Original article

Impact of 1- and 2-unit red blood cell transfusions on continuously monitored vital signs: a longitudinal study

Kevin M. Trentino[1,2], Adam Lloyd[1], Kevin Murray[3], Grant Waterer[2,4], Shannon L. Farmer[5,6], Michael F. Leahy[2,7], Wayne B. Dyer[5,8,9], Jonathon Burcham[1], Tim Bowles[1,10], Wendy N. Erber[7,11]

[1]*East CareConnect, East Metropolitan Health Service, Perth, Australia;*
[2]*Medical School, The University of Western Australia, Perth, Australia;*
[3]*School of Population and Global Health, The University of Western Australia, Perth, Australia;*
[4]*East Metropolitan Health Service, Perth, Australia;*
[5]*Discipline of Surgery, Medical School, The University of Western Australia, Perth, Australia;*
[6]*Department of Hematology, Royal Perth Hospital, Perth, Australia;*
[7]*Department of Hematology, PathWest Laboratory Medicine, Royal Perth Hospital, Perth, Australia;*
[8]*Australian Red Cross Lifeblood, Sydney, Australia;*
[9]*Kirby Institute, University of NSW, Sydney, Australia;*
[10]*Critical Care, Royal Perth Bentley Group, Perth, Australia;*
[11]*School of Biomedical Sciences, The University of Western Australia, Perth, Australia*

Background - We measured trends in continuous vital sign parameters and hemoglobin concentration in adult patients before and after 1- and 2-unit red cell (RBC) transfusions.

Materials and methods - A multi-center longitudinal study of 72 patients connected to a remote continuous monitoring service transfused 1 or 2 RBC units. Primary outcome was changes in heart rate (HR), respiratory rate (RR), and oxygen saturation (SpO_2), and secondary outcome was changes in hemoglobin concentration.

Results - Fifty-one patients received 1 RBC unit, 21 received 2 units. During the 10-hour pre-single-unit transfusion period, there were no clinically meaningful trends in HR (0.05, 95% CI, −0.36 to 0.46), RR (0.13, 95% CI, 0.02 to 0.25), or SpO_2 (0.08%, 95% CI, −0.02 to 0.18). There were no clinically meaningful differences in trends in the 24-hour period post-single-unit RBC transfusion when compared to the pre-transfusion trend (HR: 0.03, 95% CI, −0.44 to 0.51; RR: −0.09, 95% CI, −0.22 to 0.05; SpO_2: −0.15%, 95% CI, −0.27 to −0.02). The mean hourly hemoglobin trend 48 hours pre-single-unit transfusion was −0.07 g/dL (95% CI, −0.09 to −0.05) and 0.08 g/dL (95% CI, 0.05 g/dL to 0.10 g/dL) in the 48 hours post transfusion when compared to the pre-transfusion trend. Similar results were observed pre- and post-double-unit RBC transfusion.

Discussion - Despite hemoglobin concentration declines pre-single and double-unit RBC transfusion, and expected increases post-transfusion, there were no clinically meaningful trends in vital signs in the 10 hours before single- or double-unit transfusion or changes in trend in vital signs 24 hours post-transfusion.

Keywords: *Patient Blood Management, continuous vital sign monitoring, transfusion, anemia, remote monitoring.*

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INTRODUCTION

Continuous monitoring of patient vital signs is a promising field of study for red blood cell (RBC) transfusion research. Yet few studies have investigated the impact of RBC transfusion on pre- and post-transfusion physiological parameters in general medical

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Correspondence: Kevin Trentino
e-mail: kevin.trentino@health.wa.gov.au

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and surgical patients. Several studies have investigated the relationship between vital signs in the context of monitoring for acute transfusion reactions[1-3]. However, the parameters collected were not continuous, with many studies taking measurements at 3 different time intervals (before, after 15 mins, and at completion of the transfusion). Furthermore, as the aim of these studies was specifically to monitor patients for acute transfusion reactions, they were not designed to investigate changes in trends in vital signs before and after RBC transfusion.

There are at least two key reasons why continuously monitored vital parameters are valuable to transfusion research. First, it may provide insights into objective physiological metrics for RBC transfusion that may overcome the limitations of using a single arbitrary hemoglobin threshold for groups of patients[4]. This would move assessment towards individualized patient care and monitoring the clinical effectivesness of RBC transfusion on tissue oxygenation. Furthermore, there has been an explosion in artificial intelligence (AI) and machine learning based predictive algorithms and early warning systems[5]. High frequency real-time physiological data collected from continuous monitors could improve the accuracy of adaptive prediction models.

We implemented a continuous remote monitoring service for high-risk medical and surgical inpatients on general hospital wards in December 2020, in the East Metropolitan Health Service (EMHS) in Western Australia[6,7]. This service, known as Health in a Virtual Environment (HIVE), is novel as continuous vital sign monitoring is not standard care outside critical care areas. The data generated by this service provides a unique opportunity to analyze continuous physiological parameters pre- and post-RBC transfusion events.

The purpose of this study was to describe changes in trends in continuously monitored measurements of heart rate (HR), respiratory rate (RR), and oxygen saturation (SpO_2) in hemodynamically-stable adult patients before and after transfusion of 1 or 2 units of RBCs. We hypothesized RBC transfusion would result in changes in parameters post-transfusion.

MATERIALS AND METHODS

The study was approved by the Human Research Ethics Committee of Royal Perth Hospital (protocol code: RGS4830). The Human Research Ethics Committee approved a waiver of consent, noting compliance with Section 2.3.10 of the Australian National Statement 2023. To address our study aim we designed a multi-center, retrospective, longitudinal study. We included all patients admitted to general surgical and medical wards (non-critical care areas) at Royal Perth Hospital or Armadale Hospital and connected to the HIVE continuous remote monitoring service between January 2021 and June 2024 who were transfused 1 or 2 units of RBCs. As our aim was to investigate the effect of a 1- or 2-unit RBC transfusion in hemodynamically-stable patients on general wards, we excluded patients with signs of active bleeding, patients transfused fresh-frozen plasma, platelets, or cryoprecipitate, and patients transfused RBCs in the previous 7 days.

Outcomes

Our main outcomes of interest were continuously monitored vital signs. Vital signs typically refer to HR, RR, SpO_2, blood pressure, and temperature. The HIVE system does not support continuous blood pressure monitoring and instead relies on intermittent cuff-based measurements. As these measurements were not captured in our dataset, they were excluded from the study. Temperature data were also not available as a continuously recorded parameter.

Therefore patients who met inclusion criteria were assessed for changes in HR (beats per minute), RR (breaths per minute), and SpO_2 (%). These parameters were continuously recorded while patients were connected to the HIVE service and were available for analysis as 5-minute median values. The HIVE service uses the Philips IntelliVue MX400/MX550 physiological monitor with a Philips IntelliVue X2/X3 transport monitor. HR and SpO_2 was measured by the Nellcor OxiMax SpO_2 finger probe that utilizes photoplethysmography (PPG) as its core measurement method. RR was measured by impedance pneumography[6].

As with any continuous monitoring system, short periods of signal loss or artefact can occur due to movement or sensor displacement. These were handled by extracting the continuous vital sign data as median values at 5minute intervals, which is designed to minimize the influence of transient artefacts. Additionally, our statistical modelling approach (mixed-effects regression methods) inherently

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accommodates any potential irregularities in data across patients.

Hemoglobin concentration was included as a secondary outcome to contextualize changes in vital signs before and after 1- and 2-unit RBC transfusions. While continuous hemoglobin monitoring was not available, values were obtained from routine full blood count tests conducted as part of standard patient care. Furthermore, we collected data on patient demographics (patient sex, age, weight), and relevant admission details (diagnoses, specialty, ward, transfusion details).

Exposure

The exposure investigated by our study was the administration of a 1 or 2 unit RBC transfusion. The time of transfusion was considered time zero with continuous physiological parameters collected 10 hours pre- and 24 hours post-transfusion, and hemoglobin results collected 48 hours pre- and 48 hours post transfusion. A 3-hour window was excluded from the primary analysis to account for the duration of the blood infusion, to avoid analyzing acute changes in vital signs relating to the transfusion event itself. Results of the trends during the 3-hour window are presented in this manuscript as a secondary analysis.

Statistical analysis

To assess the change in HR, RR, SpO_2, and hemoglobin concentration pre- and post-RBC transfusion we applied a segmented linear mixed-effects regression model[8]. This statistical model was chosen to estimate the trend (slope) in parameters before exposure to an RBC transfusion, the immediate shift after transfusion, and the gradual trend (slope) after exposure to the transfusion. Data trends were expressed as mean and 95% CI.

Using this model the continuous HR, RR, and SpO_2 measures, and hemoglobin concentration were the dependent variable. The fixed effects included a "time" variable (continuous time in 5-minute increments from study inclusion, capturing the overall temporal trend), a "pre-post intervention" variable (a binary indicator distinguishing pre- and post-transfusion periods), and a "time post intervention" variable (time in minutes since transfusion, set to zero for all pre-transfusion observations). Random intercepts and slopes for each term were included at the patient level to account for individual variability in baseline parameters and response trajectories. Time was modelled in 5-minute increments to preserve the granularity of the data, however for interpretability, regression coefficient outputs were subsequently scaled to reflect changes per hour to allow for more intuitive interpretation of temporal effects in the context of hourly changes.

To interpret the model, the fixed intercept (β_0) represents the baseline level of the outcome at t=0. β_1 is the rate of change (slope) of the outcome over time (t) before the intervention (RBC transfusion). β_2 is the immediate shift in the outcome variable at the conclusion of the intervention and represents a "level shift". β_3 represents how the slope of the outcome changes (rate of change) after the intervention, quantifying the difference in the rate of change in the outcome variable before and after the intervention. *Online Supplementary* **Figure S1** provides a visualization of *hypothetical* segmented regression model coefficients to assist with the interpretation of model output presented in the Results Section (it does not represent actual model output from this study).

To visualize the actual model trajectories, we generated time-series plots of predicted values from linear mixed-effects model at hourly intervals across the observation window. Predictions were obtained using the fitted model parameters and plotted against time relative to the intervention (RBC transfusion), with separate segments for pre- and post-intervention periods. These plots illustrate the estimated population-level trends and immediate level changes. To quantify uncertainty around predicted trajectories, we applied nonparametric bootstrap resampling at the subject level. For each model, 1,000 bootstrapped samples were generated and predicted values were recalculated for each hour within the observation window. The 2.5th and 97.5th percentiles of the bootstrap distribution were used to construct 95% confidence intervals for the predicted estimates, which were displayed as shaded bands on the plots.

RESULTS

Participants

Between January 2021 and June 2024 there were 10,217 adult admissions connected to the HIVE service. Of these, 350 had an RBC transfusion event while connected to physiological monitors. After excluding admissions

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that had a transfusion event in the previous 7 days and admissions with transfusions of thawed plasma, cryoprecipitate, or platelets, our final cohort consisted of 72 patients, with 51 being transfused 1 unit of RBCs and 21 being transfused 2 units of RBCs (*Online Supplementary*, **Figure S2**). The 51 patients transfused 1 unit had 49,403 data points collected; HR (17,004), RR (16,100), SpO_2 (16,032), and hemoglobin (267). The 21 patients transfused 2 units had 19,626 data points collected; HR (6,687), RR (6,573), SpO_2 (6,247), and hemoglobin (119).

Descriptive data

Mean patient age was 67.7 years (SD, 17.2 years), and 42 (58.3%) were women. The mean weight at admission was 75.2 kg (SD, 25.4 kg). Most patients had undergone surgical procedures (63.9%), and the most common admission specialties were general surgery (41.7%) and orthopedic surgery (9.7%). Major small and large bowel procedures accounted for 16.7% of all patients. The mean pre-transfusion hemoglobin concentration was 7.39 g/dL (SD, 0.90 g/dL), and the post-transfusion concentration was 9.06 g/dL (SD, 0.81 g/dL). Overall, patients had a median (Q1, Q3) length of hospital stay of 8.00 days (5.75, 16.25), and 19.4% of patients had an ICU admission (**Table I**).

Hemoglobin

The mean pre- and post-transfusion hemoglobin values for 1-unit and 2-unit RBC transfusions are listed in **Table I**. The mean hemoglobin concentration for patients in the 1-unit group 48 hours before transfusion was 10.87 g/dL (95% CI, 9.93 g/dL to 11.80 g/dL), and hourly rate of change in hemoglobin was −0.07 g/dL (95% CI, −0.09 g/dL to −0.05 g/dL). Post-1-unit RBC transfusion, hemoglobin increased by 1.40 g/dL (95% CI, 1.15 g/dL to 1.64 g/L). The hourly hemoglobin increase during the 48 hours post-1-unit RBC transfusion compared to the pre-transfusion period was 0.08 g/dL (95% CI, 0.05 g/dL to 0.10 g/dL).

At baseline, the mean hemoglobin concentration for patients in the 2-unit group 48 hours before transfusion was 11.25 g/dL (95% CI, 9.74 g/dL to 12.76 g/dL). The mean hourly rate of change over the 48-hour period pre-transfusion was −0.09 g/dL (95% CI, −0.12 g/dL to −0.07 g/dL). Post-2-unit RBC transfusion, the hemoglobin shifted up by 2.61 g/dL (95% CI, 2.15 g/dL to 3.07 g/dL). There was a mean difference of 0.10 g/dL (95% CI, 0.07 g/dL to 0.14 g/dL) in trend in hemoglobin in the 48 hours post-2-unit RBC transfusion when compared to the pre-transfusion trend.

Table I - *Characteristics of patients connected to a remote continuous monitoring service (HIVE) in general wards receiving a 1- or 2-unit red cell transfusion*

Patient characteristics	Red cell units transfused		Overall (No.=72)	p-value
	1 unit (No.=51)	2 units (No.=21)		
Mean age, years (SD)	68.98 (16.37)	64.67 (19.05)	67.72 (17.17)	0.336
Male (%)	22 (43.1)	8 (38.1)	30 (41.7)	0.895
Mean weight, kg (SD)	74.91 (26.22)	75.78 (23.94)	75.17 (25.40)	0.896
Admission category (%)				0.034
Medical	14 (27.5)	12 (57.1)	26 (36.1)	
Surgical	37 (72.5)	9 (42.9)	46 (63.9)	
Specialty (%)				0.259
Cardiology	0 (0.0)	1 (4.8)	1 (1.4)	
Gastroenterology	2 (3.9)	2 (9.5)	4 (5.6)	
Gerontology	3 (5.9)	0 (0.0)	3 (4.2)	
General surgery	20 (39.2)	10 (47.6)	30 (41.7)	
General medicine	5 (9.8)	3 (14.3)	8 (11.1)	
Gynecology	1 (2.0)	0 (0.0)	1 (1.4)	
Hematology	1 (2.0)	0 (0.0)	1 (1.4)	
Nephrology	3 (5.9)	0 (0.0)	3 (4.2)	
Neurology	0 (0.0)	1 (4.8)	1 (1.4)	
Orthopedics	7 (13.7)	0 (0.0)	7 (9.7)	
Plastic reconstructive surgery	2 (3.9)	0 (0.0)	2 (2.8)	
Respiratory medicine	2 (3.9)	0 (0.0)	2 (2.8)	
Spinal surgery	1 (2.0)	1 (4.8)	2 (2.8)	
Urology	0 (0.0)	1 (4.8)	1 (1.4)	
Vascular surgery	4 (7.8)	2 (9.5)	6 (8.3)	
Median length of stay, days [Q1, Q3]	8.00 [6.00, 17.50]	9.00 [5.00, 15.00]	8.00 [5.75, 16.25]	0.527
Median vital sign monitoring, hours [Q1, Q3]	65.00 [41.00, 115.00]	43.00 [30.00, 62.00]	57.50 [36.75, 109.25]	0.031
ICU admission (%)	10 (19.6)	4 (19.0)	14 (19.4)	1
Mean pre-transfusion Hb, g/dL (SD)	7.66 (0.74)	6.82 (0.96)	7.39 (0.90)	<0.001
Mean post-transfusion Hb, g/dL (SD)	8.92 (0.86)	9.39 (0.59)	9.06 (0.81)	0.04

Hb: hemoglobin.

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Vital signs

Monitored vital signs (HR, RR, SpO_2) before and after 1-unit and 2-unit RBC transfusions including baseline, pre-transfusion trend (hourly change), shift after transfusion, post-transfusion trend (hourly change), and difference in pre vs post transfusion slopes (hourly change), with mean and 95% CIs, are presented in **Table II** with plots presented in **Figures 1-4**.

Table II - *Trends in continuously monitored vital signs before and after the administration of 1 unit or 2 units of red cells, estimated by segmented linear mixed-effects regression models*

Timepoint	RBC units	Continuous vital sign		
		Heart rate	Respiratory rate	Oxygen saturation (%)
Baseline	**1 unit**	86.09 (80.37 to 91.81)	17.65 (16.25 to 19.05)	95.44 (94.50 to 96.37)
	2 units	90.54 (82.75 to 98.33)	16.87 (14.91 to 18.82)	97.45 (95.34 to 99.56)
Pre-transfusion trend (hourly change)	**1 unit**	0.05 (−0.36 to 0.46)	0.13 (0.02 to 0.25)	0.08 (−0.02 to 0.18)
	2 units	−0.73 (−1.51 to 0.05)	0.13 (−0.06 to 0.32)	−0.20 (−0.55 to 0.14)
Shift after transfusion	**1 unit**	-2.13 (-4.10 to −0.16)	−1.06 (−1.55 to −0.57)	0.05 (−0.49 to 0.59)
	2 units	4.41 (−0.4 to 9.22)	0.75 (−0.72 to 2.22)	0.45 (−1.03 to 1.94)
Post-transfusion trend (hourly change)	**1 unit**	0.09 (−0.06 to 0.23)	0.05 (0.00 to 0.09)	−0.07 (−0.12 to −0.02)
	2 units	−0.30 (−0.65 to 0.06)	−0.04 (−0.13 to 0.05)	−0.04 (−0.10 to 0.03)
Difference in slope: pre *vs* post transfusion (hourly change)	**1 unit**	0.03 (−0.44 to 0.51)	−0.09 (−0.22 to 0.05)	−0.15 (−0.27 to −0.02)
	2 units	0.43 (−0.46 to 1.32)	−0.17 (−0.36 to 0.02)	0.16 (−0.13 to 0.46)

Heart rate (beats per minute), respiratory rate (breaths per minute), oxygen saturation (%). RBC: red blood cells.

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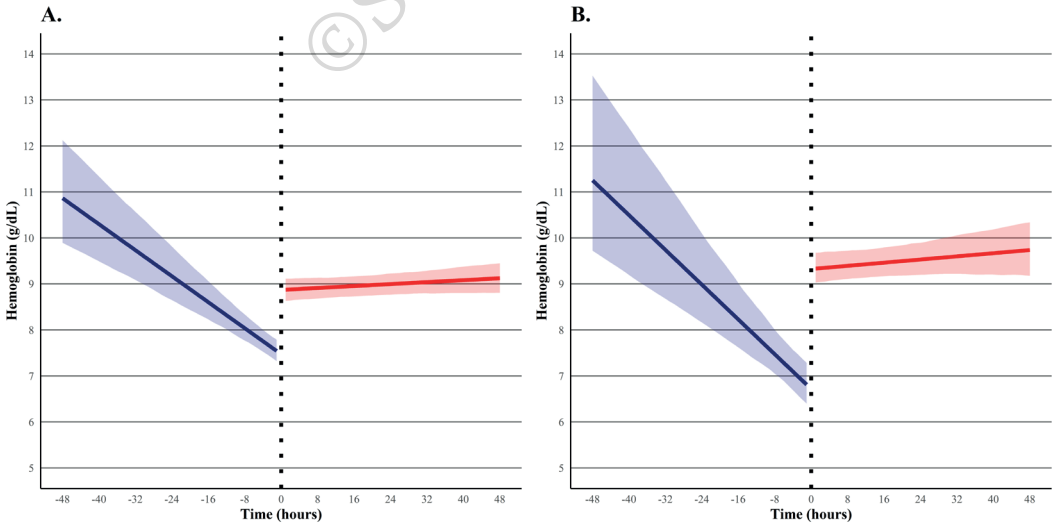


Figure 1 - Trends in hemoglobin (g/dL) before and after the administration of 1 unit (A.) or 2 units (B.) of red cells, estimated by segmented linear mixed-effects regression models

Predicted population-level trajectories from the linear mixed-effects model are shown as solid lines (blue = pre-transfusion, red = post-transfusion), with shaded ribbons representing 95% confidence intervals derived from non-parametric boostrap. Time is expressed in hours relative to transfusion (0 = intervention). dL= deciliter.

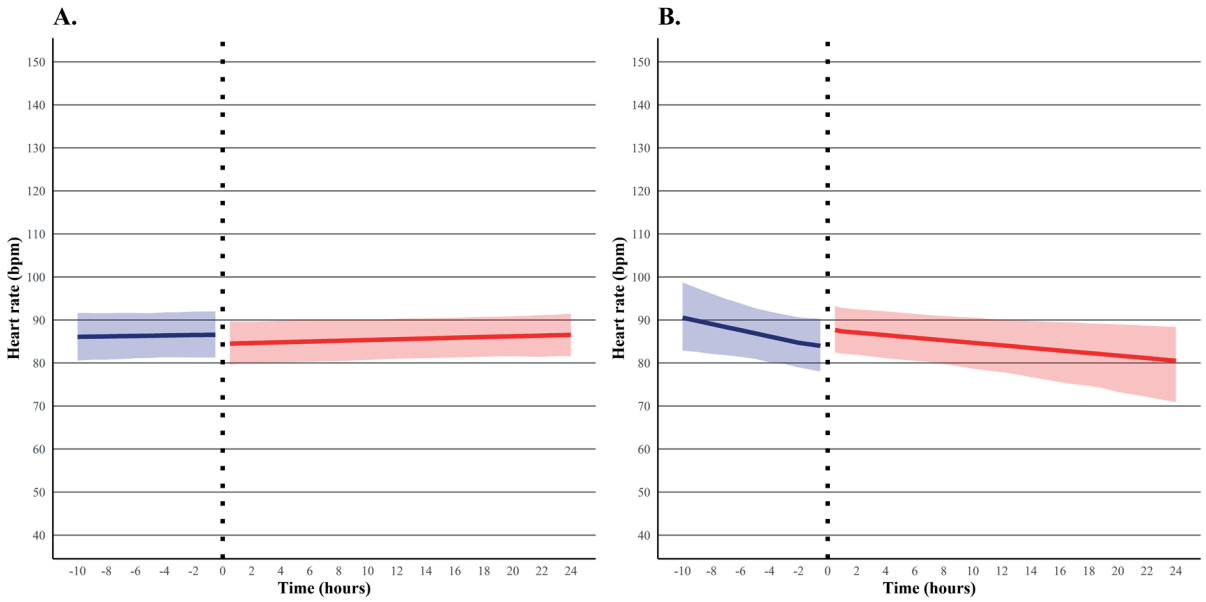


Figure 2 - Trends in heart rate (bpm) before and after the administration of 1 unit (A.) or 2 units (B.) of red cells, estimated by segmented linear mixed-effects regression models
Predicted population-level trajectories from the linear mixed-effects model are shown as solid lines (blue = pre-transfusion, red = post-transfusion), with shaded ribbons representing 95% confidence intervals derived from non-parametric boostrap. Time is expressed in hours relative to transfusion (0 = intervention).
bpm= beats per minute.

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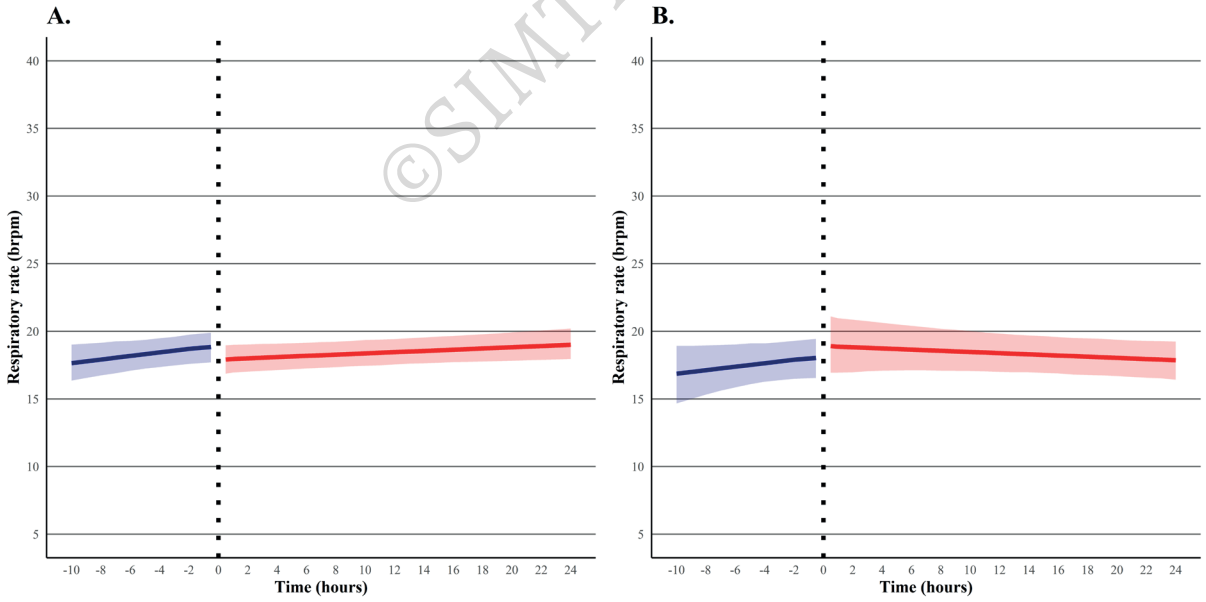


Figure 3 - Trends in respiratory rate (brpm) before and after the administration of 1 unit (A.) or 2 units (B.) of red cells, estimated by segmented linear mixed-effects regression models
Predicted population-level trajectories from the linear mixed-effects model are shown as solid lines (blue = pre-transfusion, red = post-transfusion), with shaded ribbons representing 95% confidence intervals derived from non-parametric boostrap. Time is expressed in hours relative to transfusion (0 = intervention).
brpm= breaths per minute.

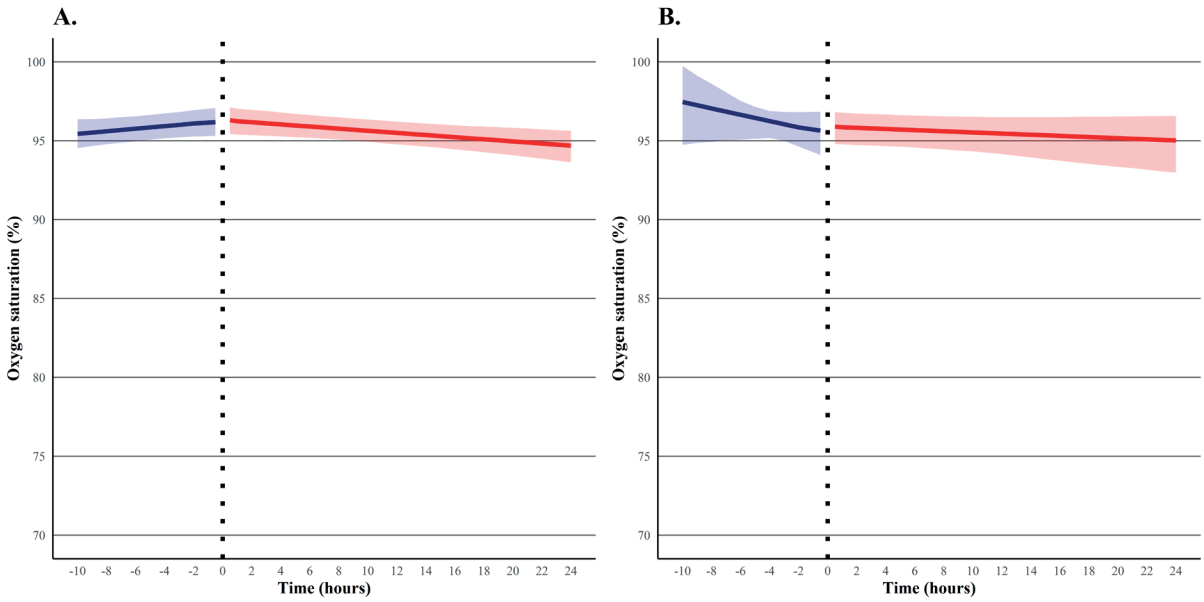


Figure 4 - Trends in oxygen saturation (%) before and after the administration of 1 unit (A.) or 2 units (B.) of red cells, estimated by segmented linear mixed-effects regression models
Predicted population-level trajectories from the linear mixed-effects model are shown as solid lines (blue = pre-transfusion, red = post-transfusion), with shaded ribbons representing 95% confidence intervals derived from non-parametric boostrap. Time is expressed in hours relative to transfusion (0 = intervention).

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Before transfusion of 1 RBC unit, the hourly trend in HR, RR, and SpO_2 was 0.05 (95% CI, −0.36 to 0.46), 0.13 (95% CI, 0.02 to 0.25), and 0.08 (95% CI, −0.02 to 0.18) respectively. Following transfusion of 1 unit of RBCs, the difference in pre- and post-intervention hourly trends in HR, RR, and SpO_2 were 0.03 (95% CI, −0.44 to 0.51), −0.09 (95% CI, −0.22 to 0.05), and −0.15 (95% CI, −0.27 to −0.02) respectively. Similar trends were observed in the 2 RBC unit transfusion group.

Secondary analysis: 3-hour transfusion window

During the 3-hour 1-unit RBC transfusion period the mean hourly trend in HR was 0.01 (95% CI, −0.99 to 1.00), the mean hourly trend in RR was −0.11 (95% CI, −0.35 to 0.14), and the mean hourly trend in SpO_2 was 0.28 (95% CI, −0.08 to 0.63). Among patients receiving 2-unit RBC transfusions, the 3-hour mean hourly trend in HR was −0.73 (95% CI, −1.86 to 0.40), the 3-hour mean hourly trend in RR was −0.18 (95% CI, −0.69 to 0.32), and the 3-hour mean hourly trend in SpO_2 was 0.00 (95% CI, −0.38 to 0.37).

DISCUSSION

Active real-time monitoring of clinical parameters at thousands of data points provides a novel means to monitor the physiological effects of blood transfusion. Our longitudinal study, measuring HR, RR and SpO_2, showed no clinically meaningful shifts immediately following transfusion, or trends before or after 1 or 2 units of transfused RBCs.

In patients receiving 1-unit of RBCs, there was a statistically significant trend in the 10-hour pre-transfusion window for respiratory rate (+0.1 breaths/min per hour), however this trend was small and probably of no clinical significance[9]. In terms of immediate shifts in vital signs following transfusion, 1 unit of RBCs was associated with a statistically significant reduction in heart rate (−2.1 bpm) and respiratory rate (−1.1 breaths/min), however these small shifts fall within normal variability and are unlikely to have clinical implications for most adults[9]. When comparing the 24-hour post transfusion trends to the 10-hour pre-transfusion window there was a statistically significant downward trend in oxygen saturation (−0.2% per hour). In context, at this rate cumulative declines over 8-24 hours could reach 1-3 percentage points which for most patients has no clinical

significance. The 2-unit transfusion group had no statistically significant trends pre or post-transfusion or immediate shifts following transfusion.

The finding of no clinically meaningful changes in trends in the vital signs pre- and post-1- and 2-unit RBC transfusion is interesting, raises questions, and may be indicative of several things.

The mean pre-transfusion hemoglobin concentration of 7.4 g/dL is consistent with current guidelines based on RBC transfusion threshold trials[10]. As the hemoglobin concentration drifted down to guidelines' threshold levels, one may assume there would have been changes in vital signs. However, there were no clinically meaningful changes in vital signs pre-1 or 2-unit transfusion. This is an important finding, given several transfusion guidelines recommend more restrictive but individualized transfusion thresholds, stressing that transfusion decisions should not be dictated solely by a hemoglobin concentration, rather, take into consideration patient clinical signs and symptoms including tachycardia and dyspnea, chest pain thought to be of cardiac origin, volume status, rate of hemoglobin decline, and availability of other therapies[10-13]. These guidelines also advise a 1-unit RBC transfusion policy in symptomatic anemic non-actively bleeding patients not responding to volume replacement and other therapies, followed by clinical assessment of need before administering a second unit[10-13]. Although the actual determinants for transfusion were not identified in this study, the changes in hemoglobin concentration in the pre-transfusion timeframe in the absence of significant changes in HR, RR, and SpO_2 could suggest that hemoglobin concentration may have been the primary determinant and indication for the transfusion[14]. The absence of clinically meaningful changes in vital signs pre-1 or 2-unit transfusion may also suggest that the anemia in this cohort of patients was not severe enough to contribute to abnormal vital signs measured in this study. This possibility is supported by studies on the physiological tolerance of anemia and hemoglobin concentration alone as a poor surrogate measure of tissue oxygenation[15-17].

Post-transfusion, there were no changes in trends in measured physiological parameters despite the expected increase in Hb. This raises questions. Does the absence of clinically meaningful changes in vital signs with either 1 or 2 unit transfusions infer that transfused RBCs may not confer immediate physiological benefits in hemodynamically stable patients within the hemoglobin concentration ranges or time frame of this study? And, were all these transfusions clinically needed? Guidelines state that with Hb concentration <7 g/dL RBC transfusion may be appropriate, however, transfusion may not be required in well-compensated patients or where other specific therapy is available[12,13]. Studies have shown a remarkable tolerance of anemia when standard supportive measures are given[15].

The purported aim of an RBC transfusion is to increase oxygen carrying capacity to facilitate tissue oxygenation. However, studies examining the clinical effectiveness of RBC transfusion have shown that, while transfusion increases Hb and oxygen delivery, it does not always increase oxygen consumption or tissue oxygenation[15,18]. There are multiple biophysical and biochemical changes that take place with red cell storage lesions that may negatively impact microcirculation function and tissue oxygenation[19]. These changes may provide an explanation for our findings of a lack of measurable post-transfusion physiological benefit irrespective of 1- or 2-unit transfusions.

The novelty of our study is that continuous patient monitoring was used to assess the effect of transfused red cells on cardiorespiratory parameters that are associated with oxygen delivery. Other studies have investigated changes in vital signs measured at discrete timepoints before and after transfusion. For example, Gehrie *et al.* measured differences in temperature, blood pressure, and heart rate at pre- and post-transfusion timepoints and concluded transfusion was not associated with significant changes[20]. Guo *et al.* investigated heart rate, mean arterial pressure, and stroke volume variation before and 10 minutes after RBC transfusion in patients undergoing cesarean section[21]. They also reported transfusion had little effect on these parameters. Gou *et al.* found no significant changes in heart rate in patients with severe trauma who underwent emergency transfusion, but they did find a significant increase in blood pressure[22].

In contrast to these findings and our study results, Tonino *et al.*[23] reported a dose-dependent reduction in heart rate following liberal transfusion strategies. While patients in their study received continuous monitoring with a wearable device, the primary outcome (heart rate) was

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summarized as a pre/post comparisons (comparing 7 days post-transfusion to 2 days pre-transfusion) rather than modeled as continuous trends. By contrast, our study applied segmented mixed-effects regression to thousands of high-frequency data points from bedside monitors in acute care inpatients, reporting granular assessment of temporal trajectories.

The difference in findings could also be due to the significant differences in population studied. Tonino's cohort consisted of chronically transfusion-dependent outpatients with sustained anemia and compensatory tachycardia whereas our population consisted of acutely hospitalized, hemodynamically stable patients receiving one or two units of red blood cells under a restrictive transfusion policy.

Our study population offers unique advantages: real-world ward-based monitoring without additional patient burden, integration of continuous physiological data into routine care, and advanced statistical modeling of trends rather than discrete snapshots. These strengths add to the research published by Tonino *et al.* highlighting feasibility and analytical rigor in acute care inpatient settings.

When interpreted with the findings of Tonino *et al.*[23], Gehrie *et al.*[20], Guo *et al.*[21], and Gou *et al.*[22] our results reinforce guideline recommendations to consider clinical symptoms and overall status rather than hemoglobin alone.

Strengths and weaknesses

A strength of our study is the analysis of continuously monitored HR, RR, and SpO_2 in patients in non-critical care settings. Other research presents a simpler pre-post study design which is limited as it only compares vital sign outcomes at two discrete time points (before and after transfusion)[8]. Our longitutinal analysis of continuous measures with a segmented linear mixed-effects regression model approach extends the pre-post design and models trends in parameters over time.

Our study has several limitations. For example, as a retrospective observational study our research may include confounding factors that could influence both the decision to transfuse and the associated impact on vital sign outcomes. However, with our longitudinal study design patients acted as their own control, allowing for within-subject comparisons of outcomes before and after transfusion. This design reduces confounding from inter-individual variability and enhances the validity of observed temporal trends. While residual confounding cannot be entirely excluded, the longitudinal structure and exclusion of actively bleeding patients help mitigate this risk.

In addition to excluding patients with active bleeding, we also excluded those who received other blood components (thawed plasma, platelets, cryoprecipitate) or who had recent transfusions. We chose these exclusions before starting our analysis to isolate the impact of 1- and 2-unit RBC transfusion. While there are strengths to this approach it may limit the generalizability of our results to patients in critical care settings. Another limitation of our study is the relatively small sample size (albeit with thousands of data points) which limited our ability to investigate potential differences in trends of physiological parameters pre- and post-transfusion among different patient subgroups preventing the identification of phenotypes that may potentially be associated with different physiological responses to transfusion.

Future research

This research with real-time assessment of patients has raised questions about the benefit of transfusion in patients who are not actively bleeding, with moderate to severe anemia and relatively stable hemoglobin concentrations. The data showing no significant alteration in measures of cardiorespiratory function and oxygen saturation raises questions as to whether the perceived benefits outweigh the known complications of transfusion. This requires further assessment.

Another key area for future research is with AI and machine learning applications. Our data could be the basis to develop or test algorithms that use continuous vital signs to predict transfusion administration. If successful, the integration of hemoglobin trends with other physiological data could be developed to enhance early warning systems.

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Authorship contributions

KMT, WE conceived the study and led the overall project.

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KMT, AL, KM, GW, SF, ML, WBD, JB, TB, WE designed the study methodology and developed the analytical approach. KMT and KM conducted the statistical modelling and performed the primary data analysis. All Authors interpreted the analytical findings and contributed to refining the interpretation of findings in the context of transfusion medicine practice. All Authors contributed to substantial revisions, provided intellectual content, and critically reviewed each iteration for important methodological and clinical accuracy. All Authors approved the final manuscript and agree to be accountable for all aspects of the work.

Conflict of interest disclosure

All Authors have completed the ICMJE uniform disclosure form. AL, KM, GW, ML, WBD, JB, TB, WE declare no conflicts of interest. KMT reports honoraria from Event Troop, support for attending meetings from the International Foundation for Patient Blood Management, Malaysian Society of Patient Blood Management, Korean Society for Patient Blood Management, outside the submitted work. SF reports consulting fees from the International Foundation for Patient Blood Management, lecture honoraria from Ethicon Biosurgery, travel support from the National Blood Authority (Australia), International Foundation for Patient Blood Management, and World Anemia Awareness, is a lead author of two books on PBM, and had a leadership role in the WHO External Steering Committee for PBM Implementation and the Executive Committee of the Western Australia Patient Blood Management Group.

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