Editorial

Should perioperative management target oxygen delivery?

Several strategies have been proposed to improve outcome after surgery. One of these is the use of fluids and catecholamines to achieve ‘supra-normal’ oxygen delivery, an approach variously termed ‘goal directed therapy’, ‘pre-optimization’, and ‘haemodynamic optimization’. This attractive concept is the basis of the study by Stone and colleagues, published in this issue of the journal. In this placebo controlled trial, patients who were given doxapamine at a rate of 0.25 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) during surgery and for 24 h thereafter had a significantly higher cardiac index than patients given placebo, but morbidity and mortality were unaffected. Fluid therapy was used to increase stroke volume, measured using an oesophageal Doppler, before commencing the doxapamine. Oxygen delivery was not measured but the authors’ estimate, that it would have been between 500 and 550 ml min\(^{-1}\) m\(^{-2}\) in the placebo group and over 600 ml min\(^{-1}\) m\(^{-2}\) in the doxapamine group, is likely to be accurate. The mortality rate in both groups was less than the rate predicted using the POSSUM scoring system, an observation that the authors consider significant and suggest is likely to be attributable to the targeting of stroke volume. What does this study add to our understanding of the role of doxapamine and of attempts to target oxygen delivery?

Dopexamine

With regard to the specific role of doxapamine, the results of Stone and colleagues support those of a previous study, which found no benefit from the use of doses of 0.5 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) or 2 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) in patients undergoing abdominal surgery. It appears that the theoretical attractions of doxapamine, particularly with regard to hepatosplanchnic blood flow, do not translate into better outcomes for patients. There is a parallel with the once widespread use of prophylactic dopamine to prevent renal failure. This has now been shown not to be effective, and concerns have arisen about potentially harmful endocrine effects. Although doxapamine has a different dopaminergic receptor profile from dopamine, it has similar potential for adverse effects, particularly at higher doses. Dopexamine is licensed for the treatment of exacerbations of chronic heart failure, or heart failure associated with cardiac surgery. The use of fixed dose ‘prophylactic’ doxapamine in general surgery seems inadvisable on present evidence, however.

Oxygen delivery

Deliberately increasing cardiac output in order to raise oxygen delivery is a different issue. The study by Stone and colleagues largely presumes its value, but adds little new evidence, as mortality is compared with a statistical model rather than a control group. It is now accepted that haemodynamic optimization is not of benefit once organ failure has developed, but it remains of interest in the early stages of critical illness, and has been strongly advocated in the perioperative situation. A recent meta-analysis concluded that it was effective when started early in studies where the control group mortality was more than 20%. In contrast, mortality was not reduced if the control group mortality was less than 15%, if the goals were ‘normal values’, or when treatment did not improve oxygen delivery. It is unfortunate that this analysis used control group mortality, which is actually an outcome measure, as an indicator of severity of illness. Four of the six studies cited with control group mortality greater than 20% were related to surgery, although in one of these the control group mortality was actually 17%. The case for targeting oxygen delivery in high-risk surgery is largely based on these studies and so their reliability is a key issue. All aimed for a cardiac index of 4.5 litre min\(^{-1}\) m\(^{-2}\) and oxygen delivery of 600 ml min\(^{-1}\) m\(^{-2}\). They had similar entry criteria, based on combinations of co-morbidities and the nature of surgery, but the actual patients recruited differed markedly. The study by Shoemaker and colleagues was the first prospective trial in this field and is also the weakest methodologically. The results appear impressive (control mortality 38%, protocol 4%) but could be because of chance.

In two studies, all patients were admitted to intensive care unit (ICU) and had their oxygen delivery measured. Boyd and colleagues found that 28-day mortality was 22% in the control group and 5.7% in the treatment group. A mixture of elective and emergency patients was included, and there does not appear to be any difference in outcome between the 81 patients enrolled preoperatively and the 26
enrolled postoperatively. Surgeons and anaesthetists, but not the ICU staff, were blinded to patient allocation. Although there was a statistically significant difference in oxygen delivery between the groups, only 23 of the 43 patients in the protocol group actually reached the target value before surgery and most did not do so afterwards. Lobo and colleagues\(^\text{13}\) studied 37 patients undergoing elective cancer or aortic aneurysm surgery. These patients were mechanically ventilated for a median of 2.5 days postoperatively, which would be unusual in UK practice. The probability of cardiac complications (Goldman index) was lower in the protocol group. No difference was found in 28-day mortality. The mortality rate at 60 days was lower in the protocol group (15.7 vs 50%) because of three late deaths in the control group. Again, the differences between the groups in terms of oxygen delivery were not great. The difference was only statistically significant at one point during the 24 h studied, and the targets were achieved by 28% of the control group as well as by 42% of the protocol group. The authors suggested that it might be the use of dobutamine rather than differences in oxygen delivery that affected the outcome.

Wilson and colleagues\(^\text{14}\) randomized 138 patients undergoing elective surgery. In two groups they aimed to achieve an oxygen delivery of 600 ml min\(^{-1}\) m\(^{-2}\) using either epinephrine or dopamine. These patients were admitted to ICU or high dependency unit (HDU) before surgery, and returned there afterwards. In the control group, who had ‘standard management’, oxygen delivery was not measured and 30% of patients returned to a general ward postoperatively. Mortality was 17% in the control group and 3% in the treatment groups. Clearly, the study design precluded blinding and the different location of postoperative care is a potential confounding factor. The goals were relatively easily met in many patients in this study. This, and the observation that morbidity appeared less in the dopexamine group, stimulated the study by the same group published in this issue.\(^\text{1}\)

A large study of 1994 patients by the Canadian Critical Care Clinical Trials Group,\(^\text{16}\) has been published since Kern and Shoemaker’s meta-analysis.\(^\text{8}\) The patients studied were over 60 yrs old, ASA class III or IV, having urgent or elective surgery. These criteria differ from those used by Shoemaker, but the median Goldman cardiac risk index was 8, which is greater than in the study by Lobo.\(^\text{13}\) The intervention group had pulmonary artery catheters inserted before surgery and therapy aimed for an oxygen delivery of 550–600 ml min\(^{-1}\) m\(^{-2}\), which was reached in 63% of patients. All patients were managed in ICU for at least 24 h after surgery. The groups were well matched and very similar to those patients screened but not randomized, suggesting that selection bias was unlikely. The number of patients, the universal use of ICU, and the multi-centre nature make this a robust study, despite the long recruitment period. There was no difference in mortality at hospital discharge (control 7.7%, protocol 7.8%), or at 6- and 12-month follow-up.

In several studies, many patients given active treatment were unable to achieve an oxygen delivery of 600 ml min\(^{-1}\) m\(^{-2}\). It is worth asking whether this is the correct target, and whether the lower mortality rate associated with this treatment plan in some studies is caused by other factors.

A target of 600 ml min\(^{-1}\) m\(^{-2}\) is based on the median of values achieved by survivors in observational studies,\(^\text{11}\) so not all patients would be expected to achieve this value. Kern and Shoemaker\(^\text{8}\) suggest that this goal was not intended to apply to all patients, although it is difficult to see what other practical guidance could be given to clinicians as they found no benefit in trials that did not set ‘supra-normal’ values. Their proposal to calculate goals for individual patients is certainly not possible at present. The lack of benefit in the Canadian trial\(^\text{16}\) might be because a slightly lower target was set, but this seems unlikely. Other studies have used different goals such as Doppler derived values or mixed venous oxygen saturations.

There are other possible causes for the apparent treatment effect. There could be a specific drug effect of dobutamine\(^\text{13}\) or dopamine,\(^\text{14}\) but we have seen that prospective studies\(^\text{12}\) do not support this hypothesis. The benefit in some studies could relate to ICU admission,\(^\text{14}\) but other studies have admitted all patients to ICU and still found a difference.\(^\text{12,13}\) ICU staff were not blinded to treatment allocation, however, and this may affect the results, particularly where the investigators believe strongly in the hypothesis. Such bias is less likely in a multi-centre trial and the failure of the Canadian trial\(^\text{16}\) to show a difference is important.

**Implications for clinical practice**

The limitations of the evidence mean that it is premature to suggest that the time has come to implement goal-directed therapy for large numbers of high-risk surgical patients.\(^\text{10}\) Not only are the advantages of doing so uncertain, but also the patients who might benefit are not clearly defined. The recognition that the majority of postoperative complications occur in a relatively small group of high-risk patients was key to the initial development of this approach. This means that if efficacy is uncertain even for high-risk patients, then there can be even less confidence for lower risk groups.\(^\text{8}\) Despite suggestions that morbidity may be reduced. There are few groups of patients with a greater than 20% mortality rate, the threshold suggested by Kern and Shoemaker. Mortality after surgery for upper gastrointestinal malignancy\(^\text{17}\) or aortic aneurysm repair,\(^\text{16}\) precisely the types of operation often included in these trials, is around 3–7%, although there are certainly sub-groups with poorer outcomes. Studies from Australia argue persuasively\(^\text{19}\) that a low anaerobic threshold on an exercise test before surgery is

---

616
much more predictive of operative risk than myocardial ischaemia. More widespread use of this test might help in identifying high-risk patients, but clearly this is only practicable for planned surgery.

Addressing the unanswered questions

Preliminary results of another meta-analysis, performed under the auspices of the Cochrane collaboration, were presented to the Intensive Care Society in December 2002. These also appear to favour the targeting of oxygen delivery or some flow measurement. The full results will be of interest, but are unlikely to settle the debate, because a meta-analysis can only be as good as the constituent studies and there is, inevitably, considerable overlap with Kern and Shoemaker. Meta-analysis may not in fact be the most appropriate tool for several reasons. There is great heterogeneity in patients and protocols. It is unlikely to consider how this approach can fit with other strategies such as perioperative beta-block, avoidance of hypothermia, and even calls for a return to fluid restriction in perioperative management. Perhaps flow measurements can help rationalize fluid therapy to avoid both hypovolaemia and fluid overload. Whether postoperative deaths are a result of cardiac ischaemia or cardiac failure remains in dispute, and both cause and response may depend on the patient populations studied, which frequently differ.

The recognition that perioperative management can have a positive effect on long-term outcome is welcome, and the concept of ensuring adequate organ perfusion remains appealing, but we should not allow enthusiasm to lead us into error. A properly convened consensus conference could consider the different approaches, the different patients, and the different timing of interventions more effectively than a meta-analysis. It would also help raise awareness of the issues. Such a conference would now be an appropriate step, accepting that the outcome might well be a more focussed research agenda rather than a final conclusion.

S. J. Mackenzie
Department of Anaesthetics
Critical Care and Pain Medicine
Royal Infirmary of Edinburgh
Edinburgh EH16 5SA
UK
E-mail: simon.mackenzie@luht.scot.nhs.uk

References

2 Takala J, Meier-Hellman A, Eddleston J, Hulstaert P, Sramek V.

3 Galley HF. Renal-dose dopamine: will the message now get through? Lancet 2000; 356: 2112–2


DOI: 10.1093/bja/aeg229