Blood transfusion and oxygen extraction ratio in patients admitted to the general intensive care unit: A quasi experimental study

Transfusion sanguine et ratio d’extraction de l’oxygène chez des patients admis en unité de soins intensifs généraux: Une étude quasi expérimentale

Vitalis Mung’ayi, Thikra Sharif, David Samuel Odaba *

Department of Anaesthesia, Aga Khan University Hospital, Nairobi, Kenya

Received 21 January 2013; revised 24 May 2013; accepted 7 June 2013

KEYWORDS
Blood transfusion;
Oxygen extraction ratio;
Intensive care unit;
Critically ill patients

Abstract
Introduction: Blood transfusion is commonly undertaken in critically ill patients; and studies have suggested the use of oxygen extraction ratio (O₂ER) as an additional transfusion trigger in critically ill patients. The aim of this study was to establish the relationship between blood transfusion and oxygen extraction ratio in adult patients admitted to the general intensive care unit, using central venous oxygen saturation instead of mixed venous oxygen saturation. Methods: Arterial and central venous blood samples were drawn and a blood gas analysis immediately before commencement of blood transfusion was undertaken. At least 15 min after completion of the transfusion, similar samples were drawn and the blood gas analysis was repeated. The O₂ER before and after transfusion was then calculated. Using paired student’s t-test, we checked whether the mean difference between the two O₂ERs was statistically significant. Results: We enrolled 58 patients in the study, the mean (± SD) haemoglobin concentration before transfusion was 7.38 g/dl (± 1.71). The mean change in haemoglobin concentration following blood transfusion was 2.29 g/dl (±1.18), after transfusing an average of 1.95 (±0.83) units of packed cells. Mean O₂ER was 0.27 (±0.11) before, and 0.25 (±0.12) after RBC transfusion. The mean change in O₂ER was −0.018 SD ± 0.10 (95% CI, −0.043–0.007; P = 0.15). Linear regression
Abstract

Introduction: La transfusion sanguine est effectuée de façon courante chez les patients en état critique ; et des études ont suggéré l’utilisation du ratio d’extraction de l’oxygène (REO₂) comme déclencheur supplémentaire d’une transfusion chez les patients en état critique. Le but de cette étude était de déterminer le lien entre transfusion sanguine et ratio d’extraction de l’oxygène chez les patients adultes admis en unite de soins intensifs généraux en utilisant la saturation veineuse centrale en oxygène au lieu de la saturation veineuse mixte en oxygène.

Méthodes: Des échantillons sanguins artérielles et veineuses ont été prélevés et une analyse de gaz du sang a été effectuée juste avant le commencement de la transfusion sanguine. Au moins 15 min après l’achèvement de la transfusion, des échantillons similaires ont été prélevés et l’analyse des gaz du sang a nouveau effectuée. Le REO₂ avant et après la transfusion a ensuite été calculé. En utilisant des tests de Student appariés, nous avons vérifié si la différence moyenne entre les deux REO₂ était statistiquement significative.

Résultats: Nous avons inclus 58 patients dans l’étude, le taux moyen (±écart-type) d’hémoglobine avant la transfusion était de 7.38 g/dl (±1.71). Le changement moyen de taux d’hémoglobine à la suite de la transfusion sanguine était de 2.29 g/dl (±1.18), après avoir transfusé une moyenne de 1.95 (±0.83) unités de globules concentrés. Le REO₂ moyen était de 0.27 (±0.11) avant, et de 0.25 (±0.12) après la transfusion de globules rouges. Le changement moyen de REO₂ était de -0.018, l’écart-type de ±0.10 (intervalles de confiance de 95%, -0.043–0.007; P = 0.15). Une analyse de régression linéaire n’a montré aucun lien statistiquement significatif entre le changement du taux d’hémoglobine et le changement de REO₂; p = 0.12.

Discussion: Le changement du ratio d’extraction de l’oxygène n’était pas statistiquement significatif chez les patients adultes admis aux soins intensifs généraux dans un centre hospitalier universitaire. Des études supplémentaires sont nécessaires surtout chez les patients dont le REO₂ avant la transfusion a augmenté afin d’évaluer l’utilité de cette mesure comme déclencheur possible d’une transfusion.

Introduction

Little is known about oxygen extraction ratio and its relationship with anaemia and red blood cell (RBC) transfusion, as well as its ability to potentially supplement haemoglobin (Hb) concentration as a transfusion trigger. Oxygen extraction ratio (O₂ER) is the amount of oxygen consumed (VO₂), as a fraction of oxygen delivered (DO₂); the latter being a product of cardiac output (CO) and arterial oxygen content (CaO₂). VO₂ is essentially the difference between CaO₂ and venous oxygen content (CvO₂); CvO₂ being determined mainly by the Hb concentration and mixed venous oxygen saturation (SvO₂), while CaO₂ is determined by Hb concentration and arterial oxygen saturation (SaO₂). Orlov et al. examined temporal changes in Hb concentration and O₂ER following RBC transfusion post cardiac surgery with cardiopulmonary bypass, and suggested that; O₂ER, a readily available index of systemic oxygenation may be used to supplement Hb concentration as a RBC transfusion trigger. Oxygen extraction ratio is used as a marker for tissue oxygen extraction, and is expected to increase in the presence of

African relevance

- Minimising unnecessary blood transfusion by using accurate transfusion triggers may ensure appropriate use of a scarce resource.
- Samples from central venous catheters can be used to measure central venous oxygen saturation.
- Oxygen extraction ratio is a useful, additional transfusion trigger to haemoglobin when deciding on blood transfusion.

What’s new?

- Patients whose blood transfusion was solely based on the haemoglobin do not seem to benefit physiologically from the increased haemoglobin.
- Incorporation of oxygen extraction ratio as a transfusion trigger in addition to haemoglobin could reduce the number of patients transfused in the ICU.
either increased VO₂ or decreased DO₂. A reduction in DO₂ may be due to decreased CaO₂ from anaemia and/or low SaO₂, while an increase in VO₂ may be due to stress, fever, shivering and pain. Studies have shown that oxygen extraction ratio can be used to supplement haemoglobin concentration as a trigger for blood transfusion in ICU patients; however, for purposes of measuring SvO₂ these studies involved placement of a Swan-Ganz catheter which requires technical expertise. In addition, the benefit of inserting a Swan-Ganz catheter in critically ill patients is still questionable.

To the best of our knowledge, no published study has investigated the value of using blood samples from the central venous catheter to measure central venous oxygen saturation (ScvO₂) for purposes of calculating the oxygen extraction ratio; despite oxygen saturations in this samples showing good correlation with those from the pulmonary artery (SvO₂), drawn via the pulmonary artery catheter.

The purpose of our study therefore, was to investigate how blood transfusion affects O₂ER in adult patients admitted to the general ICU at a tertiary teaching hospital; using ScvO₂ instead of SvO₂ in the calculation of O₂ER.

Methods

The study was undertaken in the ICU at the Aga Khan University hospital, Nairobi; between July 2011 and January 2012. We obtained written approval from the institution’s research and ethics committee followed by written informed consent from patients themselves whenever possible; or from the next of kin as indicated in the hospital records; and in adherence to the declaration of Helsinki. The study was funded by the post-graduate medical education programme through the department’s budget. Patients were included if they underwent blood transfusion (packed red blood cells or whole blood), were aged above 18 years and a written informed consent was given, had a mean arterial blood pressure (MAP) not less 65 mmHg and an hourly urine output of at least 0.5 mls/kg. The exclusion criteria included age below 18 years, MAP below 65 mmHg, oliguria, on-going haemorrhage, congestive heart failure, carbon monoxide or cyanide poisoning and shock of any origin. Since there are no blood transfusion protocols in place, the attending physician for each patient made all RBC transfusion decisions; based on his or her own judgement. Patient’s age, gender and physiological parameters (temperature, mean arterial blood pressure, heart rate and central venous pressure) were collected in all study patients as per protocol.

The number of units of blood (packed cells or whole blood) transfused per study patient during the study period was recorded. The reasons for the blood transfusion, the Hb concentration and O₂ER immediately before and a minimum of 15 min after the end of the blood transfusion were subsequently recorded.

To calculate O₂ER, blood gas analysis on samples obtained from indwelling arterial and central venous catheters was undertaken. The primary outcome was the change in O₂ER following blood transfusion; while our secondary outcomes were: how the APACHE II score on admission correlated with the change in O₂ER after blood transfusion and the effect of haemoglobin concentration on O₂ER.

A total of fifty-eight patients were included in the study; 36 (62.1%) were non-surgical patients while 22 (37.9%) were surgical (post-operative). The patient’s baseline characteristics are summarised in Table 1. Measured clinical variables pre and post blood transfusion are summarised in Table 2.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.7</td>
<td>16.7</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>18.9</td>
<td>9.5</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.0</td>
<td>0.6</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76.9</td>
<td>10.1</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>98.1</td>
<td>16.5</td>
</tr>
<tr>
<td>CVP (cmH₂O)</td>
<td>14.4</td>
<td>5.7</td>
</tr>
</tbody>
</table>

SD, standard deviation; APACHE, acute physiology and chronic health evaluation; MAP, mean arterial pressure; mmHg, millimetres of mercury; HR, heart rate; CVP, central venous pressure; cmH₂O, centimetres of water.

Please cite this article in press as: Mung’ayi V et al. Blood transfusion and oxygen extraction ratio in patients admitted to the general intensive care unit: A quasi experimental study, Afr J Emerg Med (2013), http://dx.doi.org/10.1016/j.afjem.2013.06.004
### Table 2 Clinical variables (n = 58).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Std. deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units of blood transfused</td>
<td>1.95</td>
<td>0.83</td>
</tr>
<tr>
<td>Hb before transfusion (g/dl)</td>
<td>7.37</td>
<td>1.71</td>
</tr>
<tr>
<td>Hb after transfusion (g/dl)</td>
<td>9.67</td>
<td>1.68</td>
</tr>
<tr>
<td>Change in Hb concentration</td>
<td>2.29</td>
<td>1.18</td>
</tr>
<tr>
<td>SaO2 before transfusion</td>
<td>0.96</td>
<td>0.03</td>
</tr>
<tr>
<td>ScVO2 before transfusion</td>
<td>0.70</td>
<td>0.11</td>
</tr>
<tr>
<td>SaO2 after transfusion</td>
<td>0.96</td>
<td>0.03</td>
</tr>
<tr>
<td>ScVO2 after transfusion</td>
<td>0.72</td>
<td>0.12</td>
</tr>
<tr>
<td>O2ER before transfusion</td>
<td>0.27</td>
<td>0.11</td>
</tr>
<tr>
<td>O2ER after transfusion</td>
<td>0.25</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Hb, haemoglobin; g/dl, gram per decilitre; SaO2, arterial oxygen saturation; ScVO2, central venous oxygen saturation; O2ER, oxygen extraction ratio.

### Table 3 Linear regression output for change in O2ER compared to various patient variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.08</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>-0.02</td>
<td>0.01</td>
<td>-.20</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0004</td>
<td>0.001</td>
<td>-.07</td>
</tr>
<tr>
<td>Sex</td>
<td>0.002</td>
<td>0.03</td>
<td>.01</td>
</tr>
<tr>
<td>APACHE II</td>
<td>-0.003</td>
<td>0.001</td>
<td>-.31</td>
</tr>
<tr>
<td>Temperature</td>
<td>-0.0002</td>
<td>0.02</td>
<td>-.001</td>
</tr>
<tr>
<td>MAP</td>
<td>0.0002</td>
<td>0.001</td>
<td>.03</td>
</tr>
<tr>
<td>CVP</td>
<td>0.001</td>
<td>0.002</td>
<td>.04</td>
</tr>
</tbody>
</table>

Note: $R^2 = 0.15$ ($p = 0.28$).

* $p < 0.05$; SE, standard error; Hb, haemoglobin; APACHE, Acute Physiology And Chronic Health Evaluation; MAP, mean arterial pressure; CVP, central venous pressure.

Linear regression analysis showed no statistically significant relationship between change in Hb concentration and change in O2ER with a $p$-value of 0.119. Further regression analysis that included other variables (age, sex, APACHE II score, temperature, MAP, and CVP) in addition to O2ER did not show any statistically significant relationship, with the exception of the APACHE II score which had a $p$-value of 0.036 (Fig. 1 and Table 3). Patients with higher APACHE II scores on admission had a larger reduction in O2ER compared to those with a lower score.

### Discussion

In this study, blood transfusion did not significantly change the oxygen extraction ratio in adult patients admitted to the general ICU at a tertiary teaching hospital. Furthermore, change in haemoglobin concentration following blood transfusion and change in the oxygen extraction ratio did not correlate. There was a statistically significant relationship ($p$-value of 0.036) between the APACHE II score and the change in oxygen extraction ratio following blood transfusion; however, our study was not adequately powered to assess the significance of this finding, raising the need for further studies in this area.

These findings suggest lack of significant improvement in tissue oxygenation, despite the increase in oxygen content that arose after increasing haemoglobin concentration by transfusing red blood cells. However, there was a trend suggesting benefit from RBC transfusion in patients who had a higher APACHE II score at admission. O2ER reduced by 0.02 but still remained within the normal range of 0.25-0.30, meaning the body may have adjusted its O2ER in the presence of increased oxygen delivery (DO$_2$) to maintain oxygen consumption (VO$_2$) constant.

All the blood transfusions administered during the study period, were based on haemoglobin concentration regardless of what the oxygen extraction ratio was. Subgroup analysis of the patients who had a pre-transfusion O2ER of more than 0.30 yielded a mean reduction in O2ER of 0.055 (SD 0.11; $p$-value of 0.24). This may imply that majority of the patients who were transfused (60.3%), did not physiologically require RBC transfusion, and so did not benefit from the increased oxygen content. Orlov et al. in their study demonstrated that O2ER does not significantly change after blood transfusion if the baseline value was normal.2 It is therefore possible that lack of a significant change in the O2ER in our study resulted from the fact that about 60% of the patients had a baseline O2ER below 0.30.

Sehgal et al. demonstrated that using O2ER as a transfusion trigger could potentially reduce the number of blood transfusions.4 They showed that if they had used an O2ER of 0.50 as the transfusion trigger, then only 7 out of 41 patients in the transfusion group would have been transfused. Since they planned to account for the possibility of patients being unable to increase their cardiac output as a compensatory mechanism, they settled on a transfusion trigger of 0.45; this resulted in doubling of the number of patients who would be transfused. In this study therefore, if we utilised a transfusion trigger O2ER of 0.45, then only 3 out of the 58 patients would have been transfused.

It is important to note that unlike the two studies quoted above, we used central venous oxygen saturation. Scheinman et al. demonstrated that mean central venous oxygen saturation (ScvO2) was significantly greater than mean mixed venous oxygen saturation (SvO2) by about 5%. ScvO2 is measured in blood sampled from the superior vena cava (SVC), which contains venous blood, from the upper body (head, neck, upper limbs and upper trunk). Blood from the lower body (intra-abdominal organs and lower limbs) drains via the inferior vena cava.
Blood transfusion and oxygen extraction ratio in patients admitted to the general intensive care unit

Michelle et al. further demonstrated that increasing DO₂ improves outcome, and that it was followed by a fall in oxygen extraction.

Another argument is with regard to how useful oxygen extraction ratio is in ICU patients. It is thought that O₂ER is impaired during critical illness. Several studies have supported this hypothesis by showing that there is lactate acidosis in critically ill patients despite an increased oxygen delivery; implying anaerobic metabolism is required despite increased oxygen supply. It had therefore been concluded that oxygen consumption (VO₂) could be pathologically dependent on delivery (DO₂) in critically ill patients and that ineffective oxygen extraction maybe due to either poor oxygen uptake or poor utilisation by the cells. However, both VO₂ and DO₂ in the these studies were calculated, and this may have introduced mathematical coupling errors which could falsely increase the strength of the relationship between VO₂ and DO₂. This led to subsequent studies which measured VO₂ and DO₂ independently. Bruining et al. demonstrated in their study that, in a certain group of patients (septic and postoperative), there is a minimal positive relationship between VO₂ and DO₂. They therefore concluded that in this group of patients who are haemodynamically stable, VO₂ might not be pathologically dependent on DO₂ and that lactacidosis does not necessarily mean the presence of an oxygen debt.

Potential confounders include: RBC storage lesions, arterial blood pH, and accuracy of O₂ER in ICU patients; all of which might affect the findings of this study. During storage, RBC’s undergo a series of changes that reduce their survival and function; the so called “storage lesions”.

There is a reduction in 2,3-diphosphoglycerate (2,3-DPG) in RBC’s after 48 h of storage, leading to impaired unloading of oxygen to the tissues. Several studies have however disputed the clinical significance of the reduction in 2,3-DPG levels in stored blood. Weiskopf et al. in their study concluded that, despite erythrocytes stored for 3 weeks in citrate phosphate dextrose adenine (CPDA) being depleted of 2,3-DPG with reduction in their P50 (the partial pressure of oxygen in the blood at which the haemoglobin is 50% saturated), they still release adequate oxygen to reverse the deficits of acute anaemia to an extent equivalent to that of erythrocytes with a normal P50. Orlov et al. further demonstrated that there was no latency in oxygenation following red blood cell transfusion.

In our study, post transfusion O₂ER was undertaken at least 15 min after completion of blood transfusion, it is therefore unlikely that depletion of 2,3-DPG contributed significantly to the calculated value.

The other possible confounder which may have affected the oxyhaemoglobin dissociation curve is the arterial pH. Alkalosis would result in a leftward shift of the oxyhaemoglobin dissociation curve (decreased P50) causing reduced dissociation of oxygen from haemoglobin. Acidosis would have had the opposite effect. In this study, since each patient was acting as their own control, the resulting effect would have equally affected both the pre and post transfusion O₂ER. This would therefore have had no effect on the change in the O₂ER following RBC transfusion. However, we cannot completely rule out the effect of pH because the duration of blood transfusion varied in each patient; and the pH may have changed during that period in some patients. A controlled study may eliminate this confounder.

Conclusion

In this study, we concluded that the change in oxygen extraction ratio was not statistically significant following red blood cell transfusion in patients admitted to the general ICU at a tertiary teaching hospital. Further studies are required especially in patients with increased pre transfusion O₂ER to...
evaluate the usefulness of this measurement as a possible transfusion trigger.

Conflict of interest statement

None of the authors listed has a competing interest that could unduly influence his or her involvement in the publication process for this article.

Appendix A. Short answer questions

Test your understanding of the contents of this original paper (answers can be found at the end of the regular features section).

1. With regard to oxygen extraction ratio.
   a. It remains constant irrespective of changes in either oxygen consumption or oxygen delivery.
   b. Is the amount of oxygen consumed as a fraction of oxygen delivered.
   c. Can be calculated using central venous oxygen saturation as a surrogate marker of mixed venous oxygen saturation.
   d. Using it as a transfusion trigger could potentially reduce the number of blood transfusions in critically ill patients.
   e. Has no role in current practise of critical care medicine.

2. With regard to central venous oxygen and mixed venous oxygen saturations.
   a. Measured central venous oxygen saturation is usually lower than mixed venous oxygen saturation.
   b. Insertion of a Swan-Ganz catheter is mandatory for measuring central venous oxygen saturation.
   c. Blood samples for measuring central venous oxygen saturation can be obtained from the superior vena cava.
   d. Mixed venous oxygen saturation is essential in the calculation of venous oxygen content.
   e. Presence of a correctly placed central venous catheter is all that is required to obtain blood samples for measuring mixed venous oxygen saturations.

3. With regard to blood transfusion in the intensive care unit.
   a. The indications for blood transfusion are clear cut in all critically ill patients.
   b. Transfusion of stored blood does not impair the unloading of oxygen to the tissues.
   c. Blood transfusion is rare among critically ill patients.
   d. Red blood cell transfusion may be reduced if other transfusion triggers in addition to haemoglobin concentration are adopted.
   e. It is proven that “storage lesions” do significantly affect the clinical efficacy of transfused red blood cells.

References