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A physiology-based trigger score to guide perioperative transfusion of allogeneic red blood cells: A multicentre randomised controlled trial

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Abstract

Background: Restrictive blood transfusion is recommended by major guidelines for perioperative management, but requires objective assessment at 7–10 g/dl haemoglobin (Hb). A scoring system that considers the physiological needs of the heart may simply the practice and reduce transfusion.

Methods: Patients (14–65 years of age) undergoing non-cardiac surgery were randomised at a 1:1 ratio to a control group versus a Perioperative Transfusion Trigger Score (POTTS) group. POTTS (maximum of 10) was calculated as 6 plus the following: adrenaline infusion rate (0 for no infusion, 1 for ≤0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 2 for higher rate), FiO_2 to keep SpO_2 at ≥95% (0 for ≤35%, 1 for 36%–50%, and 2 for higher), core temperature (0 for <38°C, 1 for 38–40°C, and 2 for higher), and angina history (0 for no, 1 for exertional, and 2 for resting). Transfusion is indicated when actual Hb is lower than the calculated POTTS in individual patients. Transfusion in the control group was based on the 2012 American Association for Blood Banks (AABB) guideline. The primary outcome was the proportion of the patients requiring transfusion of allogeneic red blood cells (RBCs) during the perioperative period (until discharge from hospital), as assessed in the intention-to-treat (ITT) population (all randomised subjects).

Result: A total of 864 patients (mean age 44.4 years, 244 men and 620 women) were enrolled from December 2017 to January 2021 (433 in the control and 431 in the POTTS group). Baseline Hb was 9.2 ± 1.8 and 9.2 ± 1.7 g/dl in the control and POTTS

groups, respectively. In the ITT analysis, the proportion of the patients receiving allogeneic RBCs was 43.9% (190/433) in the control group versus 36.9% (159/431) in the POTTS group ($p = 0.036$). Lower rate of allogeneic RBCs transfusion in the POTTS group was also evident in the per-protocol analysis (42.8% vs. 35.5%, $p = 0.030$). Transfusion volume was 4.0 (2.0, 6.0) and 3.5 (2.0, 5.5) units (200 ml/unit) in the control and POTTS groups, respectively ($p = 0.25$). The rate of severe postoperative complications (Clavien-Dindo grade IIIa and higher) was 3.9% in the control group versus 1.2% in the POTTS group ($p = 0.010$).

Conclusion: Transfusion of allogeneic RBCs based on the POTTS was safe and reduced the transfusion requirement in patients undergoing non-cardiac surgery.

KEYWORDS

blood transfusion, perioperative transfusion trigger score, restrictive blood transfusion

1 | INTRODUCTION

Restrictive blood transfusion is the golden standard for perioperative management in patients undergoing non-cardiac surgery. It has been recommended by a variety of professional societies and organisations, including American Society of Anesthesiologists (ASA), American Association of Blood Banks (AABB), Association of Anesthesiologists of the United Kingdom and Ireland (AAGBI), blood transfusion therapy of Miller's Anaesthesia, and Chinese Association of Anesthesiology. Haemoglobin (Hb) considered to be appropriate in initiating blood transfusion is either 6 or 7 g/dl.[1–5] In patients with Hb at a level between 7 and 10 g/dl, however, the decision requires subjective judgement based on a variety of factors, including cardiorespiratory fitness, metabolic rate, and the presence of active bleeding.

A scoring system that considers the physiological needs of the heart (referred to as the Perioperative Transfusion Trigger Score; POTTS) has been proposed in a previous study.[6] The POTTS is based on real-time assessment of the following four variables: adrenaline infusion rate to maintain adequate cardiac output (0 for no infusion, 1 for ≤0.05 µg·kg^{-1}·min^{-1}, and 2 for higher rate), inspired oxygen concentration to maintain pulse oxygen saturation (SpO$_2$) at ≥95% (0 for ≤35%, 1 for 36%–50%, and 2 for higher), core body temperature (0 for <38°C, 1 for 38–40°C, and 2 for higher), and history of angina (0 for no, 1 for exertional, and 2 for resting). The POTTS score is calculated as 6 plus all subscores in the four variables. Red blood cells (RBCs) transfusion is indicated when the actual Hb value is less than the POTTS score.

2 | METHODS

2.1 | Patients

This multicentre, parallel-group randomised controlled trial was conducted at the Third Affiliated Hospital of Guangxi Medical University, Affiliated Hospital of Youjiang Medical University for Nationalities and Hospital of Guangxi Zhuang Autonomous Region during a period from December 2017 to January 2021 (http://www.chictr.org.cn; ChiCTR-INR-17014085). Trial protocol was approved by the Ethics Committees of all three participating centres. All participants provided written informed consent.

Patients (14–65 years of age) undergoing non-cardiac surgery (either emergency or elective) were eligible. Exclusion criteria included: (1) ASA grade of V or VI; (2) permanent residence at ≥2500 metres above the sea level; (3) severe haematological disorders (hemolytic anaemia, thalassemia, iron-deficiency anaemia, megaloblastic anaemia, and aplastic anaemia); (4) burn surgery; (5) any other reason deemed not appropriate for this trial by the investigator (e.g., language barrier, psychiatric disorders, unable to physically attend the scheduled follow-up).

2.2 | Randomisation, concealment and blinding

Written informed consent was obtained prior to surgery in patients at risk of Hb <10 g/dl during surgery, but randomisation (1:1 ratio) was performed only when the actual Hb decreased to <10 g/dl during surgery. The random sequence was generated using a centralised service (www.medresman.org.cn). Allogeneic RBCs transfusion in the control group was conducted based on the 2012 American Association of Blood Banks (AABB) Guideline. Briefly, transfusion was not recommended if Hb was >10 g/dl, always recommended at <7 g/dl, and decided based on the discretion of the attending physicians at 7–10 g/dl. Transfusion in the POTTS group was based on the POTTS score, calculated as 6 plus the following: adrenaline infusion rate (0 for no infusion, 1 for ≤0.05 µg·kg^{-1}·min^{-1}, and 2 for higher rate), FiO$_2$ to keep SpO$_2$ ≥ 95% (0 for ≤35%, 1 for 36%–50%, and 2 for higher), core temperature (0 for <38°C, 1 for 38–40°C, and 2 for higher), and angina history (0 for no, 1 for exertional, and 2 for resting).[6] Transfusion is indicated when actual Hb is lower than the calculated POTTS score in individual patients. The anaesthesiologists and surgeons in the trial were aware of the group assignment. Patients,

research staff who conducted the follow-up, as well as the statisticians were blinded to group allocation.

2.3 | Anaesthesia and surgery

Anaesthesia protocol (types of anaesthetic drugs, doses, methods of anaesthetic management, as well as ICU treatment) were based on the standard policy at each participating centre. All participating centres adopted limited fluid resuscitation.[7] Crystalloid solution was mainly sodium lactate Ringer's injection. Fluid expansion was conducted using hydroxyethyl starch 130/0.4 and 0.9% saline. The use of coagulation components (e.g., plasma, platelets, cryoprecipitate) was based on the AABB Guideline in both groups.[8,9] Intraoperative blood salvage transfusion was conducted for clean surgeries (e.g., orthopaedic, neurosurgical procedures, and bleeding from ruptured ectopic pregnancy) in patients with >400 ml expected bleeding using an autologous-P3000 blood recovery machine (Beijing Jingjing, Beijing, China). Recovered blood was heparinised at 200 U per 100 ml blood, centrifuged and washed prior to infusion.[10] Transfusion of allogeneic RBCs was always conducted after intraoperative blood salvage transfusion.

2.4 | Outcome assessment

The primary outcome was the proportion of patients receiving allogeneic RBCs transfusion, as assessed using an intention-to-treat principle. Secondary outcomes included: (1) transfusion volume; (2) transfusion-related complication; (3) severe surgery-related complications during hospital stay (Clavien-Dindo classification grade IIIa or higher)[11–13]; (4) Hb level upon discharge. The last follow-up was conducted at 12 weeks after the surgery.

2.5 | Sample size

Sample size calculation was based on the following assumptions: (1) transfusion of allogeneic RBCs in 45.5% in the control group, and
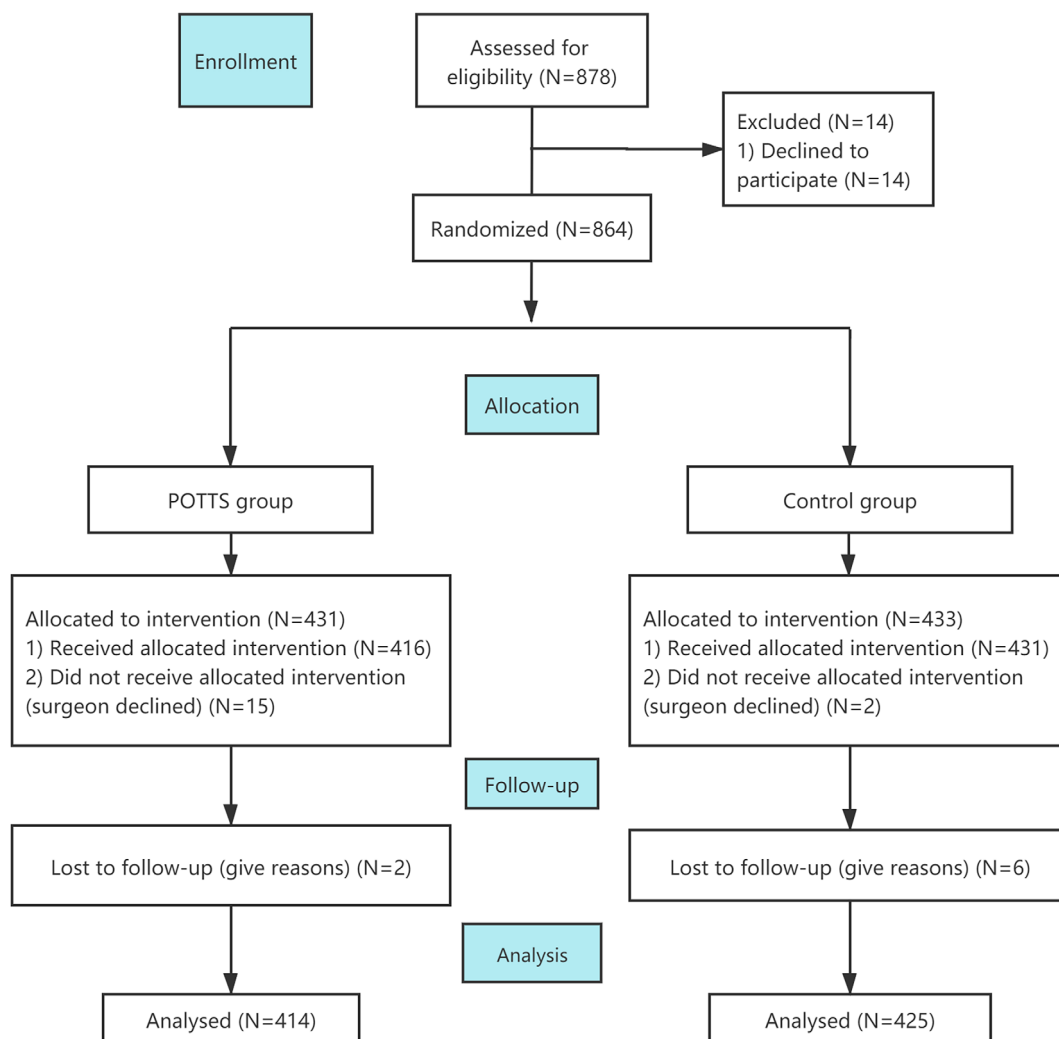

FIGURE 1 Flow diagram of the study

in 30.5% of the patients in the POTTS group (based on our pilot study); (2) single-side α of 0.025, power of 0.8, and a superiority margin of -0.10. The calculation yielded 390 patients in each group. Considering an estimated 20% dropout rate, 488 patients in each group are needed in each group.

2.6 | Statistical analysis

All statistical analyses were conducted using SPSS22.0 (IBM, Armonk, NY, USA). Normally distributed continuous variables are presented as mean $\pm$ standard deviation and analysed using Student's t-test. Non-normally distributed continuous variables are presented as median (interquartile range) and analysed using the Mann–Whitney test. Categorical variables are presented as proportions and analysed using the chi-square test. Statistically significant differences were defined as $p < 0.05$ (two-sided). The primary endpoint was assessed in the intention-to-treat (ITT) population (all randomised subjects) as well as in the per-protocol population (those who actually received the intended intervention).

3 | RESULTS

3.1 | Demographic and baseline characteristics

Patient flow through the trial is shown in Figure 1. Briefly, a total of 878 patients were screened from 28 December 2017 to 8 January 2021 and 864 patients were randomised. Demographics and baseline characteristics were generally comparable in the two groups (Table 1). The protocol was violated in 17 patients (2 and 15 patients in the control and POTTS groups, respectively) at the discretion of attending surgeons in surgical ward. Eight patients were lost to the follow-up (6 and 2 in the control and POTTS groups, respectively). The analysis included all randomised patients ($n = 864$).

3.2 | Surgery and anaesthesia

The two groups were comparable in surgery type (elective vs. emergency), specialty, malignant tumour surgery, anaesthesia method, and surgery time (Table 2).

3.3 | Intraoperative blood salvage transfusion

Blood loss, the proportion and volume of intraoperative blood salvage transfusion were similar between the two groups (Table 3).

3.4 | Allogeneic RBCs transfusion

In the ITT analysis, the rate of perioperative allogenic RBCs transfusion was 43.9% (190/433) in the control group versus 36.9%

TABLE 1 Demographic information and baseline characteristics

	POTTS ($n = 431$)	Restrictive transfusion ($n = 433$)
Male sex, n (%)	115 (26.7%)	129 (29.8%)
Age (y), mean $\pm$ standard deviation	44.6 $\pm$ 11.3	44.2 $\pm$ 10.9
Body mass index (kg/m^2), mean $\pm$ standard deviation	22.4 $\pm$ 3.0	22.3 $\pm$ 3.2
Preoperative Hb (g/dl), mean $\pm$ standard deviation	9.2 $\pm$ 1.7	9.2 $\pm$ 1.8
ASA class, n (%)		
I	68 (15.8%)	77 (17.8%)
II	290 (67.3%)	261 (60.3%)
III	63 (14.6%)	81 (18.7%)
IV	10 (2.3%)	14 (3.2%)
Co-morbidity, n (%)	84 (19.5%)	90 (20.8%)
Hypertension	36 (8.4%)	37 (8.5%)
Diabetes	22 (5.1%)	19 (4.4%)
Anaemia	14 (3.2%)	9 (2.1%)
Chronic hepatitis	10 (2.3%)	9 (2.1%)
Hepatic cirrhosis	2 (0.5%)	4 (0.9%)
Heart disease	16 (3.7%)	12 (2.8%)
NYHA classification, n (%)		
I	15 (3.5%)	9 (2.1%)
II	1(0.2%)	3 (0.7%)
III	0 (0%)	0 (0%)
IV	0 (0%)	0 (0%)

Abbreviations: ASA, American Society of Anesthesiologists; Hb, haemoglobin; NYHA, New York Heart Association; POTTS, Perioperative Transfusion Trigger Score.

(159/431) in the POTTS group ($p = 0.036$; Table 4). Lower rate of allogeneic RBCs transfusion in the POTTS group was also evident in the per-protocol analysis (42.8% vs. 35.5%, $p = 0.030$). The POTTS group also had lower use of coagulation components (14.6% vs. 23.1%, $p = 0.001$), mainly plasma (14.4% vs. 22.6%, $p = 0.002$) and cryoprecipitate (1.6% vs. 3.9%, $p = 0.040$).

3.5 | Secondary outcomes

The rate of postoperative complications did not differ between the two groups (33 events in 21 patients in the control group versus 27 events in 24 patients in the POTTS group; Table 5). The complications included transient ischemic attack, pneumonia, hemopneumothorax requiring closed drainage, pleural effusion, deep vein thrombosis, hypertensive crisis, acute exacerbation of chronic bronchitis, respiratory failure requiring mechanical ventilation with tracheal intubation, anastomotic stoma and stricture

TABLE 2 Surgical information and anaesthesia methods

	POTTS (n = 431)	Restrictive transfusion (n = 433)	p
Type of surgery, n (%)			0.17
Elective	381 (88.4%)	369 (85.2%)	
Emergency	50 (11.6%)	64 (14.8%)	
Surgery time (min), median (IQR)	130 (80, 205)	130 (80, 220)	0.67
Surgical specialty, n (%)			0.30
Gynaecology	209 (48.5%)	201 (46.4%)	
Orthopaedics	75 (17.4%)	96 (22.2%)	
Gastrointestinal tract	49 (11.4%)	58 (13.4%)	
Urology	33 (7.7%)	19 (4.2%)	
Hepatobiliary and Pancreatic	27 (6.3%)	24 (5.5%)	
Obstetric	10 (2.3%)	10 (2.4%)	
Thoracic	7 (1.6%)	10 (2.4%)	
Thyroid and breast	7 (1.6%)	6 (1.4%)	
Otolaryngology	6 (1.4%)	2 (0.5%)	
Neurosurgery	5 (1.2%)	2 (0.5%)	
Others	3 (0.7%)	5 (1.2%)	
Malignant Tumour, n (%)	33 (7.7%)	30 (6.9%)	0.68
Anaesthesia methods, n (%)			0.91
General	403 (93.5%)	402 (92.8%)	
Intraspinal	24 (5.6%)	26 (6.0%)	
Nerve block	4 (0.9%)	5 (1.2%)	

Abbreviation: POTTS, Perioperative Transfusion Trigger Score.

TABLE 3 Intraoperative blood salvage transfusion

	POTTS (n = 431)	Restrictive transfusion (n = 433)	p
Blood loss (ml), median (IQR)	60 (20, 200)	100 (30, 300)	0.12
Intraoperative blood salvage transfusion (%)	35 (8.1%)	41 (9.5%)	0.48
Volume (ml), median (IQR)	750 (400, 1250)	750 (480, 1075)	0.87

Abbreviation: POTTS, Perioperative Transfusion Trigger Score.

TABLE 4 Perioperative blood transfusion

	POTTS (n = 431)	Restrictive transfusion (n = 433)	p
Allogenic red blood cells, n (%)	159 (36.9%)	190 (43.9%)	0.036
Amount (U), median (IQR)	3.5 (2.0, 5.5)	4.0 (2.0, 6.0)	0.25
Coagulation factor, n (%)	63 (14.6%)	100 (23.1%)	0.001
Plasma transfusion, n (%)	62 (14.4%)	98 (22.6%)	0.002
Volume (ml), median (IQR)	600 (400, 1000)	560 (400, 1013)	0.84
Cryoprecipitate transfusion, n (%)	7 (1.6%)	17 (3.9%)	0.040
Amount (U), median (IQR)	30 (10, 30)	10 (10, 20)	0.036
Platelet transfusion, n (%)	6 (1.4%)	11 (2.5%)	0.22
Amount (U), median (IQR)	1.0 (1.0, 2.3)	2.0 (1.0, 3.0)	0.41

Abbreviation: POTTS, Perioperative Transfusion Trigger Score.

after gastrointestinal surgery, intestinal obstruction, chronic osteomyelitis, urethral injury and stricture, mixed haemorrhoids requiring surgical treatment, and active bleeding requiring treatment. The rate of severe surgery-related complications (Clavien-Dindo grade IIIa and higher) was 1.2% in the control group versus 3.9% in the POTTS group (p = 0.010). Transfusion-

TABLE 5 Surgery-related complications, mortality, Hb level upon discharge, hospital stay

	POTTS (n = 431)	Restrictive transfusion (n = 433)	p
Complications			
patient, n (%)	24 (5.6%)	21 (4.8%)	0.65
event, n	27	33	0.43
Clavien-Dindo classification, n (%)			
I, II	12 (2.8%)	16 (3.7%)	0.45
IIIa and higher	5 (1.2%)	17 (3.9%)	0.010*
Mortality, n (%)	0 (0%)	1 (0.2%)	0.32
Hb upon discharge (g/dl), median (IQR)	8.5 (5.6, 10.7)	8.5 (4.5, 10.8)	0.43
Hospital stay (day), median (IQR)	14.0 (10.0, 22.0)	15.0 (9.0, 24.0)	0.80

Abbreviation: POTTS, Perioperative Transfusion Trigger Score.

related complication occurred in one patient in the control group (autoimmune haemolysis). The two groups did not differ in Hb levels upon discharge (Table 5).

One patient (a 54-year-old man) in the control group died on the third day after surgery due to upper gastrointestinal bleeding, hemorrhagic shock, and eventually acute respiratory distress syndrome and multiple organ failure.

4 | DISCUSSION

The results from this trial demonstrated that using POTTS as a trigger for perioperative transfusion could reduce the rate of allogeneic RBCs transfusion, without increasing severe surgery-related complications. Lower rate of allogeneic RBCs transfusion was apparent in both the ITT analysis (36.9% vs. 43.9% with restrictive transfusion in the control group, p = 0.036) and per-protocol analysis (35.5% vs. 42.8% with restrictive transfusion in the control group, p = 0.030).

Allogeneic RBCs transfusion can be lifesaving,[14] but also carries the risk of transfusion-related complications, including transfusion reaction,[15] blood related diseases,[16,17] allergic reaction,[18,19] transfusion-related acute lung injury,[20,21] and transfusion-related circulatory overload.[22-24] Previous studies in patients undergoing orthopaedic surgery showed that improper blood transfusion increases the medical costs.[25,26] In patients undergoing surgery for cancers, improper intraoperative blood transfusion may lead to poor oncologic outcomes and reduce quality of life.[27-32] The risks and benefits of blood transfusion must be carefully weighed.[33]

Another factor that must be considered in blood transfusion is the increasing need for blood transfusion. Since 2015, the number of surgeries in China has been increasing by about 10% per year.[34] In contrast, the increase of blood supply is <3%.[35-37]

Significant research efforts have been devoted to individualise and refine blood transfusion.[38] For example, a revised patient blood management (PBM) programme was launched at Cardiac Surgery Department of Eastern Maine Medical Center and Korea University Anam Hospital to minimise RBCs transfusion.[39,40] The PBM programme relies on three key strategies to achieve its goals: optimise erythropoiesis,

minimise blood loss, and manage anaemia.[41] The PBM strategy has since been incorporated in other parts of the world, including the USA, Austria, Australia and Netherlands.[42] Tranexamic acid has also been shown to consistently reduce RBCs transfusion in a wide range of surgical populations.[43] Despite of these advances, Hb at a level between 7 and 10 g/dl represent an area for further refinement in perioperative blood transfusion. The POTTS system included four variables that are readily available during routine practice.[33] All four measures reflects the balance between oxygen supply and demand.[44] Adrenaline infusion reflects insufficient CO. The current study was a proof-of-concept trial that attempted to validate a physiology-based score in managing perioperative blood transfusion. If the concept is validated, the score could be further adjusted for use in centres where vasopressors other than adrenaline is used frequently.

In a previous trial in patients undergoing elective spine surgery with expected blood loss more than 800 ml or exceeding 20% total blood volume,[6,45] the rate of RBCs transfusion was 36.5% in the POTTS group versus 89.4% in the control group with liberal transfusion strategy. The current study compared POTTS versus restrictive blood transfusion, a strategy recommended by major guidelines and widely used in clinical practice. Also, we included emergency surgery in this trial. As a result, reduced RBCs transfusion observed in this trial is more relevant to the real world.

In contrast to reduced transfusion volume with POTTS in a previous trial by Zhu et al,[46] transfusion volume did not differ between the two groups in the current study. Such a discrepancy may be attributed to several reasons, including higher percentage of transfusion due to higher percentage of patients with cancer in the previous trial, and the use of intraoperative blood salvage in the current study.

In a retrospective case–control study of 1049 patients, Hua Xiao et al[47] found that perioperative blood transfusion (OR = 2.13, 95% CI: 1.38–3.29, p < 0.01) is an independent risk factor of complications. In another retrospective study of 250 consecutive patients who underwent curative gastric resection for stage II/III gastric cancer, Kanda et al.[30] also showed that blood transfusion is an independent prognostic factor for shorter long-term survival. Consistent with these studies, surgery-related complications did not differ significantly between the two groups in this trial, but the POTTS group had lower

rate of Clavien-Dindo grade IIIa or higher complications (1.2% vs. 3.9% in the control group).

Despite of the lower rate of blood transfusion in the POTTS group, Hb level upon discharge did not differ between the two groups in this trial. Possible reasons for such a phenomenon may include: (1) small amount of blood loss during surgery (100-ml median); (2) 48.5% in the POTTS group and 46.4% in the control group were gynaecological surgery, and postoperative anaemia management of such surgery was often associated with the use of intravenous iron and erythropoiesis-stimulating agents.

The median length of hospital stay was 14.0 and 15.0 days in the POTTS group and control group ($p = 0.80$), respectively (Table 5). The length of hospital stay in this trial was indeed longer than expected in most Western health systems. This could be a source of bias, but in our opinion, does not necessarily undermine either the validity or generalisability of the results since most transfusion occur during the surgery and early days after the surgery.

Other blood products (plasma, cryoprecipitate, platelet) are often transfused together with RBCs in clinical practice. Consistent with the lower rate of allogeneic RBCs transfusion, the use of plasma and cryoprecipitate was lower in the POTTS group than in the control group in this trial. Correlation analysis revealed that consumption of plasma was positively correlated with consumption of RBCs during perioperative period, which suggested that RBCs and plasma were bundling administrated in clinical practice in three centres, and widespread application of POTTS in surgical patients would reduce the RBCs and plasma use. The median of cryoprecipitate transfusion in POTTS group was higher was because of one patient due to cirrhotic patients and oesophagogastric varices underwent laparoscopic total splenectomy, a total of 100 units of cryoprecipitate was infused during the perioperative period. If this patient was excluded, the median of cryoprecipitate transfusion was 25 (10, 30) and 10 (10, 20) units in the POTTS and control groups, respectively ($p = 0.329$).

A major limitation in the current study is that we only included adrenaline but not other types of vasopressors. Secondly, the lack of SvO_2 and lactate metabolism indices is another limitation because of the limited budget. Finally, long-term outcomes will be observed in the long follow-up (more than 12 weeks). More trials are needed in the future.

5 | CONCLUSIONS

This trial demonstrated that a physiology-based score system for perioperative transfusion (POTTS) could reduce the requirement for allogeneic RBCs without increasing severe surgery-related complications in patients undergoing non-cardiac surgery.

AUTHOR CONTRIBUTIONS

Kejian Lu and Zehan Huang prepared and written the manuscript. Yanjuan Huang and Ren Liao contributed to the design and development of the study protocol. Zehan Huang, Ailan Huang and Yanjuan Huang supervised and revised the manuscript. Yanjuan Huang, Zehan Huang and Ailan Huang were the head of the three centres and they were responsible for the data of centre respectively. Shucong Liang, Fengting Pan, Huijun Wei participated in the enrollment of patients, execution of the study and management. Jinqing Wei, Chunying Zhang and Yafeng Huang collected the data and follow-up. All authors reviewed the results and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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