Assessment of oxygen extraction rate changes following red blood cell transfusion in the intensive care unit: a protocol for a prospective observational non-interventional study

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ABSTRACT
Introduction Haemoglobin transfusion thresholds have been used in the intensive care unit (ICU) to guide red blood cell transfusion (RBCT) decisions. Recent research has also focused on physiological indicators of tissue oxygenation as trigger points for blood transfusion. This study aims to assess the oxygen extraction rate (O2ER) as a critical indicator of the oxygen delivery–consumption balance in tissues and investigate its potential as a reliable trigger for blood transfusion in ICU patients by analysing clinical outcomes. The utilisation of physiological indicators may expedite the decision-making process for RBCT in patients requiring immediate intervention, while simultaneously minimising the risks associated with unnecessary transfusions.

Methods and analysis This prospective, single-centre, observational cohort study will include 65 ICU patients undergoing RBCT. We will evaluate essential markers such as arterial oxygen content, central venous oxygen content, arteriovenous oxygen difference, O2ER and near-infrared spectroscopy before and 15 min after transfusion. The primary outcome is the percentage increase in O2ER between the two groups relative to the initial O2ER level. Secondary outcomes will assess complications and patient outcomes in relation to baseline O2ER. A 90-day comprehensive follow-up period will be implemented for all enrolled patients.

Ethics and dissemination This study has obtained ethics committee approval from the Izmir Katip Celebi University Non-Interventional Clinical Studies Institutional Review Board. Written informed consent will be obtained from all patients before their enrolment in the study. The findings will be disseminated through publication in peer-reviewed journals and presentation at national or international conferences.

Trial registration number NCT05798130

INTRODUCTION
Red blood cell transfusion in intensive care
Red blood cell transfusion (RBCT) plays a crucial role in the treatment of approximately 50% of intensive care unit (ICU) patients. However, the administration of unnecessary blood transfusions has been linked to elevated risks of infectious and respiratory complications, prolonged ICU and hospital stays, and ultimately, increased mortality and healthcare expenses. Clinicians have prioritised efforts to reduce patients’ exposure to RBCTs in the ICU.

RBCT thresholds
The decision regarding RBCT for patients with anaemia in the ICU presents a significant challenge for clinicians. Balancing the potential risks of not transfusing when necessary and the risks of unnecessary transfusion is complex. As a result, intensivists often rely on guideline recommendations and established transfusion approaches. However, recent
Physiologically based approaches to guide blood transfusion

Haemoglobin, as the primary component responsible for oxygen transport in the body, performs a crucial role in tissue oxygenation. Extensive research has been conducted to determine the critical haemoglobin level necessary for adequate oxygen delivery to tissues. Various methods, including arterial oxygen content (CaO₂), central venous oxygen content (Ccvo₂), arteriovenous oxygen (AV-O₂) difference, oxygen extraction ratio (O₂ER) and tissue oxygenation monitoring through near-infrared spectroscopy (NIRS), have been investigated to assess this value. These methods aim to evaluate tissue oxygen demand and assess whether the current haemoglobin level is sufficient to meet that demand. Thus, the minimum haemoglobin value required for optimal tissue oxygenation represents the threshold for RBCT. When making individualised transfusion decisions, clinicians can assess patients not only based on their haemoglobin concentration but also by considering the balance between global oxygen delivery and consumption. Prompt transfusion in necessary cases and the avoidance of transfusion-related complications in patients who do not require it are of significant benefit to clinicians.

METHODS AND ANALYSIS

Study design

This prospective, single-centre, observational cohort study will enrol 65 ICU patients who received RBCTs. Based on a previous similar study, we will compare O₂ER results before and 15 min after the completion of transfusion in this study. Key markers, including CaO₂, Ccvo₂, O₂ER, AV-O₂ difference and NIRS, will be evaluated two time points. The primary outcome will calculate the percentage increase in O₂ER between the two groups relative to the initial O₂ER level. Secondary outcomes will include the assessment of complications and patient outcomes in relation to the baseline O₂ER. A comprehensive follow-up period of 90 days will be conducted for all enrolled patients. The study adheres to the STROBE (Strengthening the Reporting of OBservational studies in Epidemiology) guidelines (online supplemental file 1). Written informed consent will be obtained from the first-degree relatives of all patients prior to enrolment.

Study population

The inclusion criteria for this study are as follows: patients aged 18 years or older, who have been admitted to the ICU and have been under observation for a minimum of 24 hours, have a central venous catheter in place and have received RBCT as per critical care protocols (online supplemental file 2). Patients who meet any of the following exclusion criteria will not be included in the study: (1) haemodynamically unstable patients (receiving inotropes and vasopressors); (2) patients with acute bleeding; (3) patients with haemorrhagic shock; (4) patients with acute traumatic brain injury and (5) pregnant patients.

Patient recruitment

The screening of potential participants for this study will be performed by research personnel who are not affiliated with the ICU team. Patients who meet the inclusion criteria and for whom the critical care team has already made a decision to perform an RBCT as part of the critical care protocols will be approached for enrolment in the study. Informed consent forms will be obtained from the patients’ families before transfusion. The RBCT procedure will follow the critical care transfusion protocol outlined in online supplemental file 2. The critical care team will record patients’ clinical data on case forms. Additionally, a 90-day follow-up will be conducted by a separate research team not directly involved in the ICU, ensuring an unbiased assessment of patient outcomes without knowledge of the treatment decision. Patient enrolment commenced on 4 April 2023, initiating data collection. The process of patient recruitment is currently ongoing. All data analyses will be performed on the completion of patient enrolment.

Study procedures

Biomarkers' measurements

Arterial and central venous blood gas samples obtained from each patient will be analysed using the ABL800 FLEX blood gas analyzer (Radiometer Medical ApS, Denmark). These analyses will be conducted at two time points for each patient: immediately before the blood transfusion and 15 min after the completion of the transfusion. Routine blood samples collected from patients on the day of transfusion will also be analysed using the AU5800 Series Clinical Chemistry Analyzers (Beckman Coulter, Indianapolis, Indiana, USA) for standard blood chemistry parameters, while the haemoglobin results will be analysed using the Sysmex XN-1000 (Sysmex Corporation, Japan) for complete blood count parameters. The patients will be closely monitored for a period of 90 days following the transfusion. The flow chart, as depicted in figure 1, illustrates the flow and organisation of the study. Complications and outcome definitions will be assessed in accordance with established guidelines, which are provided in online supplemental file 3. The treatment approach will be determined at the discretion of the intensivist, considering the patient’s risk factors and current guideline recommendations. Based on recommendations from previous studies, an O₂ER cut-off value of 30% will be used.

Follow-up

All patients who are enrolled in the study will be closely monitored by investigators throughout their hospital stay.
following the decision to undergo RBCT. Observers will be responsible for tracking the occurrence of specific events during the patients’ stay in the ICU or hospital (if discharged) for a period of up to 90 days. These events include acute lung injury, transfusion-associated circulatory overload, acute renal failure, infections, acute myocardial infarction, delirium, thromboembolic events, stroke and death, as outlined in online supplemental file 3. Additionally, patients who are discharged home will be followed up via telephone for up to 90 days to ensure ongoing monitoring and assessment.

Outcomes
The primary outcome of this study is the percentage change in patients’ O2 ER before undergoing RBCT compared with 15 min after the transfusion. This measurement will provide valuable information on the impact of transfusion on oxygen utilisation in the body. The secondary outcome includes various complication rates such as acute lung injury, acute kidney failure, infections and thromboembolic events. The number of days stay in the ICU and hospital, as well as the duration of mechanical ventilation and vasopressor-independent days, will also be assessed. Furthermore, the presence of mortality at the 7th, 28th and 90th day will be documented to examine the overall impact of transfusion on patient outcomes. These outcomes will collectively contribute to a comprehensive evaluation of the effects of RBCT on oxygen utilisation, tissue oxygenation and clinical outcomes in the study population.

Variables
1. Variables before RBCT: (a) age; (b) sex; (c) BMI; (d) comorbidities: hypertension, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, past or current smoking, chronic renal failure, chronic liver failure, history of stroke, active malignancy; (e) reason for ICU admission: sepsis, respiratory failure, acute renal failure, trauma, cerebrovascular events, postoperative hospitalisation; (f) number of days in ICU stay before transfusion; (g) number of vasopressor-dependent days before transfusion; (h) patient ventilation status; (i) number of ventilator-dependent days before transfusion; (j) haemoglobin from arterial and venous blood gas, pH, arterial partial pressure of oxygen (PaO₂), arterial partial pressure of carbon dioxide (PaCO₂), arterial oxygen saturation (SaO₂), base deficit, HCO₃, lactate values, venous partial pressure of oxygen (PvO₂), venous partial pressure of carbon dioxide (PvCO₂), venous oxygen saturation (SvO₂); (k) right and left hemisphere NIRS values; (l) heart rate, systolic and diastolic blood pressure; (m) Vasoactive Inotropic Score; (n) central venous pressure; (o) fraction of inspired oxygen (FiO₂); (p) simplified acute physiology score-II (SAPS-II), acute physiology and chronic health evaluation-II (APACHE-II), sequential organ failure assessment (SOFA) Scores; (r) haemoglobin, haematocrit, mean corpuscular volume (MCV), mean platelet volume (MPV), red cell distribution width (RDW), platelet values from the haemogram result; (s) international normalised ratio (INR) and activated partial thromboplastin clotting time.
time (aPTT) values; (t) blood urea nitrogen (BUN), creatinine, total bilirubin values; (u) \(\text{CaO}_2\), \(\text{Cvo}_2\), AV-O\(_2\) difference, O\(_2\) ER, \(\text{PaO}_2/\text{FiO}_2\) values.

2. Variables after transfusion of red blood cells: (a) the amount of blood product used; (b) haemoglobin from arterial and venous blood gas, pH, \(\text{PaO}_2\), \(\text{PaCO}_2\), \(\text{SaO}_2\), base deficit, HCO\(_3\), lactate values, \(\text{PvO}_2\), \(\text{PvCO}_2\), \(\text{So}_2\); (c) right and left hemisphere NIRS values; (d) heart rate, systolic and diastolic blood pressure; (e) Vasoactive Inotropic Score; (f) the number of days in the ICU stay after transfusion; (g) the number of vasopressor-dependent days after transfusion; (h) number of ventilator-dependent days after transfusion; (I) central venous pressure; (j) \(\text{FiO}_2\); (k) SOFA day-5 Score; (l) haemoglobin and haematocrit values for the first 5 days; (m) \(\text{CaO}_2\), \(\text{Cvo}_2\), AV-O\(_2\) difference, O\(_2\) ER, \(\text{PaO}_2/\text{FiO}_2\) values; (n) presence of events that may occur in the patient after transfusion: acute lung injury, transfusion-associated circulatory overload, acute renal failure, infections, thromboembolic events, acute myocardial infarction and delirium.

**Data collection and data management**

Data collection for the study will involve recording information from the hospital’s electronic clinical records and conducting clinical bedside assessments at various stages of patient care (admission, intensive care assessment, discharge to the ward and hospital discharge). Throughout the 90-day follow-up period after RBCT, patients’ clinical data will be collected and documented. To ensure data quality and integrity, an electronic case report form (eCRF) will be developed using a secure online database called REDCap (Research Electronic Data Capture; www.projectredcap.org). This platform will enable the systematic collection of all necessary information specified in the study protocol for each patient. All relevant clinical records, source documents, follow-up protocols and completed case report forms will be securely stored and locked in study files at the facility. Access to protected health information will be restricted to authorised members of the study team to ensure confidentiality. On completion of the study, certain data may be made publicly available on reasonable request. The specifics of which data will be shared and under what conditions will be determined and communicated by the researchers responsible for the study.

**Statistical considerations**

**Sample size**

The primary objective of the study is to assess the percentage change in the O\(_2\) ER following RBCT. The study will compare two groups of patients based on their initial O\(_2\) ER level: one group with O\(_2\) ER <30% and the other with O\(_2\) ER ≥30%. In a reference study, significant differences were observed between the two groups in terms of the change in O\(_2\) ER after 15 min. The mean±SD values for the groups were −5.2±7.8 and 0.7±5.8, respectively, with a p value of 0.004. To determine the sample size for the current study, a power analysis was conducted assuming a type I error of 0.05 and a study power of 0.80. Based on these calculations, it was determined that a total of 29 patients in each group would be sufficient. Taking into account a potential dropout rate of 10%, a sample size of 65 subjects was planned for the study.

**Statistical analysis**

Prior to conducting the analyses, tests for skewness, kurtosis, normality and histogram graphs will be performed to assess if the data follow a normal distribution. For variables that follow a normal distribution, independent samples t-test or paired samples T-test will be used to determine differences in means between groups or within groups, respectively. For variables that do not follow a normal distribution, the Mann-Whitney U test or Wilcoxon test will be employed. Continuous variables will be presented as mean and SD or median and IQR, while categorical variables will be presented as numbers and percentages (%). To assess differences between groups for categorical variables, the χ\(^2\) test or Fischer’s exact test will be used. In cases where there are more than two time periods, the two-way analysis of variance for repeated measures will be used to evaluate the effects of time, groups and their interactions. Post hoc analyses will be conducted using the Bonferroni test. Logistic regression analysis will be employed to assess the effect of independent variables on mortality. A significance level of p<0.05 will be used to determine statistical significance.

**Study organisation**

To ensure the high quality and integrity of the study data, an oversight committee consisting of experienced investigators in critical care medicine will be established. The committee’s role will be to oversee the study, monitor data quality, ensure consistency and accuracy of data entries in the eCRF and ensure compliance with the study protocol. The oversight committee will actively review the data collected, identify any potential inconsistencies or errors, and work closely with the study team to address any issues that arise. They will also provide guidance and support to ensure that the study protocol is followed correctly and that data collection is complete.

**Patient and public involvement**

Patients were not involved in the selection of outcome measures, study design or study implementation. The intensive care team, in collaboration with the departments of thoracic diseases, infectious diseases, cardiology and nephrology, will be responsible for managing any complications that may arise following blood transfusion in the observed patients. There are no plans to share the results of the study with the study participants.

**Ethics considerations**

The study protocol, with the identification number 00085 and the approval date of 23 February 2023, has obtained ethical approval from the Institutional Review Board for Non-Interventional Clinical Studies at Izmir...
Katip Celebi University. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, which governs medical research involving human subjects. Prior to enrolment, the research team, following good clinical practice guidelines, will obtain written informed consent from each patient who expresses willingness to participate in the study. The clinical data collected will be accessible only to the investigators and the ethics committees involved in the study, ensuring confidentiality. To maintain strict confidentiality, all data will be securely stored in an online database with unique identification numbers assigned to each participant.

DISCUSSIONS
Executive summary
Haemoglobin-based transfusion strategies are commonly employed in determining blood transfusions for ICU patients. However, the existing evidence regarding which patients truly benefit from transfusion and who may experience avoidable complications remains inconclusive, particularly for stable patients without acute bleeding. Addressing this knowledge gap has generated considerable interest, emphasizing the importance of research focusing on physiologically based transfusion targets, particularly in perioperative and critical care medicine. This is of particular significance in ICU patients, where preventing complications takes precedence. In addition to haemoglobin-targeted transfusion approaches, O₂ ER as an indicator of tissue oxygenation adequacy can be considered when making transfusion decisions. We believe that incorporating O₂ ER as a predictive factor can enhance our ability to anticipate transfusion-related complications in this patient population. Our study aims to offer a comprehensive overview, optimising transfusion decision-making and enhancing patient outcomes by mitigating complications associated with blood transfusions.

Our study in the context of previous research
This study is anticipated to draw significant attention as it represents a pioneering investigation into tissue oxygenation-based blood transfusion decision-making among haemodynamically stable patients without acute bleeding in the ICU. We hypothesise that adopting individualised transfusion strategies guided by assessments of tissue oxygenation adequacy may offer superior predictive value for transfusion-related complications compared with approaches solely based on haemoglobin levels. These personalised strategies have the potential to enhance patient management and prognosis in this specific population. Moreover, establishing diagnostic thresholds of these biomarkers for risk stratification related to transfusion can not only reduce patient morbidity and mortality but also lead to shorter hospital stays, thereby mitigating associated costs. By emphasising the significance of adequate tissue oxygenation in transfusion decision-making, this study aims to provide valuable insights that can positively impact patient outcomes and optimise resource utilisation in clinical settings.

Implications for practice and research
This study aims to explore the association between personalised O₂ ERs and the decision-making process for RBC Ts, highlighting the significance of integrating physiologically based transfusion targets with current protocols. By adopting a patient-centred approach that considers individual physiological characteristics and oxygenation requirements, clinicians can make well-informed and optimised transfusion decisions. This has the potential to enhance patient outcomes, decrease transfusion-related complications and improve overall transfusion practices in clinical settings.

Study’s strengths and limitations
Our study has several acknowledged limitations. First, it is a single-centre study conducted in a facility following a restrictive blood transfusion strategy, potentially limiting the generalisability of our results to patients managed under different transfusion approaches. Second, our unique methodology may hinder direct comparisons with previous studies using different approaches. Despite these limitations, our study boasts notable strengths. To our knowledge, it is the first investigation exploring the O₂ ER as a transfusion indicator in stable ICU patients outside of perioperative care and acute bleeding scenarios. A distinct advantage of our study is the exclusion of patients with acute head trauma, enabling us to evaluate NIRS in terms of tissue oxygenation and its correlation with actual blood transfusion outcomes in different clinical conditions.

Contributors
AST (principal investigator), MA and AS wrote the first draft of the protocol manuscript. AST, MA and BEG planned the conception and design of the study and the protocol. GK, OS and SG contributed to the design and implementation of the protocol. All authors provided critical revisions to the manuscript before approving the final version.

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Competing interests
None declared.

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Patient consent for publication
Consent obtained from parent(s)/guardian(s).

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Supplemental material
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