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$P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ as a red blood cell transfusion trigger and prognostic indicator for sepsis-related anaemia: protocol for a prospective cohort study

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ABSTRACT

Introduction Red blood cell (RBC) transfusion primarily aims to improve oxygen transport and tissue oxygenation. The transfusion strategy based on haemoglobin concentration could not accurately reflect cellular metabolism. The ratio of venous-arterial carbon dioxide tension difference to arterial-venous oxygen content difference ($P(v\text{-}a)CO_2/C(a\text{-}v)O_2$) is a good indicator of cellular hypoxia. We aim to explore the influence of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ as an RBC transfusion trigger on outcomes in septic shock patients.

Methods and analysis The study is a single-centre prospective cohort study. We consecutively enrol adult septic shock patients requiring RBC transfusion at intensive care unit (ICU) admission or during ICU stay. $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ will be recorded before and 1 hour after each transfusion. The primary outcome is ICU mortality. Binary logistic regression analyses will be performed to detect the independent association between $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ and ICU mortality. A cut-off value for $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ will be obtained by maximising the Youden index with the receiver operator characteristic curve. According to this cut-off value, patients included will be divided into two groups: one with the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ >cut-off and the other with the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ≤cut off. Differences in clinical outcomes between the two groups will be assessed after propensity matching.

Ethics and dissemination The study has been approved by the Institutional Review Board of Affiliated Hospital of Weifang Medical University (wyfy-2021-ky-059). Findings will be disseminated through conference presentations and peer-reviewed journals.

Trial registration number ChiCTR2100051748.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study addresses the potential benefits of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ in guiding red blood cell transfusion in septic shock patients where there are limited data.
⇒ The prospective study design would assure high-quality follow-up data for analysis.
⇒ Although the sample size in our exploratory study is small, it is appropriate in the context of relevant previous studies.
⇒ Although the single-centre design limits its external extrapolation, patients will be recruited from different types of intensive care unit (medical or emergency).

INTRODUCTION

Anaemia is commonly observed in septic shock and associated with poor outcomes such as prolonged mechanical ventilation,[1] increased myocardial damage[2] and acute renal injury.[3] Red blood cell (RBC) transfusion is an effective and frequently used intervention for anaemia.[4 5] However, RBC transfusion is not without potential pitfalls, including the potential for transfusion-related complications. Current international guidelines for the management of sepsis and septic shock recommend a restrictive transfusion strategy determined by haemoglobin (Hb) triggers.[6] Hb concentration is the most direct parameter reflecting blood oxygen carrying capacity in a healthy state. However, due to the uneven distribution of blood flow, poor deformation of RBCs and impaired oxygen uptake of the tissue cells in septic shock,[7–9] Hb concentration cannot fully represent the oxygen delivery levels and reflect tissue perfusion and cellular metabolism. Thus, it might not be appropriate to guide RBC transfusion with Hb level in all septic patients.

As the usual indicators of tissue hypoxia, blood lactate and central venous oxygen saturation ($ScvO_2$) have been reported to have certain reference to guide RBC transfusion.[10–13] In addition, a recent observational study on using arterial-venous oxygen difference to guide RBC transfusion found that this strategy may be associated with lower 90-day mortality in anaemic and non-bleeding critically ill patients.[14] Unfortunately, these indicators could be intervened by some factors such as cytopathic hypoxia and adrenergic stimulation, not necessarily reflecting anaerobic metabolism secondary to cellular hypoxia.[15]

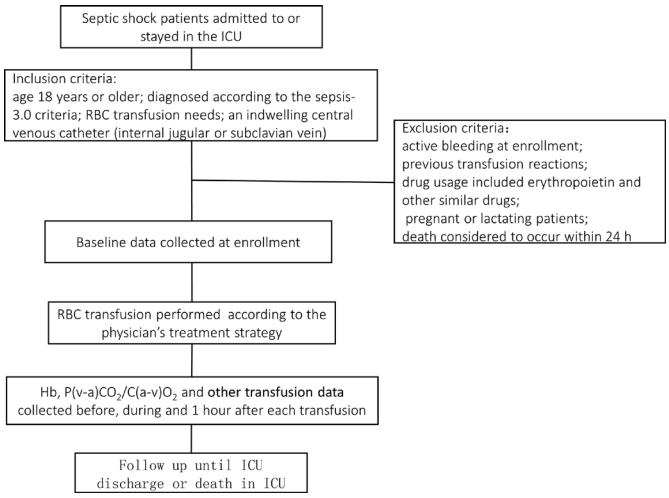

Figure 1 Patient flowchart. Hb, haemoglobin; ICU, intensive care unit; P(v-a)CO_2/C(a-v)O_2, the ratio of venous-arterial carbon dioxide tension difference to arterial-venous oxygen content difference.

The ratio of venous-arterial carbon dioxide tension difference to arterial-venous oxygen content difference (P(v-a)CO_2/C(a-v)O_2) is a good marker of anaerobic metabolism in critically ill patients and may provide information on both the macrovascular and microvascular levels.[15–18] A recent randomised controlled trial on P(v-a)CO_2/C(a-v)O_2-directed resuscitation in severe sepsis and septic shock found that the P(v-a)CO_2/C(a-v)O_2 group required fewer RBC transfusions, although there was no significant difference and no improvements were observed in clinical outcomes.[19] Additionally, P(v-a)CO_2/C(a-v)O_2 has been found to be an independent predictor of intensive care unit (ICU) mortality in septic shock patients with high $ScvO_2$.[20] Therefore, we hypothesise that P(v-a)CO_2/C(a-v)O_2 is a potential effective metric for RBC transfusion guidance and prognostic assessment in septic shock. The aim of our study is to explore the influence of P(v-a)CO_2/C(a-v)O_2 as an RBC transfusion trigger on outcomes in septic shock patients.

METHODS AND ANALYSIS

Study design

This study is a single-centre, prospective cohort study conducted in two medical ICUs (46 beds) and one emergency ICU (six beds) in a university-affiliated teaching hospital in China. The study flowchart is shown in figure 1.

Patients

Patients meeting the following criteria at ICU admission or during ICU stay are consecutively screened for this study: (1) age 18 years or older, (2) septic shock diagnosed according to the sepsis-3.0 criteria, (3) RBC transfusion needs based on the sepsis-3.0 guideline and clinical evaluation, (4) an indwelling central venous catheter placed via the internal jugular or subclavian vein. The exclusion criteria include the following: (1) active bleeding at enrolment, (2) a history of previous adverse reactions with blood products, (3) drug usage including erythropoietin and other similar drugs in therapy, (4) pregnant or lactating patients, (5) death considered to occur within 24 hours.

To be clear, we exclude pregnant or lactating patients against additional health risks due to ethical consideration that maternal physiology is different from standard adults. In addition, patients with multiple ICU admissions will be enrolled only once.

Septic shock management

During the study period, no attempts will be made to change or influence the routine clinical management of septic shock by the researchers. All patients in the ICU receive routine cardiorespiratory monitoring, including continuous electrocardiography and pulse oximetry. Cardiac function will be monitored daily using non-invasive cardiac output monitoring. Central venous and arterial catheterisation will be routinely conducted for monitoring and therapeutic needs. All enrolled patients will be taken samples from the possible infected sites for microbial cultures. Routine blood tests, biochemical examinations and coagulation tests will be conducted daily or every other day according to the patient condition. Standard treatments, including fluid resuscitation, antimicrobial therapy, vasoactive agents and ventilation support, will be given by clinical staff according to the surviving sepsis campaign guidelines.[6]

RBC transfusion strategy

The management of RBC transfusion practice is performed according to institutional guidelines. Researchers are not involved in any clinical intervention. The transfusion strategy, including Hb threshold, amount and target of RBC transfusion, is at the discretion of the attending physician, based on the sepsis-3.0 guideline and patients' actual clinical status. We define each transfusion as a separate event in our study. Once an RBC transfusion episode is ordered, arterial and central venous blood gas measurements will be monitored before and after 1 hour of transfusion. O_2-derived and CO_2-derived variables and blood lactate would be collected and recorded. Arterial and venous blood samples for blood gas measurements are taken simultaneously from the arterial and central venous catheters. All blood gas measurements are conducted by the same analyzer (GEM Premier 3500, Instrumentation Laboratory).

In addition, for each RBC transfusion episode, patients' status before, during and up to 4 hours after transfusion will be observed and recorded by the bedside nurses. If any symptom suggests a transfusion reaction, the transfusion process will be terminated and patients will receive emergency treatments.

RBC units transfused in the study have undergone leukoreduction by filtration before storage in a mannitol–adenine–sodium dihydrogen phosphate solution. The maximum storage time is 35 days with an average temperature of 2–6°C.

Exclusion after the enrolment and withdrawn

During the study period, some transfusion practice may not fulfil the study protocol, such as a large RBC transfusion required in life-threatening bleeding, taking acute severe gastrointestinal bleeding as an example. Such a transfusion practice will be recorded and the patient will be excluded from the study. Of course, each enrolled patient has the right to withdraw their consent at any time during the study. The number and reasons for exclusion and/or withdrawal after enrolment will be documented.

Outcome measures

The primary outcome is all-cause mortality in the ICU. Secondary outcomes consist of transfusion requirements (ie, the number and volume of RBC transfusion) and cardiocerebral vascular events after transfusion. Cardiocerebral vascular events include non-fatal cardiac arrest, myocardial infarction, stroke or initiation of renal replacement therapy and the occurrence of any of the components would be considered a cardiocerebral-vascular event.

The transfusion intervention period in the study is the time of patients' entire ICU stay. Patients would be followed up from enrolment in the ICU until ICU discharge or death.

Outcome definitions

Non-fatal cardiac arrest is defined as successful resuscitation from cardiovascular events requiring cardiopulmonary resuscitation, pharmacological therapy or cardiac defibrillation such as ventricular fibrillation, asystole or pulseless electrical activity.[21] Myocardial infarction is defined by elevated biomarkers and either ischaemic symptoms or ischaemic electrocardiographic signs resulting in an intervention.[22] Cases of acute stroke are determined by typical symptoms and imaging (CT scan or MRI scan). Septic shock is defined as severe sepsis with persistent hypotension requiring initiation of vasopressors to achieve a mean arterial pressure ≥65 mm Hg and elevated serum lactate above 2 mmol/L after adequate fluid resuscitation.[6]

Data collection

A Case Report Form is designed for data collection. The following data of enrolled patients will be documented, including baseline data at enrolment, data before, during and after transfusion, and follow-up data. For patients with multiple ICU admissions, only the data from the first ICU admission will be recorded.

Baseline data

Relevant baseline data at enrollment will be collected from hospital record documentation and laboratory tests on the day of enrollment, including demographic characteristics (sex, age and body mass index (BMI)); major comorbidities (hypertension, diabetes mellitus, coronary artery disease, stroke, pulmonary disease and chronic kidney disease); primary site of infection; disease severity scored by Acute Physiology and Chronic Health Evaluation II Score (APCHE II)[23] and Sequential Organ Failure Assessment Score (SOFA)[24]; haemodynamic values (blood pressure (BP), heart rate (HR), cardiac index (CI)); laboratory data (blood routine examination, liver function, renal function and coagulation function); oxygenation index (OI); whether to use life support measures or not (mechanical ventilation, vasopressors and renal replacement therapy).

OI is calculated as the ratio of arterial partial pressure of oxygen (PaO_2) to the inspired fraction of oxygen (FiO_2) according to arterial blood gases, expressed as the following formula: $OI = PaO_2/FiO_2$.[25]

Transfusion data

Transfusion data will be recorded before, during and 1 hour after each transfusion by the researchers. Before transfusion, the following variables will be collected from blood routine examination and arterial and venous blood gases, including Hb, blood lactate, O_2-derived and CO_2-derived variables for $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ calculation (ie, arterial carbon dioxide tension, arterial oxygen tension (PaO_2), central venous CO_2 tension ($PcvCO_2$), central venous oxygen tension ($PcvO_2$), arterial oxygen saturation (SaO_2) and $ScvO_2$. During the transfusion process, transfusion reactions such as transmission of infections, anaphylactic reactions and haemolysis, if any, will be recorded at all times. One hour after each transfusion, the metrics above monitored before transfusion will be re-evaluated and recorded. Ultimately, we will calculate and record the value of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ before and after each transfusion episode from the O_2-derived and CO_2-derived variables. The calculation formulas of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ are as follows[26]:

$$CaO_2 = SaO_2 * Hb * 1.34 + PaO_2 * 0.0031$$

$$CcvO_2 = ScvO_2 * Hb * 1.34 + PcvO_2 * 0.0031$$

$$P(v\text{-}a)CO_2/C(a\text{-}v)O_2 = (PcvCO_2 - PaCO_2)/(CaO_2 - CcvO_2).$$

In addition, vital signs including HR, mean arterial pressure, as well as central venous pressure before and 1 hour after transfusion, will be recorded in all enrolled patients. The number and total amount of RBC transfusion for every patient will also be recorded.

Follow-up data

Patients would be followed up during the ICU stay, from enrolment until ICU discharge or ICU death. The following data will be collected from ICU nursing records and medical records: complications throughout the study period including ICU mortality, non-fatal cardiac arrest, myocardial infarction, stroke and renal replacement therapy, if any; duration of mechanical ventilation, vasoactive support and renal replacement therapy, if available; APACHE II and SOFA scores at discharge and length of ICU stay after enrolment.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of the research.

Statistical analysis

Current sample size justification

Based on the previous literature, we consider an incidence of ICU mortality (37.3%) in septic shock patients as a reference for the calculation of sample size.[27] According to the recommendations, 10 cases of interest would be required for each degree of freedom for a reliable fit in the multivariate logistic regression model.[28 29] With 10% compensation for dropouts or exclusions, 150 patients would be sufficient to allow for five risk factors of ICU mortality in our cohort.

Data analysis

Continuous data are assessed for normal distribution by the Kolmogorov-Smirnov test. Normally distributed variables are compared using unpaired t test and reported as mean (SD). Non-normally distributed variables are compared using the Mann-Whitney U test and reported as median (IQR). Categorical variables are compared using the χ^2 test or Fisher exact test and presented as number (percentage). Correlations such as Hb and $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ will be assessed by the Pearson or Spearman rank test, depending on the normality of the data. The independent association between $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ before transfusion and ICU mortality will be assessed with binary logistic regression models. Factors with statistical significance in univariate analyses and those based on clinical relevance will be used to build multivariate logistic regression models. ORs and their 95% CIs will be estimated.

The receiver operator characteristic curves will be used to analyse the ability of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ before transfusion to predict ICU mortality in patients included. An optimal cut-off value for $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ will be obtained based on the Youden index.[30 31] According to this cut-off value, patients included will be divided into two groups: one with the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ >cut off and the other with the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2 \leq$cut off.

Propensity-score (PS) matching will be used to balance baseline data between the two groups including sex, age, BMI, major comorbidities (hypertension, diabetes mellitus, coronary artery disease, stroke, pulmonary disease and chronic kidney disease), APCHE II score, haemodynamic values (BP, HR, CI), laboratory values (creatinine, bilirubin) and OI. The probability of being in the group with the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ greater than the cut-off value would be calculated through a multivariable logistic regression model that contains the above baseline covariates. Covariate balance before and after propensity matching will be evaluated by standardised differences. The balance of the covariates between groups will be compared with the standardised difference.[32] Secondary outcomes including transfusion requirements and cardio-cerebral-vascular events and changes in level of Hb and $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ between pretransfusion and post-transfusion as well as duration of mechanical ventilation, vasoactive support and renal replacement therapy, APACHE II score at discharge and length of ICU stay will be analysed after 1:1 PS matching.

A p value less than 0.05 will be considered statistically significant and data will be analysed using Software SPSS V.22.0 (IBMSPSS Statistics).

Handling of missing data

In general, there would be very few missing data in the current study because of a prospective design and a short-term follow-up period. All analyses presented would be complete case analyses. Data would be collected and analysed as recorded, so handling of missing data is not applied.

Data quality control

All researchers are trained on study procedures and will not involve in patients' clinical care. Three medical students are recruited to perform the data collection. They are trained before the initiation of the study. A streamlined case report form will be used for data collection. All data and documents will be carefully preserved by the investigators.

Ethics and dissemination

The study has been approved by the Institutional Review Board of Affiliated Hospital of Weifang Medical University (wyfy-2021-ky-059) and registered with ChiCTR2100051748. All patients will be required to sign a written informed consent form before the study. Results of the study will be submitted to an international peer-reviewed journal and presented at national and international conferences relevant to the subject fields.

Trial status

The study was initiated in October 2021 and will be completed in October 2023.

Summary

Anaemia is commonly observed in septic shock and associated with worse outcomes. RBC transfusions are the most common treatment in the ICU. Hb that serves only as the oxygen carrier in RBCs, is the current monitoring indicator of transfusion. But due to the complexity of pathophysiologies in septic shock such as impaired cellular oxygen utilisation, Hb concentration cannot fully represent the oxygen delivery levels and reflect tissue cellular metabolic state. In clinical practice, the use of RBC transfusion varies widely among clinicians despite guideline recommendations. This may cause a high rate of unnecessary RBC transfusions and raise the risk of adverse transfusion reactions. $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$, an indicator reflecting circulation perfusion and oxygen metabolism, may be a better indicator to guide RBC transfusion.

In this prospective cohort study, we aim to investigate whether the RBC transfusion threshold defined via the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ can reduce mortality and cardiocerebral vascular events in septic shock patients. We consecutively enrol adult septic shock patients requiring RBC transfusion at ICU admission or during ICU stay and

record P(v-a)CO_2/C(a-v)O_2 before and 1 hour after each transfusion. The results could provide a new direction for a more individualised and targeted transfusion strategy and data support, such as sample size estimates for further study on patients with septic shock.

Contributors The study concept was conceived by CMW and WJG. CMW and WJG contributed to the design of the work and drafted the initial manuscript. YJK contributed to statistical support. YJL participated in the critical review and the revising of the manuscript. CMW, WJG, YJK and YJL have given final approval of the final submitted manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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