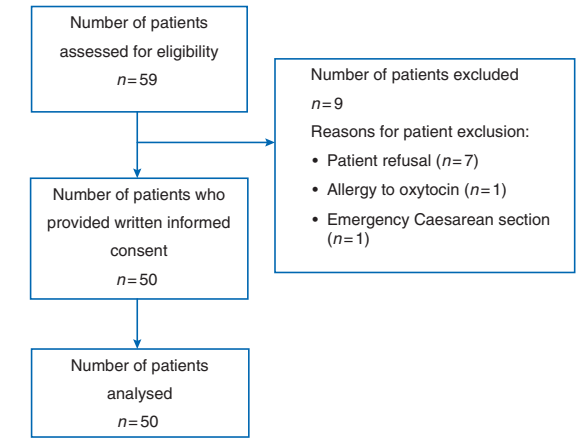

Fig 1 Flow diagram of the study protocol.

Table 1 Patient characteristics and obstetric and intraoperative data. UI, uterine incision; PD, placental delivery. Total EBL, estimated blood loss obtained by adding suction fluid volume (minus amniotic and irrigation fluid), field loss, and weighed swabs. Values expressed as mean (SD), median (IQR) or number (%)

Age (yr)	32 (5)
Height (cm)	160 (157–165)
Weight (kg)	75 (69–85)
Nulliparity	13 (26%)
Previous Caesarean section	34 (68%)
Gestational age (weeks)	39 (37–40)
UI to delivery time (min)	2 (1–3)
Delivery of fetus to PD (min)	2 (1–2)
I.V. crystalloid (ml)	1360 (359)
Total EBL (ml)	565 (424–783)

manufacturer for clinical use, in 494/500 (98%) of all SpHb measurements. No patients required blood transfusion during the study period.

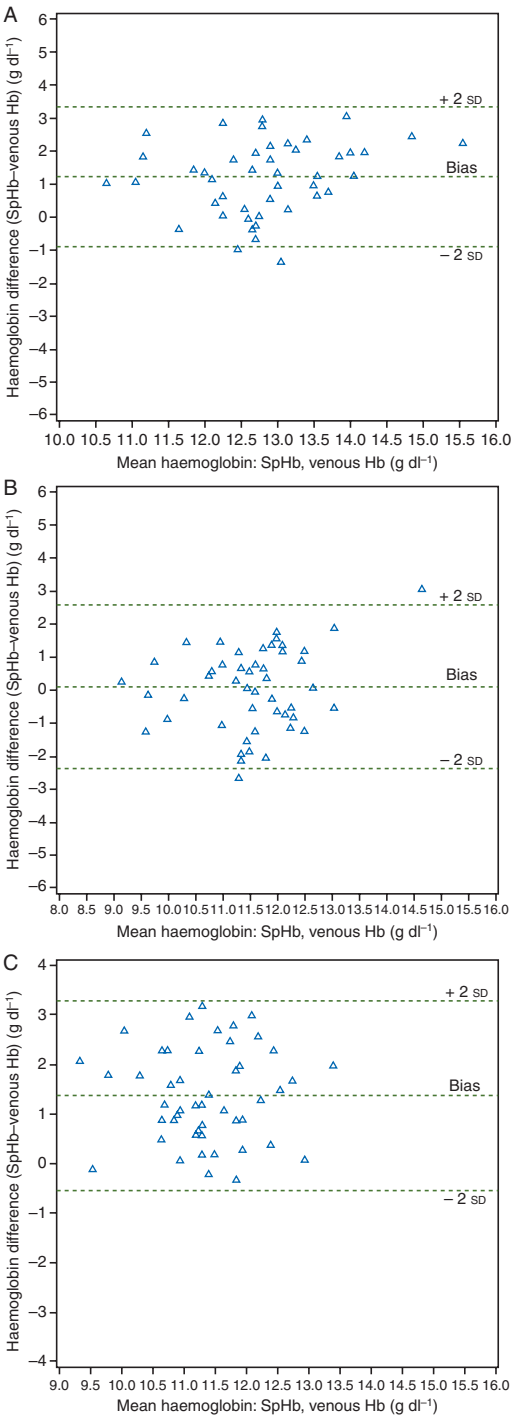

Fig 2 (A) Bland and Altman comparison of Masimo Radical-7 Pulse CO-Oximeter with SpHb™ (SpHb) and venous Hb measured by laboratory CO-Oximetry (A) at baseline, (B) in the immediate postoperative period after CS, and (C) at 24 h post-CS. The horizontal dashed lines correspond to the bias and limits of agreement.

The calculated mean bias at the three main study time points were: 1.22 g dl^{-1} at baseline, 0.14 g dl^{-1} immediately post-CS, and 1.36 g dl^{-1} at 24 h post-CS. The limits of agreement between the two measurements were: −0.9 and 3.33 g dl^{-1} at baseline, −2.35 and 2.56 g dl^{-1} immediately postoperative, and −0.55 and 3.27 g dl^{-1} at 24 h post-CS. The naive Bland–Altman plots of SpHb *vs* laboratory Hb at baseline, immediately post-CS, and 24 h post-CS are shown in Figure 2A–C. Using linear mixed-effects regression modelling, differences in mean Hb were derived at each measured time point (Table 2). There was a statistically significant bias between SpHb and laboratory Hb at baseline and at 24 h post-CS (Table 2). The magnitude of differences between Pulse CO-Oximeter (SpHb) and laboratory Hb concentration at baseline, immediately post-CS, and at 24 h post-CS is outlined in Table 3. There were no significant associations between the distribution of observations at baseline and immediately post-CS with the values at 24 h post-CS (x^2=1.3; P=0.86).

There was evidence of a time-dependent decrease in mean SpHb values from baseline up to 48 h post-CS (Fig. 3). Based on linear mixed-effects regression modelling, there was a decrease of 0.098 g dl^{-1} in SpHb for each measured time point after controlling for total EBL and total volume of i.v. fluids at 24 h post-CS. The mean (SD) decrease in measured laboratory Hb [from baseline to 24 h post-CS was 1.6 (0.94) g dl^{-1}]. There was a weak correlation observed between percentage change in SpHb and total EBL (r=0.30; P=0.04), and no significant correlation was observed between percentage change in laboratory Hb and total EBL (r=0.30; P=0.38).

Discussion

In this prospective study of women undergoing elective CS, we observed variable bias and wide limits of agreement between SpHb and laboratory Hb measurement pre-CS, immediately post-CS, and at 24 h post-CS time points. In addition, the magnitude of the differences between SpHb and laboratory Hb varied at baseline, immediately post-CS, and at 24 h post-CS.

Compared with laboratory CO-Oximetry, SpHb overestimated the laboratory Hb value at baseline and 24 h post-CS (with a mean bias of 1.22 and 1.36 g dl^{-1}, respectively). These values for bias are higher than previously reported in a study of patients undergoing spinal surgery[12] (0.26 g dl^{-1}) and in an observational study of human volunteers undergoing haemodilution[11] (−0.15 g dl^{-1}). However, the limits of agreement in our study were narrower than those observed by Miller and colleagues[12] (−3.24 g dl^{-1}; 3.77 g dl^{-1}). We speculate that the inherent differences between the study populations (obstetric or non-obstetric patients), the type of blood used for laboratory analyses (venous blood or arterial blood), the mode of anaesthesia (neuraxial or general), and the type of surgical intervention may influence the accuracy and precision of SpHb assessments.

Table 2 Differences in measured Hb at baseline, immediately post-CS, and at 24 h post-CS (least mean squares). Hb values presented as g dl^{-1}. Hb, laboratory haemoglobin; SpHb, haemoglobin from Pulse CO-Oximeter; CS, Caesarean section

Time	Difference in SpHb − laboratory Hb	*P*-value	95% confidence intervals	
			Lower	Upper
Pre-CS	1.22	<0.001	0.89	1.54
Immediately post-CS	0.14	0.39	−0.18	0.46
24 h post-CS	1.36	<0.001	1.04	1.68

Table 3 Magnitude of differences between pulse CO-Oximeter (SpHb) and laboratory venous (Hb) haemoglobin concentration (g dl^{-1}) at pre-CS, immediately post-CS, and 24 h post-CS. Data presented as *n* (%). *One laboratory Hb value missing. CS, Caesarean section

SpHb − Hb	<0.5 g dl^{-1}	0.5–1.0 g dl^{-1}	1.1–1.5 g dl^{-1}	1.6–2.0 g dl^{-1}	>2.0 g dl^{-1}
Baseline*	9 (18)	11 (22)	11 (22)	7 (14)	11 (22)
Immediately post-CS*	13 (26)	14 (28)	13 (26)	6 (12)	3 (6)
24 h post-CS	11 (22)	9 (18)	8 (16)	9 (18)	13 (26)
Total	33 (22)	34 (23)	32 (22)	22 (15)	27 (18)

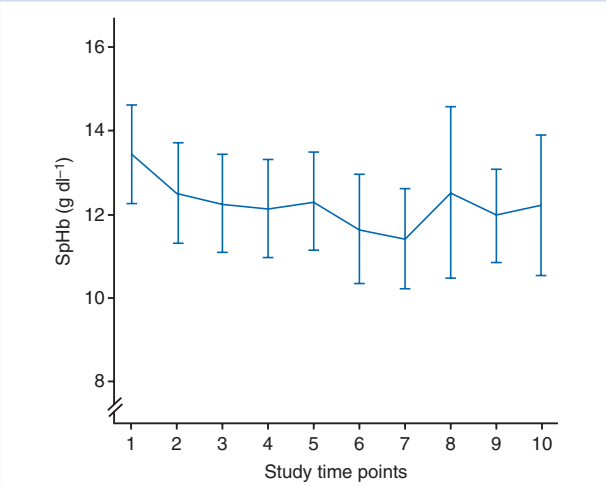

Fig 3 Mean (SD) Masimo Radical-7 Pulse CO-Oximeter SpHb™ values at 10 pre-defined study time points: 1, baseline; 2, immediately before anaesthesia; 3, neuraxial block height confirmation; 4, uterine incision; 5, adequate uterine tone; 6, within 10 min of arrival in recovery; 7, 1 h after completion of surgery; 8, 4 h after completion of surgery; 9, 24 h after completion of surgery; 10, 48 h after completion of surgery.

In our study, the bias was lower and limits of agreement were wider in the immediate post-CS period compared with baseline and at 24 h post-CS, with no significant difference between the comparisons (SpHb *vs* laboratory Hb). The bias and limits of agreement in the immediate post-CS period may have been influenced by perioperative changes in cardiac indices and intravascular volume (such as fluid preloading with hetastarch,[15] vasopressor administration,[16 17] and the effects of neuraxial anaesthesia[18] and oxytocin[16] on the systemic vasculature). The similar bias and limits of agreement at baseline and at 24 h post-CS may be explained by the presumed static physiological state of the study patients at these time points.

With regard to the magnitude of difference between SpHb and laboratory Hb, the overall proportions of patients with SpHb values that were <1.5 and >2.0 g dl^{-1} compared with laboratory Hb concentrations were 67% and 18%, respectively. These values are similar to those reported by Miller and colleagues[12] (61% and 22%, respectively). The observed variability in the magnitude of differences at baseline, immediate, and 24 h post-CS may limit the usefulness of the device for clinical purposes (e.g. decision-making for transfusion therapy) in patients undergoing CS.

We observed weak associations between percentage change in SpHb with total EBL. Previous studies have also shown weak associations between EBL and postpartum changes in Hb or haematocrit.[19 20] It is likely that these weak associations are due to inaccuracy in the subjective assessment of total EBL in patients undergoing CS.[20 21] Although we attempted to measure blood loss gravimetrically by weighing blood-soaked swabs, visual estimation of blood loss was still needed to account for blood in the suction chamber and around the surgical field. Other reconstructive studies have shown that physicians are inaccurate at visually estimating blood loss in an obstetric setting.[22 23] Until more accurate methods of measuring total EBL are scientifically validated, studies investigating associations between total EBL with other maternal parameters will continue to prove challenging.

Based on mixed-effects linear regression modelling, we estimated that the mean decrease in SpHb at 48 h post-CS was ~1 g dl^{-1}. The modest decreases in Hb and SpHb values after CS in our study are similar to those reported in

other studies of low-risk patients undergoing uncomplicated CS;[24 25] therefore, the need for routine laboratory Hb assessment has been questioned. It is possible that SpHb assessment may prove cost-efficient as a screening modality for detecting postpartum anaemia after CS, which has been reported to occur in 4.5–5.1% of patients post-CS.[26] No patients in our study had laboratory Hb values <8 g dl^{-1}; therefore, the performance of Pulse CO-Oximetry in patients with postpartum anaemia is uncertain. However, accurate non-invasive Hb monitoring may also be valuable in reducing the number of inappropriate transfusions in the peripartum and postpartum periods.[9 10]

There are a number of limitations in this study. No patients in the study cohort experienced significant obstetric haemorrhage. Further work is needed to assess the clinical utility of Pulse CO-Oximetry during acute obstetric haemorrhage including investigations on the impact of real-time, continuous, non-invasive SpHb measurement on transfusion decision-making. Our study was conducted in patients who underwent elective CS under neuraxial anaesthesia, and it is uncertain if our results apply to labouring women undergoing unplanned intrapartum CS, CS under general anaesthesia, or vaginal delivery. We collected venous blood samples that were used for the laboratory measurement of Hb concentration. Values for Hb concentrations in venous blood have been reported to be higher than in arterial blood; however, the precision of measurement using venous blood has been shown to be better compared with arterial blood.[27] In addition, four different haematology analysers were used for the laboratory assessment of Hb in the venous blood samples, which may have influenced the variability in the measurement of laboratory Hb values. As the vast majority of patients had perfusion index values $>0.75\%$, we did not perform correlation analysis of perfusion index with SpHb. However, it is possible that dynamic changes in the perfusion index occurred during the study period and these were not detected at our study time points.

In conclusion, our results show that the software and sensor versions for SpHb used in this study may not be sufficiently accurate or precise for clinical purposes in patients undergoing elective CS. However, this technology offers the potential to impact on current practice, as anaesthetists often rely on subjective clinical assessment for determining transfusion therapy due to time delays in the transportation and laboratory processing of blood samples.[28] In particular, improvements in the accuracy of SpHb monitoring would be of important clinical value for obstetric anaesthetists for patient monitoring during the peripartum and postpartum periods. Modifications are needed in the calibration of the device to improve accuracy and precision for assessing Hb concentration in obstetric patients, especially in the setting of obstetric haemorrhage.

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Declaration of interest

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