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Anaemia and massive bleeding apart from the aspect of oxygenation

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Introduction

A strong distinction must be made between the following situations of anaemia: Under *chronic* conditions, i.e. anaemia with a reduced Hb concentration (cHb), normovolaemia is given and, therefore, the patient's acid-base balance is not impaired. Oxygen supply as well as tissue oxygenation is sufficient, partly as a result of the right shifted oxygen binding curve (increase in 2,3-DPG), down to a cHb of ~5 g/dl.

In the case of *acute* conditions, however, haemodilution during massive bleeding leads to a decrease in cHb, in which case we may be faced with two different scenarios:

Either *normovolaemia* as a result of an optimal therapy with normal acid-base balance, especially lactate concentration (cLact), or *hypovolaemia* with a compromised tissue oxygenation and resulting acidosis, mostly lactic acidosis, despite the right shifted oxygen binding curve (decrease in pH). This acidosis is, in addition to hypothermia, the cause of the coagulopathy which, in turn, favours further bleeding, the so-called "lethal triad" demonstrated with about 80 thousand patients by Martin et al. in 2005 [1]. In about 8200 multiple trauma patients, a strong correlation has been shown between mortality (%) and base excess (BE, mmol/L) on hospital admission alone (4 studies) [2]: A base deficit (BD) of ~15 mmol/L predicts a mortality of ~50%.

Aggressive management of the "lethal triad", i.e. coagulopathy as a *result* of metabolic acidosis *plus* hypothermia, therefore, appears to have the greatest potential of reducing mortality in severely injured patients [3].

Base excess and clotting

Experimental studies using three selected coagulation factors have shown that *in vitro,* clotting factor activity is to a large extent determined by the pH: clotting factor activity was found to be halved at pH 7.20 (base deficit, 12.5 mmol/L) and doubled at pH 7.60 (base excess, 16.5 mmol/L) [4]. This observation has been corroborated in patients *in vivo*, as shown in Fig. 1: A significant ($p < 0.001$) correlation between prothrombin level (%) and negative base excess was found in 4066 out of a total of 20,815 severely injured (ISS ≥ 16) multiple trauma patients of the Trauma Registry of the German Society of Trauma Surgery (*Deutsche Gesellschaft für Unfallchirurgie*) receiving primary care [5].

Apart from prothrombin time (PT), the partial thromboplastin time (PTT) can also be correlated with the base deficit of trauma patients on hospital admission as well: a larger BD will substantially increase both parameters, affecting as many as 25 % of all trauma patients on admission [6, 7]. These bench and bedside findings therefore suggest that a base deficit of approx. 15 mmol/L primarily reduces clotting activity to approx. 50%, which secondarily explains the reported mortality rate of approximately 50% in multiple trauma patients.

Volume therapy

Haemodilution thus has general repercussions: Dilution means dilutional coagulopathy because the concentrations of coagulation factors are reduced. However, dilution also produces dilutional acidosis, which in turn may produce hypocoagulopathy. The latter should therefore always be avoided through the use of balanced solutions, while the use of conventional crystalloids, such as 0.9% NaCl, should be minimized [8].

Conclusion 1

During the management of haemorrhage, any acidosis must be prevented through the use of a balanced solution, and exacerbation of acidosis, in the form of dilutional coagulopathy or dilutional acidosis, must be avoided.

Balanced solutions show a potential base excess of ~ 0 mmol/L, i.e. with no influence on the patient's acid base status after infusion plus metabolism of the anions.

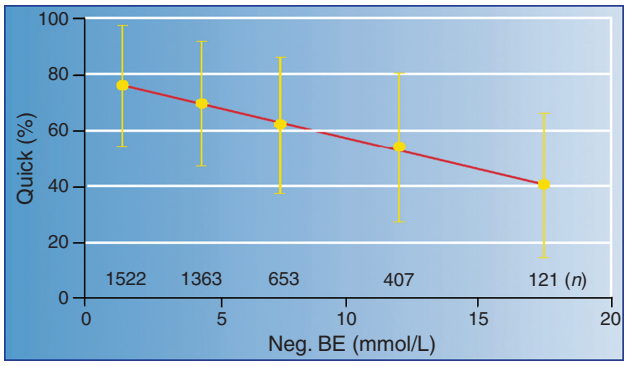

Fig. 1. Clotting activity (prothrombin level, %) as a function of BE (mmol/L) in about 4000 multiple trauma patients

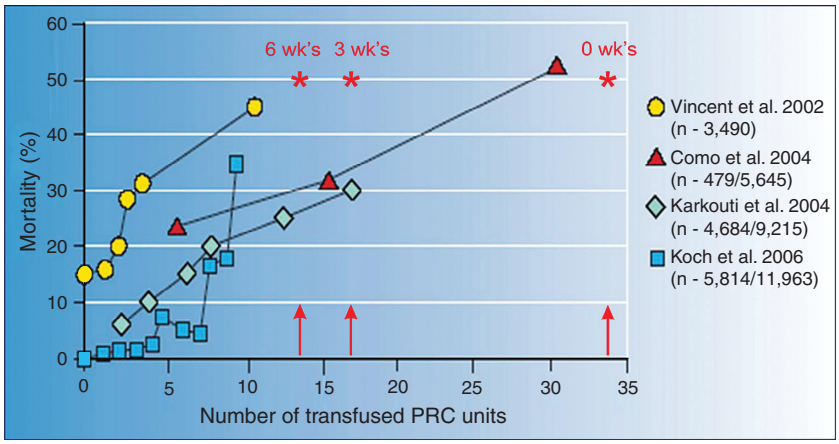

Fig. 2. Mortality (%) in about 15,000 patients from 4 studies following transfusion of PRC units

Coagulation and ionised calcium

The normal plasma calcium concentration is approx. 2.5 mmol/L, and about half of the plasma calcium is bound to proteins, mainly albumin. The calcium concentration (cCa^{2+}) that has an important role in clotting is the concentration of ionised (free) Ca^{2+} (1.25 mmol/L). In major blood loss, both albumin-bound Ca^{2+} and ionised Ca^{2+} are expected to decrease. Severe hypocalcaemia – seen in 10% of trauma patients – is defined as a $cCa^{2+} < 0.9$ mmol/L, which should be treated with calcium supplementation. Ca^{2+} binding, or reduction in free calcium, has been described for lactate (chelation). Lactate can be assumed to produce a linear decrease in cCa^{2+} by 0.05 mmol/L per 1 mmol/L of lactate [9, 10]. At a lactate concentration of 10 mmol/L, this means a reduction in cCa^{2+} from normal 1.25 to 0.75 mmol/L, or hypocalcaemia requiring therapy.

Conclusion 2

The use of lactate-containing infusion fluids (Ringer's lactate) and older packed red cell products should be avoided in acute haemorrhage because these are liable to produce or worsen hypocalcaemia. Balanced infusion fluids should contain at least the physiological cCa^{2+} of 1.25 mmol/L.

Haemotherapy using packed red cells or plasma

The transfusion of erythrocytes in the form of packed red cells (PRCs) is being viewed with an increasingly critical eye. This view was condensed in the title of a 2008 editorial: "New blood, old blood, or no blood?" [11].

The *number* of transfused PRC units shows a strong association with patient mortality, as demonstrated in Fig. 2 for almost 15,000 patients from 4 studies, but no causal relationship can be deduced from this.

The *age* of transfused PRC units was also shown to be strongly associated with the mortality of cardiac surgery patients [12]. The question of whether a causal relationship can be established for the observed association is going to be explored in the following: Even at the time of preparation, PRCs show a base deficit of about 20 mmol/L. At 21 days (3 weeks) they have a BD of 40 mmol/L, and at 42 days (6 weeks) a BD of 50 mmol/L [13]. Now, if a BD of 15 mmol/L predicts a 50% mortality for a multi trauma patient, this critical BD can be calculated for a patient with 75 kg bw. This has been done in Fig. 2, characterised by three asterisks at the 50% mortality line. Accordingly, this prediction obviously describes the mortality related to the transfused PRCs in a very good manner.

The transfusion of plasma alters the situation. The balance between the acidifying BD of red cells (production process and formation of lactic acid) and the potentially alkalising effect of citrate within the plasma produces the following result: PRC is an acidifying and plasma an alkalising product, because practically no alkalising component of citrate remains in the PRC unit (3 mmol/L).

In a retrospective study, it was demonstrated that the mortality of polytrauma patients ($n = 713$, ISS > 16) after massive transfusion (> 10 PRCs) may be reduced from 25 to only 4% (mortality < 6 h) or 46 to 24 % (30-day mortality) when the relation of PRCs to FFPs is reduced from > 1.1 to < 0.9 [14].

Conclusion 3

The transfusion of red cells (PRCs), concerning the number and age, has significant drawbacks because PRCs are liable to increase acidosis and hence coagulopathy, thus causally maintaining and perpetuating bleeding. This may be avoided by the use of the alkalising plasma (FFP).

Strategy of treating massive haemorrhage

The currently accepted transfusion approach to major haemorrhage is as follows: First crystalloids, then colloids, then PRCs, and then plasma (FFP) [15]. This regimen merits revision and should be improved as follows:

First line balanced colloids rather than crystalloids aim at normovolaemia, maintain normal BE; second line plasma for volume replacement plus clotting factors in case of dilutional coagulopathy despite normal BE; third line transfusion of fresh PRCs if at all possible once the cHb falls below a critical level.

Conclusion 4: Proposal for a new strategy of treating massive haemorrhage

1st Volume therapy: Permissive normovolaemic haemodilution to cHb of ~7.5 g/dl with balanced colloidal solutions (e.g.

HES 130/0.4) with BEpot ~0 mmol/L, acetate instead of lactate, including Ca^{2+}: prevention or normalisation of any acidosis and thus coagulopathy.

2nd Volume therapy plus coagulation therapy: Fresh frozen (FFP) or lyophilised plasma: volume, coagulation factors, prophylaxis of acidosis (citrate).

3rd Coagulation therapy: Fibrinogen, coagulation factors, rFVIIa, aprotinin, tranexamic acid, etc., but only if no metabolic acidosis is present.

4th Haemotherapy: Fresh PRCs (lactate) at cHb of 5–7 g/dl, if there are no signs of hypoxia (ECG, BE, lactate) and only after a FIO_2 of 1.0 was confirmed.

Conflict of interest

As a consultant the author has received honoraria and financial reimbursements from B. Braun Melsungen (Germany).

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