

# Acidosis: How to prevent bleeding?

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## Background

In severely injured patients aggressive management of the “lethal triad”, i.e. coagulopathy as a *result* of metabolic acidosis *plus* hypothermia, appears to have the greatest potential of reducing mortality. In about 8,200 multiple trauma patients, a strong correlation has been shown between mortality (%) and base excess (BE, mmol/l) on hospital admission: A base deficit (BD) of ~ 15 mmol/l predicts a mortality of ~ 50 %. Therefore, under clinical conditions, any kind of acidosis must be prevented as well.

## 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). This observation has been corroborated in patients *in vivo*: A significant correlation between prothrombin level (%) and negative base excess was found in 4,066 out of a total of 20,815 severely injured (ISS  $\geq$ 16) multiple trauma patients of the Trauma Registry of the German Society of Trauma Surgery receiving primary care. Apart from prothrombin time (PT), the partial thromboplastin time (PTT) can be correlated with the base deficit of trauma patients on hospital admission as well: a larger BD will substantially increase both parameters.

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 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.

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. Therefore, the use of conventional crystalloids, such as 0.9 % NaCl, should be minimised.

## 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<sup>2+</sup>) that has an important role in clotting is the concentration of ionised (free) Ca<sup>2+</sup> (1.25 mmol/l). Ca<sup>2+</sup> binding, or reduction in free calcium, has been described for lactate. 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 NEJM editorial: "New blood, old blood, or no blood?"

The *number* of transfused PRC units shows a strong association with patient mortality, as has been demonstrated for almost 15,000 patients from 4 studies.

The age of transfused PRC units was also shown to be strongly associated with the mortality of cardiac surgery patients. A possible explanation might be the fact that even at the time of preparation, PRCs show a base deficit of about 20 mmol/l, increasing to 50 mmol/l at 6 weeks during storage. However, in both cases, no causal relationship can be deduced from this.

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 alkalisating effect of citrate within the plasma produces the following result: PRC is an acidifying and plasma an alkalisating product, because practically no alkalisating citrate remains in the PRC unit.

In fact, in a retrospective study, it was demonstrated that the 30-day mortality of polytrauma patients after massive transfusion may be reduced from 46 to 24 % when the relation of PRCs to FFPs is reduced from > 1.1 to < 0.9. Therefore, 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 alkalisating 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). This regimen merits revision and should be improved as follows:

1. Balanced colloids rather than crystalloids, e.g. HES 130/0.4 with BE<sub>pot</sub> ~ 0 mmol/l, acetate instead of lactate, including  $Ca^{2+}$ : prevention or normalisation of any acidosis and thus coagulopathy.
2. Plasma for volume replacement plus clotting factors: e.g. fresh frozen (FFP) or lyophilised plasma, including prophylaxis of acidosis (citrate).
3. Coagulation therapy: Fibrinogen, coagulation factors, rFVIIa, aprotinin, tranexamic acid, etc., but only if no metabolic acidosis is present.
4. Transfusion of fresh PRCs (lactate) if at all possible once the cHb falls below a critical level and signs of hypoxia (ECG, BE, lactate) occur.

## References

1. Zander R. Anaemia and massive bleeding apart from the aspect of oxygenation. Wien Klin Wochenschr 2010; 122 (Suppl 5): 6-8