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ASSESSMENT OF OXYGEN EXTRACTION, LACTATE LEVELS, CENTRAL VENOUS OXYGEN PARTIAL PRESSURE, AND VENOUS-ARTERIAL CARBON DIOXIDE DIFFERENCE IN ONCOLOGICAL PATIENTS DURING BLOOD TRANSFUSION

A.A. ARYNOV[1], V.V. CHURSIN[2], O.Y. RYBACHEK[1]

[1]Kazakh Research Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan;
[2]S.D. Asfendiyarov Kazakh National Medical University, Almaty, the Republic of Kazakhstan

ABSTRACT

Relevance: *Anemia is a common hematologic syndrome, particularly among oncological patients, where its prevalence ranges from 40% to 90%, depending on treatment. Blood transfusion remains the primary method of anemia correction; however, hemoglo-bin (Hb) level remains the sole criterion for transfusion decisions despite not always accurately reflecting tissue oxygen demand. Consequently, alternative physiological transfusion triggers are being actively studied, including oxygen extraction ratio (O_2ER), central venous oxygen partial pressure (PvO_2), lactate (Lac), and venous-to-arterial carbon dioxide difference (ΔCO2).*

The study aimed to *assess the effect of blood transfusion on O_2ER, PvO_2, Lac, and ΔCO_2 in oncological patients with anemia and determine their potential as physiological transfusion triggers.*

Methods: *A prospective observational study included 107 oncological patients with anemia requiring blood transfusion. Arterial and central venous blood samples were collected before and 1 hour after transfusion to assess Hb, PvO_2, Lac, O_2ER, and ΔCO_2. Statistical analysis was performed using the Wilcoxon test and Spearman's rank correlation coefficient.*

Results: *After blood transfusion, a statistically significant improvement in key parameters was observed:*

- *O_2ER decreased from 35.4% (31.8; 41.9) to 29.3% (26.0; 33.4) ($p<0.001$);*
- *PvO_2 increased from 34.8 (32.7; 38) to 36 (34; 39) mmHg ($p=0.005$);*
- *ΔCO_2 decreased from 7 (5.2; 8.6) to 6.3 (4.9; 7.7) mmHg ($p=0.004$);*
- *Lac changed slightly from 1.1 (0.9; 1.7) to 1.0 (0.6; 1.55) mmol/L ($p=0.005$), remaining within the normal range.*

Correlation analysis revealed that PvO_2, ΔCO_2, and Lac were significantly associated with baseline O2ER levels but did not correlate with baseline Hb levels ($p>0.05$). This confirms that the Hb level does not accurately reflect oxygen delivery needs, whereas alternative physiological markers may serve as more reliable transfusion decision criteria.

Conclusion: *Changes in O_2ER, PvO_2, and ΔCO_2 after blood transfusion suggest their potential use as physiological transfusion triggers. Unlike the Hb level, these parameters more accurately reflect oxygen delivery changes. Although lactate correlated with baseline Hb, it cannot serve as a reliable transfusion trigger in this patient population, as its levels remained within the normal range. Further research is needed to define threshold values for physiological transfusion triggers and evaluate their impact on clinical outcomes.*

Keywords: *blood transfusion, anemia, oxygen extraction.*

Introduction: Anemia is one of the most common hematologic syndromes in clinical practice. At the same time, anemia in cancer patients occurs in more than 40% of cases, and in patients receiving chemotherapy, the incidence of anemia can reach up to 90% [1]. Anemia is an independent factor that worsens clinical outcomes in various groups of patients [1, 2]. One of the main methods of anemia treatment is a blood transfusion. In modern transfusion practice, a distinction is made between restrictive and liberal transfusion strategies. The liberal strategy involves transfusion of red blood cell components at higher hemoglobin levels. In turn, the restrictive strategy is based on minimizing transfusions. It involves prescribing blood transfusion only when lower hemoglobin levels are reached, which is aimed at reducing the risk of possible complications [3], such as volume overload, transfusion reactions, and the immunomodulatory effect of blood transfusions. The restrictive strategy is the basis for many modern recommendations for the transfusion erythrocyte-containing blood components, including the current order of the Ministry of Health of the Republic of Kazakhstan [4-8].

The hemoglobin level is the key criterion for deciding on blood transfusion. In this regard, the hemoglobin level cannot reflect the level of oxygen delivery, and increasing the latter is the main goal of blood transfusion therapy. That is why several studies show the benefits of a liberal transfusion strategy and improved clinical outcomes in patients with higher hemoglobin levels [9-11]. This is primarily indicated for patients with limited reserves for physiological compensation of reduced oxygen delivery, including those

with cardiovascular pathologies or elderly patients. A similar situation was shown in a study by P. de Almeida et al.: a liberal strategy improved the clinical outcomes in cancer patients after major surgical interventions [12]. These data also demonstrate the imperfection of hemoglobin as the only trigger for blood transfusion. In connection with this, relevant alternative physiological triggers for blood transfusion have been actively studied in recent years, which makes it possible to more accurately assess the patient's need for transfusion. These include the oxygen extraction coefficient (O_2ER), arteriovenous difference in carbon dioxide partial pressure (ΔCO_2), central venous blood saturation ($ScvO_2$), lactate (Lac), central venous oxygen partial pressure (PvO2), and other markers of oxygen delivery and tissue hypoxia. This study analyzed the effect of blood transfusion on O_2ER, ΔCO_2, Lac, PvO2 in cancer patients with anemia.

The study aimed to assess the effect of blood transfusion on O_2ER, PvO_2, Lac, and ΔCO_2 in oncological patients with anemia and determine their potential as physiological transfusion triggers.

Methods: A prospective observational study included 107 oncological patients. The main inclusion criteria were:

– anemia requiring blood transfusion;

– presence of a central venous catheter.

The exclusion criteria were:

– respiratory support (invasive/non-invasive ventilation, high-flow oxygen therapy);

– vasopressor and/or inotropic support;

– shock of any etiology;

– childhood;

– pregnancy.

The study included patients over 18 years of age, 66 (61.7%) women and 41 (38.3%) men. The median age of patients was 57 (46–65) years.

All patients received the packed red blood cell (PRB) transfusion, which triggered the hemoglobin level. Before and 1 hour after blood transfusion, the hemoglobin (Hb) levels, PvO_2, Lac have been measured.

$$O_2ER \text{ calculated as } [(CaO_2\text{-}CcvO_2)/CaO_2*00\%]. \quad (1)$$

$$\Delta CO_2 \text{ calculated as } PvCO_2\text{-}PaCO_2. \quad (2)$$

Central venous blood was taken from the central venous catheter located in the basin of the superior vena cava (subclavian or internal jugular vein), and arterial blood was taken from the radial artery.

The statistical analysis and visualization of the data obtained were carried out using the R 4.3.1 statistical software framework (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics for categorical variables are presented as absolute and relative frequencies (n (%)), and for quantitative variables, they are presented as a median (1-3rd quartile). For comparison of quantitative indicators before and after the intervention, the Wilcoxon signed-ranks test for matched pairs has been used. The Spearman's rank correlation coefficient (ρ) with a corresponding 95% confidence interval (95% CI) has been used to estimate the direction and strength of the association between quantitative variables. The association was considered statistically significant at $p<0.05$.

Results: The median hemoglobin concentration before transfusion was 73 (64.5; 78) g/L. After transfusion, the median hemoglobin increased to 85 (76.5; 93.7) g/L. The median elevation of hemoglobin after transfusion amounted to 13 (8.5; 21) g/L and was statistically significant ($p<0,001$).

The main diagnosis in all patients included in the study (n=107) was malignant neoplasms. The most common were tumors of the gastrointestinal tract – in 30 patients (28.0%), and malignant neoplasms of bones and soft tissues were detected in 30 patients (28.0%). Tumors of the female reproductive system were detected in 22 patients (20.6%), tumors of the chest organs in 8 patients (7.5%), and neoplasms of the head and neck in 4 patients (3.7%). Malignant tumors of the urinary system and male genital organs were diagnosed in 8 patients (7.5%). Primary multiple cancers were detected in 3 patients (2.8%) and other malignant tumors in 2 patients (1.9%). A brief clinical and demographic description of the enrolled patients is presented in Table 1.

The effect of blood transfusion and the dynamics of O_2ER changes in response to transfusion are presented in Figure 1.

Oxygen extraction: The level of O_2ER before blood transfusion was higher than the normative values and composed 35.4% (31.8; 41.9). After the blood transfusion, the median level of oxygen extraction was 29.3% (26%; 33.4%). Concurrently, a statistically significant normalization of the O_2ER level after transfusion of erythrocyte-containing media has been observed: the median decline in O_2ER after transfusion amounted to 5.8% (-10.7%; -1%) ($p<0.001$). The median O_2ER value before blood transfusion was higher than the normative values, and the transfusion led to the normalization of this indicator. The effect of blood transfusion and the dynamics of O_2ER changes in response to transfusion are presented in Figure 1.

Partial pressure of oxygen in central venous blood: The median level of PvO_2 before blood transfusion was 34.8 (32.7; 38) mmHg. After the blood transfusion, a statistically significant elevation of the partial pressure of oxygen in the central venous blood has been recorded - 36 (34-39) mmHg. The median change of PvO_2 after transfusion composed 1.2 (-1.35; 3) mmHg ($p=0.005$). The effect of blood transfusion and the dynamics of changes in PvO_2 indicator in response to transfusion are presented in Figure 2.

Table 1 – Clinical and demographic characteristics of the enrolled patients

Indicator	Value
Age (years), median (min; max)	57 (46; 65)
Sex, n 107 (100%)	
Female	66 (61.7%)
Male	41 (38.3%)
Body mass index (kg/m²), median (min; max)	23,9 (21; 26,7)
Type of anemia, n 107 (100%)	
Acute	71 (66,4%)
Chronic	36 (33,6%)
Tumor localization, n 107 (100%)	
Bones and soft tissues	30 (28,0%)
GIT	30 (28,0%)
Female genitalia	22 (20,6%)
Urinary system and male genital organs	8 (7,5%)
Chest organs	8 (7,5%)
Head and neck	4 (3,7%)
Primary multiple cancer	3 (2,8%)
Other tumors	2 (1,9%)
Concomitant diseases, n 107 (100%)	
Arterial hypertension	34 (31,8%)
Coronary heart disease	14 (13.1%)
Obesity	13 (12,2%)
Type 2 diabetes mellitus	10 (9,3%)
Cerebrovascular diseases	3 (2,8%)
Other	85 (79,4%)
Apache II Severity Rating Scale, Median (min; max)	12 (11; 14)
Transfusion volume, median (min; max)	340 (310; 410)

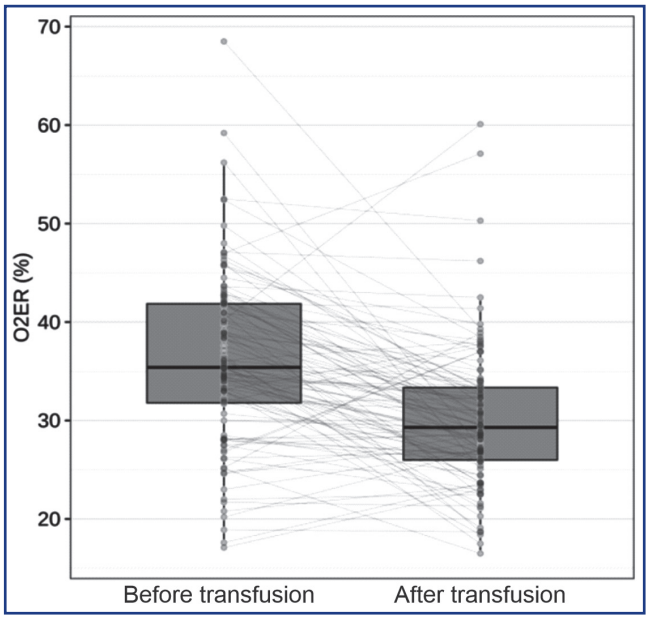

Figure 1 – O_2ER level before and after blood transfusion

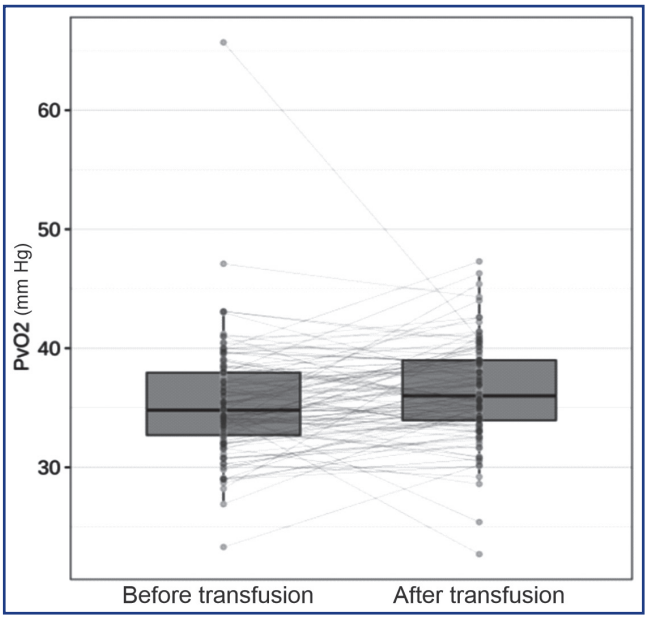

Figure 2 – PvO_2 level (mmHg) before and after blood transfusion

Lactate: The median lactate concentration amounted to 1.1 (0.9; 1.7) mmol/L before blood transfusion and 1 (0.6; 1.55) mmol/L after the blood transfusion; the median change in lactate levels in response to blood transfusion was -0.1 (-0.45; 0.1) mmol/L. Even though the median lactate concentration was within the normative values before and after blood transfusion, the change in lactate levels in response to blood transfusion was statistically significant (p=0.005). The lactate levels before and after blood transfusion are presented in Figure 3.

Venoarterial difference in carbon dioxide (ΔCO_2) levels: The median ΔCO_2 pre-transfusion level was higher than the normative level 7 (5.2; 8.6) mmHg. After the blood transfusion, the level of ΔCO_2 changed statistically significantly towards normalization; the median ΔCO_2 decline was -0.9 (-2.4; 0.8) mmHg. The ΔCO_2 median after transfusion composed 6.3 (4.9; 7.7) mmHg (p=0.004) (Figure 4). The level of ΔCO_2 before and after blood transfusion is presented in Figure 4.

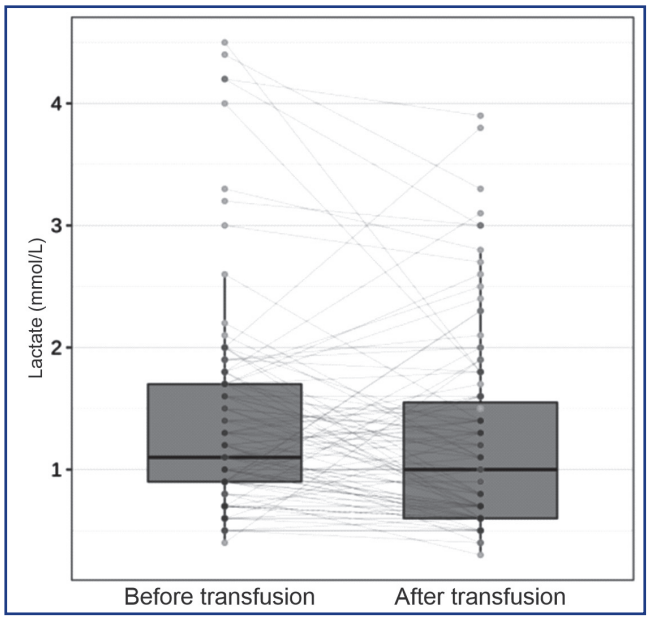

Figure 3 – Lactate levels before and after blood transfusion

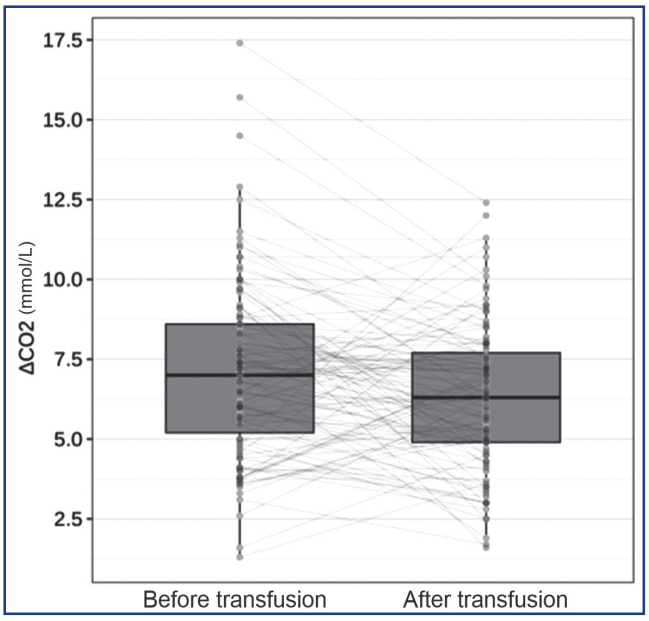

Figure 4 – ΔCO_2 levels before and after blood transfusion

Than, we analyzed the correlation between changes in the studied parameters and the initial level of oxygen extraction, which is the main indicator of oxygen delivery and consumption, and the initial level of hemoglobin, which is the main trigger for blood transfusion.

In the correlation analysis, a statistically significant correlation between the baseline oxygen extraction and the changes in blood transfusion was found in PvO_2 (ρ=0.39 (95% CI: 0.22; 0.54), p<0.001), lactate (ρ= -0.21 (95% CI: -0.39; -0.02), p=0.028) and ΔCO_2(ρ= -0.31 (95% CI: -0.47; -0.12), p=0.001) (Figures 5-7).

At that, no statistically significant correlation between the Hb baseline level and changes in response to blood transfusion was found in PvO_2 (ρ= -0.1 (95% CI: -0.28; 0.1), p=0.326) and ΔCO_2 (ρ=0.13 (95% CI: -0.07; 0.31), p=0.199) (Figures 8, 9). The lactate levels were statistically significantly and positively correlated with baseline Hb concentrations (ρ=0.35 (95% CI: 0.17; 0.51), p<0.001) (Figure 10).

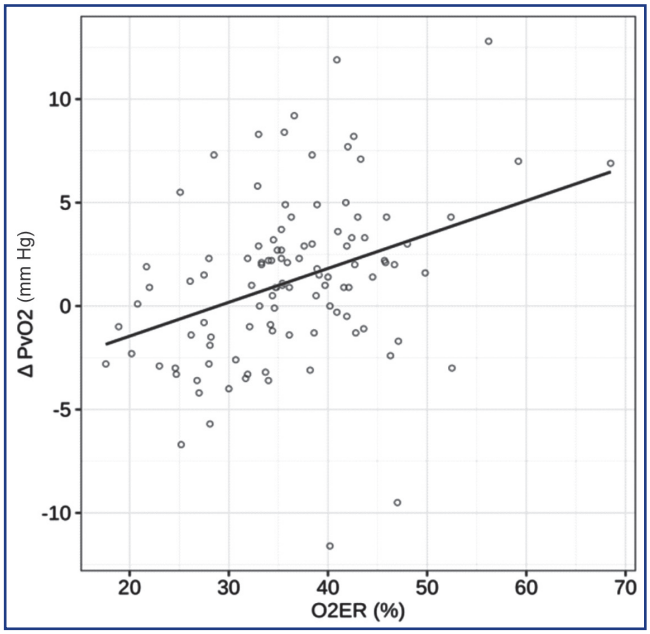

Figure 5 – Statistically significant correlation between changes of PvO2 in response to blood transfusion and O2ER baseline

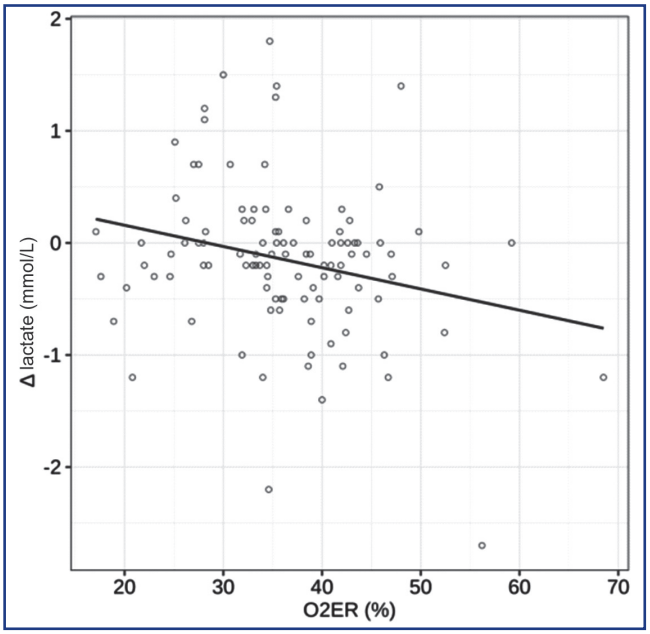

Figure 6 – Statistically significant correlation between lactate changes in response to blood transfusion and O2ER baseline

Further, the correlation between the level of O_2ER decline in response to transfusion of red blood cell components and the initial level of O_2ER, as well as between changes of O2ER and the concentration of Hb before blood transfusion, has been analyzed. The level of O_2ER decline (normalization) was statistically significantly correlat-

ed with the level of O_2ER before the intervention (ρ= -0.63 (95% CI: -0.73; -0.5), p<0.001): the higher the pre-transfusion of O_2ER level, the more significant was the level of normalization in response to transfusion of donor red blood cells. At the same time, there was no statistically significant association of O_2ER changes with baseline Hb concentration before surgery (ρ=0.16 (95% CI: -0.03; 0.34), p=0.105) (Figure 11).

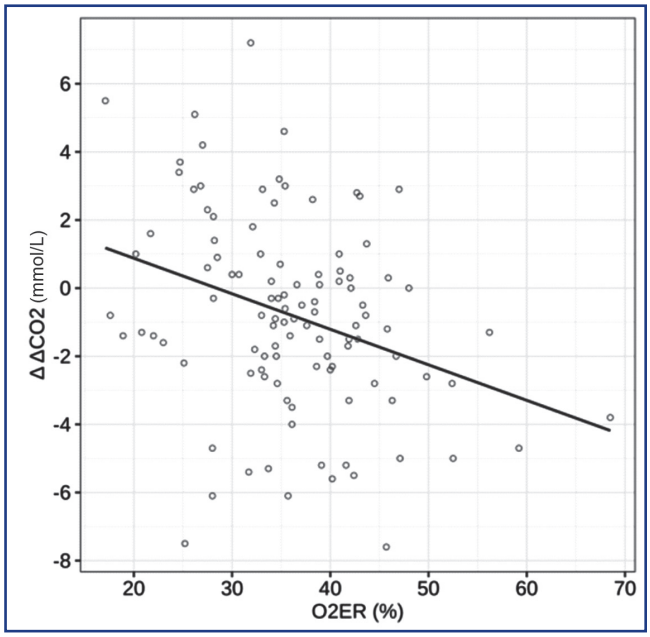

Figure 7 – Statistically significant correlation between changes in ΔCO_2 in response to blood transfusion and O_2ER baseline

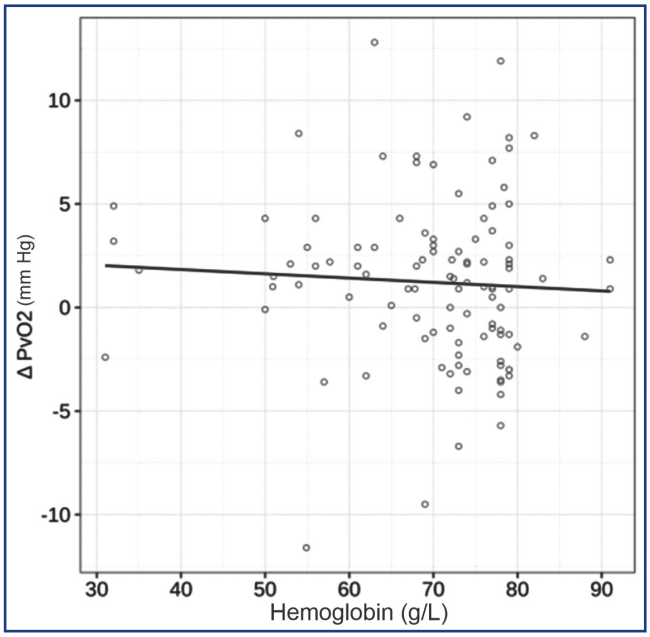

Figure 8 – No correlation between changes in PvO_2 in response to blood transfusion and baseline Hb levels

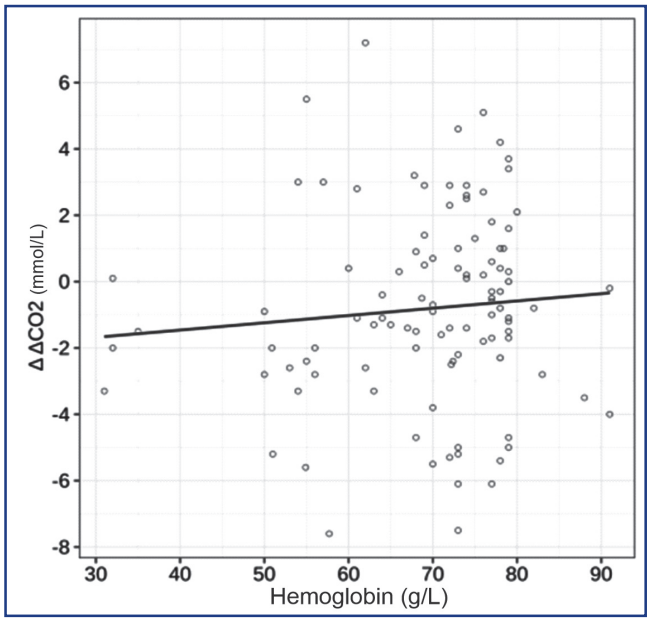

Figure 9 – No correlation between changes in ΔCO_2 in response to blood transfusion and baseline Hb levels

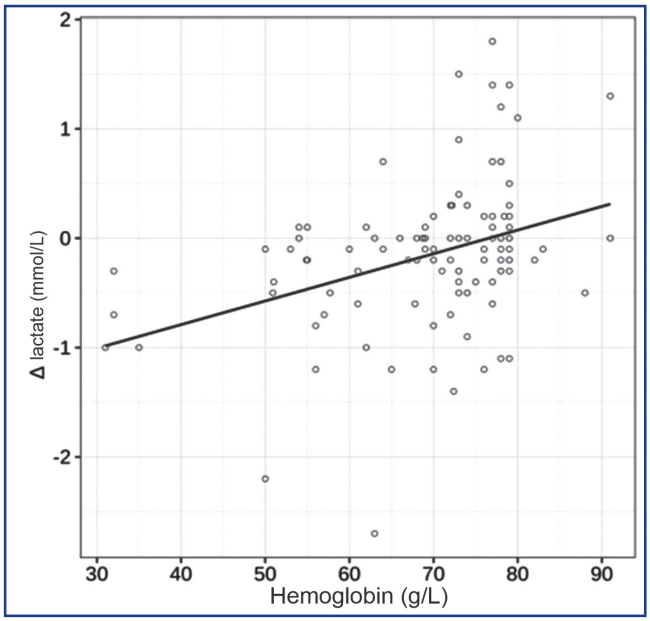

Figure 10 – Statistically significant correlation between changes in lactate levels in response to blood transfusion and baseline Hb levels

Discussion: Anemia is a multidisciplinary problem and is widespread in clinical practice. Both anemia and blood transfusion are associated with worsening clinical outcomes in different groups of patients [2,3,13-16]. However, the hemoglobin level does not reflect the true need for oxygen delivery in patients with anemia. This is especially critical in patients with concomitant cardiovascular pathology or acute cerebral insufficiency, and elderly patients. Our study demonstrated that the oxygen delivery indicators, such as PvO_2 and O_2ER, as well as tissue perfusion index ΔCO_2, were significantly changed towards normalization after the blood transfusion. Moreover, the worse the initial values of these parameters were, the more pronounced their normalization turned out to be found.

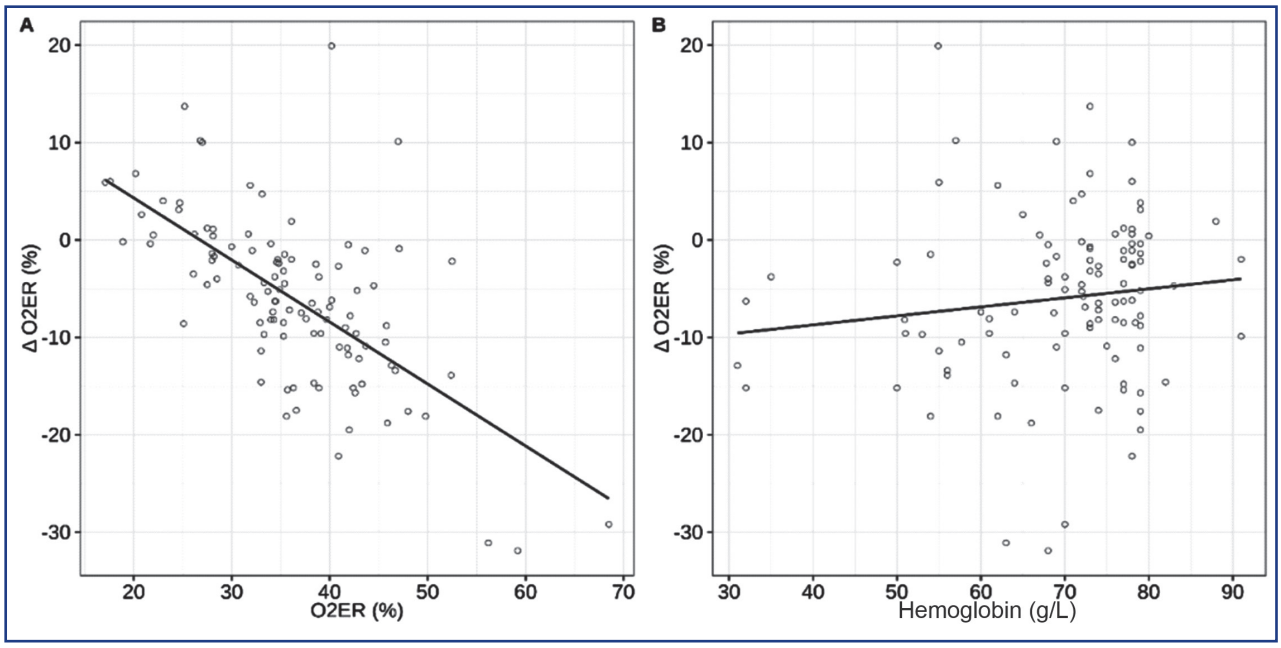

Figure 11 – Strong correlation between O2ER change in blood transfusion and baseline O2ER, no correlation between O2ER change and baseline Hb

The correlation analysis showed that all studied indicators, except for lactate, did not have a significant links with the initial level of hemoglobin. This indicates that the digital Hb index does not reflect the level of oxygen delivery and, accordingly, cannot serve as a reliable criterion for determination of the need for blood transfusion. The lactate levels showed a correlation with baseline Hb, however, their concentrations remained within the normal range both before and after the blood transfusion. The probable reason for this is the fact that the lactate levels respond to reduced oxygen delivery only when a critical threshold is reached, when compensatory mechanisms, such as increased cardiac output and tissue oxygen extraction, become inadequate [17]. Accordingly, in this clinical situation, the lactate cannot be considered as a trigger for blood transfusion. At the same time, changes in O_2ER, PvO_2 and ΔCO_2 indicate that these indicators can be used to make a decision on blood transfusion.

The results obtained are partially consistent with previously published studies. For example, B. Vallet in his studies showed the importance of using the central venous blood hemoglobin saturation as a trigger for blood transfusion [18, 19]. Another study conducted by Fogagnolo et al. demonstrated that the use of arteriovenous difference in oxygen content as a criterion for prescribing of blood transfusion leads to reduction of 90-day mortality in critically ill patients [20].

Our study has a number of limitations. First of all, it is not randomized, and blood transfusion was performed in all patients, which excludes the possibility of comparison with the control group. Secondly, critically ill patients, in whom the changes in oxygen delivery and consumption may be most pronounced, were excluded from the analysis.

Conclusion: Changes in O_2ER, PvO_2, and ΔCO_2 allow to consider these indicators as criteria for making a decision on blood transfusion. Currently, there is a growing interest in physiological and alternative triggers of transfusion, which is associated with the development of a personalized approach in transfusion practice and the desire to optimize the blood transfusion tactics in various categories of patients. Further research in this direction is needed, primarily to determine the threshold values of physiological triggers when prescribing the blood transfusion.

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АҢДАТПА

ОТТЕГІНІ ЭКСТРАКЦИЯЛАУ, ЛАКТАТ ДЕҢГЕЙІН, ОРТАЛЫҚ ВЕНОЗДЫҚ ҚАНДАҒЫ ОТТЕГІНІҢ ПАРЦИАЛДЫҚ ҚЫСЫМЫН ЖӘНЕ ВЕНОЗДЫ-АРТЕРИЯЛЫҚ КӨМІРҚЫШҚЫЛ ГАЗЫ АЙЫРМАШЫЛЫҒЫН ОНКОЛОГИЯЛЫҚ ПАЦИЕНТТЕРДЕ ГЕМОТРАНСФУЗИЯ КЕЗІНДЕ БАҒАЛАУ

А.А. Арынов[1], В.В. Чурсин[2], О.Ю. Рыбачек[1]

[1]«Қазақ онкология және радиология ғылыми-зерттеу институты» АҚ, Алматы, Қазақстан Республикасы;
[2]«С.Ж. Асфендияров атындағы Қазақ ұлттық медицина университетінің» КЕАҚ, Алматы, Қазақстан Республикасы

Өзектілігі: *Анемия – клиникалық практикада жиі кездесетін гематологиялық синдром, әсіресе онкологиялық пациенттер арасында оның жиілігі 40%-дан 90%-ға дейін жетеді. Анемияны туметудің негізгі әдісі қан құю (гемотрансфузия) болып табылады, алайда гемоглобин (Hb) деңгейі трансфузияны тағайындаудың жалғыз критерийі болып қала береді, бірақ ол әрдайым тіндердің оттегіге қажеттілігін дәл көрсете алмайды. Осыған байланысты соңғы жылдары O_2ER (оттегі экстракция коэффициенті), PvO_2 (орталық веноздық қанның оттегі парциалдық қысымы), Lac (лактат) және ΔCO_2 (веноздық-артериялық көмірқышқыл газы айырмашылығы) сияқты физиологиялық трансфузиялық триггерлер белсенді зерттелуде.*

Зерттеудің мақсаты: *Анемиясы бар онкологиялық пациенттерде гемотрансфузияның O_2ER, PvO_2, Lac және ΔCO_2 көрсеткіштеріне әсерін бағалау және оларды физиологиялық трансфузиялық триггерлер ретінде қолдану мүмкіндігін анықтау.*

Әдістер: *107 онкологиялық пациент қатысқан проспективті обсервациялық зерттеу жүргізілді. Гемотрансфузия алдында және одан 1 сағат өткен соң пациенттерден артериялық және орталық веноздық қан алынды, Hb, PvO_2, Lac, O_2ER*

және ΔCO_2 деңгейлері өлшенді. Статистикалық талдау Уилкоксон тесті және Спирмен рангілік корреляция коэффициенті көмегімен жүргізілді.

Нәтижелері: *Гемотрансфузиядан кейін негізгі көрсеткіштерде статистикалық тұрғыдан маңызды жақсару байқалды:*

- *O_2ER 35,4% (31,8; 41,9)-дан 29,3% (26,0; 33,4) дейін төмендеді ($p<0,001$);*
- *PvO_2 34,8 (32,7; 38)-ден 36 (34; 39) мм.сын.баг дейін артты ($p=0,005$);*
- *ΔCO_2 7 (5,2; 8,6)-дан 6,3 (4,9; 7,7) мм.сын.баг дейін төмендеді ($p=0,004$);*
- *Lac 1,1 (0,9; 1,7)-ден 1,0 (0,6; 1,55) ммоль/л дейін өзгерді ($p=0,005$), бірақ қалыпты шектерде қалды.*

Корреляциялық талдау нәтижесінде PvO_2, ΔCO_2 және Lac көрсеткіштері бастапқы O_2ER деңгейімен айтарлықтай байланысы анықталды, бірақ гемоглобиннің бастапқы деңгейімен корреляция байқалған жоқ ($p>0,05$). Бұл Hb деңгейі оттегіні жеткізу қажеттілігін дәл көрсетпейтінін, ал физиологиялық маркерлер трансфузияны тағайындаудың сенімдірек критерийлері болуы мүмкін екенін дәлелдейді.

Қорытынды: *Гемотрансфузиядан кейінгі O_2ER, PvO_2 және ΔCO_2 өзгерістері олардың физиологиялық трансфузиялық триггерлер ретінде қолданылу мүмкіндігін көрсетеді. Hb деңгейінен айырмашылығы, бұл параметрлер оттегімен қамтамасыз ету өзгерістерін дәлірек сипаттайды. Лактат Hb деңгейімен корреляцияланғанымен, оның деңгейі қалыпты диапазонда болғандықтан, оны сенімді трансфузиялық триггер ретінде қарастыру мүмкін емес. Болашақ зерттеулер физиологиялық трансфузиялық триггерлердің шекті мәндерін анықтау және олардың клиникалық нәтижелерге әсерін бағалау үшін қажет.*

Түйінді сөздер: *гемотрансфузия, анемия, оттегіні экстракциялау.*

АННОТАЦИЯ

ОЦЕНКА ЭКСТРАКЦИИ КИСЛОРОДА, УРОВНЯ ЛАКТАТА, ПАРЦИАЛЬНОГО ДАВЛЕНИЯ КИСЛОРОДА В ЦЕНТРАЛЬНОЙ ВЕНОЗНОЙ КРОВИ И ВЕНОАРТЕРИАЛЬНОЙ РАЗНИЦЫ ПО УГЛЕКИСЛОМУ ГАЗУ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ ПРИ ГЕМОТРАНСФУЗИИ

А.А. Арынов[1], В.В. Чурсин[2], О.Ю. Рыбачек[1]

[1]АО «Казахский научно-исследовательский институт онкологии и радиологии», Алматы, Республика Казахстан;
[2]НАО «Казахский национальный медицинский университет имени С.Д. Асфендиярова», Алматы, Республика Казахстан

Актуальность: *Анемия – распространенный гематологический синдромом, особенно среди онкологических пациентов. Гемотрансфузия остается основным методом коррекции анемии, однако единственным критерием для ее назначения служит уровень гемоглобина, который не всегда отражает доставку кислорода. В связи с этим изучаются альтернативные триггеры трансфузии: экстракция кислорода (O_2ER), парциальное давление кислорода в центральной венозной крови (PvO_2), уровень лактата (Lac) и веноартериальная разница по парциальному давлению углекислого газа ($\Delta CO2$).*

Цель исследования *– оценить влияние гемотрансфузии на O_2ER, PvO_2, Lac и ΔCO_2 у онкологических пациентов с анемией и определить возможное применение показателей в качестве физиологических триггеров трансфузии.*

Методы: *Проведено проспективное обсервационное исследование, включившее 107 онкологических пациентов с анемией, требующей гемотрансфузии. Всем пациентам выполняли забор артериальной и центральной венозной крови до и через 1 час после трансфузии. Оценивались концентрация гемоглобина (Hb), PvO_2, Lac, O_2ER и ΔCO_2. Для статистического анализа использовались критерий Уилкоксона и коэффициент ранговой корреляции Спирмена.*

Результаты: *После гемотрансфузии наблюдалось статистически значимое улучшение ключевых параметров:*

- *O_2ER снизился с 35,4% (31,8; 41,9) до 29,3% (26,0; 33,4) ($p<0,001$);*
- *PvO_2 увеличился с 34,8 (32,7; 38) до 36 (34; 39) мм рт. ст. ($p=0,005$);*
- *ΔCO_2 снизился с 7 (5,2; 8,6) до 6,3 (4,9; 7,7) мм рт. ст. ($p=0,004$);*
- *Lac изменился незначительно: 1,1 (0,9; 1,7) до 1,0 (0,6; 1,55) ммоль/л ($p=0,005$), оставаясь в норме.*

Анализ корреляций показал, что PvO_2, ΔCO_2 и Lac имели статистически значимую связь с исходным уровнем O_2ER, однако не коррелировали с базовым уровнем гемоглобина ($p>0,05$). Это подтверждает, что уровень Hb не отражает истинную потребность в доставке кислорода, а физиологические маркеры могут быть надежными критериями для назначения трансфузии.

Выводы: *Изменения O_2ER, PvO_2 и ΔCO_2 после гемотрансфузии позволяют рассматривать их в качестве триггеров трансфузии. В отличие от уровня гемоглобина, они точнее отражают снижения в доставке кислорода. Лактат не может быть надежным триггером трансфузии в данном исследовании, так как его уровень оставался в пределах нормы. Необходимы дальнейшие исследования в данном направлении.*

Ключевые слова: *гемотрансфузия, анемия, экстракция кислорода.*

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Authors' data:
Arynov A.A. (corresponding author) – Head of the Resuscitation, Anesthesiology and Intensive Care Department, Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan, e-mail: ardak6183307@gmail.com, tel. +77016183307, ORCID: 0000-0003-0379-5411;
Chursin V.V. – Candidate of Medical Sciences, Associate Professor, Head of the Anesthesiology and Resuscitation Department No. 2, Asfendiyarov Kazakh National Medical University, Almaty, the Republic of Kazakhstan, e-mail: vvch64@mail.ru, tel. +77051801962, ORCID: 0000-0002-8653-1421;
Rybachek O.Y. – anesthesiologist-resuscitator, Kazakh Institute of Oncology and Radiology, Almaty, the Republic of Kazakhstan, tel. +77087638838, e-mail: olya_lya14@mail.ru, ORCID: 0009-0007-1964-9845.

Correspondence address: Arynov A.A., Kazakh Institute of Oncology and Radiology, Abay Ave. 91, Almaty 050000, the Republic of Kazakhstan.