Commentary

Recently published papers: What not to do and how not to do it?

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Abstract

Controversies abound in the areas of blood transfusion, albumin, lipoproteins in sepsis and pulmonary artery catheters. We are also making too many errors, but at least there is a new nitric oxide therapy in the offing.

How to deliver oxygen?

The delivery of oxygen to tissues remains a central tenet of intensive care medicine. Much of the attention has focused on optimizing cardiac output and perfusion pressure, not least because we possess therapeutic tools that affect these parameters. The second element in the equation is oxygen carrying capacity, which is primarily determined by haemoglobin concentration and hence red cell mass. Transfusion of stored red blood cells is used to maintain oxygen carrying capacity, although the optimal use of this therapy remains an area of considerable controversy. It is well established that transfused red blood cells carry but do not efficiently release oxygen for at least 24 hours, because of 2,3-diphosphoglycerate depletion. In addition, they do not deform to facilitate transit through the microcirculation. Use of a low transfusion threshold has been shown to be of benefit [1], as has a more permissive approach [2]. Habib and colleagues [3] have added to this controversy in their detailed study of the effects of anaemia and red blood cell transfusion in patients undergoing cardiopulmonary bypass. They measured changes in renal function as an index of end-organ damage due to impaired tissue oxygen delivery. The results, which are eloquently discussed in an accompanying editorial [4], demonstrate renal injury caused both by anaemia and transfusion. In the words of the editorialist, 'damned if you do/damned if you don't!'

However, a recent animal study may yet offer us some salvation. Young and colleagues have been developing a substitute for red blood cell transfusion by conjugating haemoglobin tetramers with polyethylene glycol (PEG). In their most recent paper [5] they resuscitated a pig model of intraoperative haemorrhagic shock with a single, small volume bolus of Ringer's acetate, 10% pentastarch, 4 g/dl stroma-free haemoglobin, or their PEG-conjugated human haemoglobin. The animals then received an autologous blood transfusion, the blood having been removed as the first of two insults, the second being an aortic tear that was surgically controlled after 30 min. Six of the seven animals that received the PEG-conjugated human haemoglobin survived, as compared with only two of the seven that received the Ringer's acetate, two of the seven that received the stroma-free haemoglobin, and one of the seven that received the pentastarch. Survival was predicted by the trends in physiological parameters monitored. In their discussion, the authors emphasized that maintenance of oxygen carrying capacity as well as functional capillary density, by preserving blood viscosity, are essential if fatal tissue hypoxia is to be prevented. Further insightful comments also appear in an editorial concerning the importance of blood viscosity [6]. Human trials of this alternative intervention are keenly awaited.

A further consideration in increasing oxygen delivery is the fraction of inspired oxygen. In a well argued hypothesis piece, Iscoe and Fisher [7] remind us that oxygen is a respiratory stimulant; thus, administering 100% oxygen results in hyperventilation with consequent hypocapnia and regional vasoconstriction. The net effect, they suggest, will in fact be a reduction in oxygen delivery to a wide variety of vascular beds caused by disadvantageous changes in the microcirculation. This adds further credence to maintaining normocapnia or even mild hypercapnia in patients with borderline tissue perfusion and actively monitoring this parameter. By the same token, aiming for normoxia, as opposed to hyperoxia, is probably desirable.

Albumin: SAFE, but useful or predictable?

Editorials often reflect on the fashionable nature of a wide variety of intensive care unit (ICU) interventions. The use of albumin is a classic example, with a series of contradictory meta-analyses [8-11] and a recent large scale, prospective, multicentre trial [12]. Given the available evidence base,

ALI = acute lung injury; ICU = intensive care unit; NO = nitric oxide; PEG = polyethylene glycol; ppm = parts per million.

few would dispute that albumin is safe but the evidence for its efficacy remains limited. Two new studies are worthy of note.

Martin and colleagues [13] presented their second interventional study into the efficacy of albumin-supported diuresis in the nonacute phase of acute lung injury (ALI) in patients with hypoproteinaemia. This group previously reported an observational study establishing a link between hypoproteinaemia and poor outcome in ALI [14]. They then went on to conduct a randomized controlled trial of albumin and furosemide versus placebo in a small group of hypoproteinaemic patients with ALI [15]. They demonstrated short-term improvements in fluid balance, oxygenation and haemodynamics in the treatment group.

To establish whether the combination or furosemide alone was superior, they conducted this follow-up study [13]. They randomized a heterogeneous group of patients with ALI to receive 72 hours of continuous, low-dose furosemide with either 8 hourly boluses of 25% albumin or 0.9% saline (placebo). They successfully recruited 20 patients into each arm and measured both short-term physiological effects together with longer term clinical outcomes, although the study was not powered to detect meaningful differences in the latter. The treatment group achieved greater cumulative, negative fluid balance at 72 hours (−5480 ml versus −1490 ml; $P < 0.01$), in part because of a greater requirement for intravenous fluid support in the saline group (1050 ml versus 275 ml; $P = 0.06$). There was a small but statistically significant improvement in the arterial oxygen tension/fraction of inspired oxygen ratio in the treatment group at 24, 48 and 72 hours. In terms of clinical outcomes, 30-day mortality was 7/20 (35%) in the treatment arm and 9/20 (45%) in the placebo arm, and median ventilator-free days over 30 days of follow up were 5.5 in the treatment arm and 1.0 in the placebo arm. The authors' well argued discussion and the accompanying editorial [16] both conclude that a larger randomized trial of this intervention is warranted. Of note, this second study fails to answer whether albumin alone is efficacious, or indeed whether low-dose furosemide, necessitating saline resuscitation, is harmful. They comment (as does the editorial) that the effects of albumin remain unclear.

To add further murkiness to the issue, a timely laboratory analysis of commercially available albumin solutions was reported by Bar-Or and colleagues [17]. They found that a high proportion of post-translational oxidation had occurred in the commercial samples as compared with healthy human serum. The quantity of this oxidation varied markedly between manufacturers and within batches from the same manufacturer. Thus, before any study claims a beneficial effect from albumin they would appear to need to demonstrate that they have analyzed what they have administered.

And other antioxidants, scavengers and inflammatory modulators?

Staying on the topic of antioxidants, a trial of *N*-acetylcysteine in high-risk patients undergoing pump coronary artery bypass graft surgery [18] has failed to demonstrate any benefit – a further negative study for this agent. In contrast, ascorbate (vitamin C) may yet prove to be a useful adjunct in managing sepsis, if the results of the study reported by Tyml and coworkers [19] in a rat model of sepsis translate into useful outcomes in human trials. Another agent on the distant horizon of sepsis interventions is chemically modified tetracycline (an anti-inflammatory with no antimicrobial properties), which appears to produce dramatic results in a standard model of rat sepsis [20].

Finally, two partially contradictory observational studies into the relationship between severity of disease and fatal outcomes from sepsis, and levels of serum lipoproteins [21,22] suggest that measuring total cholesterol and quantifying its high-density and low-density fractions may provide useful prognostic information. It appears that lipoproteins may act as functionally important scavengers of bacterial toxins and as 'good guys' in the seemingly ever-expanding innate immune response. Finding low levels of lipoproteins correlates with greater severity of illness and fatal outcome, although the exact pattern is not clear from these two studies. This may reflect different responses to varying bacterial species (*Neisseria meningitides* [21] versus a mixed group of pathogens, almost certainly excluding *Neisseria meningitides* [22]). Although it is understandable to leap to the conclusion that restoring lipoprotein levels to the normal range will be of therapeutic benefit in sepsis, this is a path often trodden in the past with a very poor record of success.

Nitric oxide: the end of lung therapy but a newly discovered role in the stomach

The European experts have considered the evidence and published their recommendations regarding the use of inhaled nitric oxide (NO) [23]. In summary, they suggest that with little evidence of efficacy, if any, except in the diagnosis of reversible pulmonary hypertension, and in the light of escalating costs, the use of inhaled NO – outside of well designed clinical trials – cannot be defended. By contrast, evidence is accumulating that NO plays an important role in gastric mucosal health, demonstrating bactericidal activity and increasing both mucosal blood flow and mucus production [24]. The source of this miraculous molecule appears to be nitrites in saliva [25]. In this study, Björne and colleagues performed gastric tonometry for NO in healthy volunteers and intubated critically ill patients. The level of NO in healthy individuals was 21.6 parts per million (ppm; range 11.4–22.3 ppm) whereas in the patient group levels were only 0.1 ppm (range 0.06–0.4 ppm). The patients had normal levels of salivary nitrite and gastric infusion of nitrite successfully increased intragastric NO levels, implying that saliva is not reaching the stomach. Trials of intragastric nitrite

are keenly awaited, but in the meantime any spare supplies of NO for inhalational therapy could be redirected …?

Error

We all make mistakes, but few of us have a dedicated team of watchers on our ICUs pointing out all our faults. One institution did install such an arrangement and has reported their sobering findings [26]. In this centre of excellence there was a daily rate of 0.8 adverse events and 1.5 serious errors per 10-bed critical care unit. Most errors were described as, 'slips and lapses, in particular, failures to carry out intended plans of action'. It would unfeasible to provide anything close to this level of vigilance in ICUs routinely, but reducing the incidence of errors by any and all means should be a priority.

And finally …

The eagerly awaited UK PAC-Man study has been reported [27]. Yet again, a cornerstone of ICU practice wanes in the light of our inability to demonstrate any benefit from its use, or should it? The design of the trial was to ascertain the safety of pulmonary artery catheters, which it did by demonstrating no difference in the outcomes of patients randomly allocated to have a pulmonary artery catheter or not. The majority of patients allocated to the control arm had access to alternative methods of cardiac output monitoring and no element of care was protocolized. There was a 10% complication rate associated with insertion, but the vast majority of these were clinically insignificant. Hopefully, this should end the safety debate and allow research resources to be directed toward improving the haemodynamic care of critically ill patients.

Competing interests

The author(s) declare that they have no competing interests.

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