Randomized trials in cardiogenic shock: what’s the problem?

The ingredients for a promising randomized study might be expected to include a common condition, a high event rate and existing evidence to suggest at least measurable benefit from the tested intervention. These criteria would seem to apply to cardiogenic shock complicating acute myocardial infarction; even in the thrombolytic era the incidence is almost 10% of hospital admissions with myocardial infarction and mortality hovers persistently about the 90% mark[1]. Pooled results from historical reviews examining the effects of early revascularization in these patients have given cause for optimism, with mortality reduced following CABG or PTCA to 33%[2] and 42%[3], respectively. Why then do we read in this issue of a prospective, randomized study that was terminated prematurely in the absence of a result[4]?

The study aims and trial design were soundly based. Patients in shock for at least 30 min, and within 48 h of infarct symptoms, were allocated to either immediate investigation with a view to emergency revascularization, or medical therapy. With historical data suggesting an 80% mortality in the conservative group and an anticipated mortality of 50% with urgent revascularization, the usually accepted statistical criteria dictated 57 patients to be randomized into each group. Inclusion and exclusion criteria were by no means stringent and reflected practical issues often encountered in managing such critically ill patients. Enrolment of patients in shock despite inotropic support may, however, have selected a group less likely to benefit from intervention and a 30-day mortality of 69% in the actively managed group would support this view.

The definition of shock has varied in previous reviews which may have resulted in disparate outcomes and thereby apparently encouraging data to support active management. The result of an intervention in a patient with hypotension alone is likely to be better than when associated with signs of poor peripheral perfusion and markedly deranged haemodynamic indices refractory to fluid replacement or inotropic support.

This study faltered on a slow recruitment rate, a problem common to the three other randomized trials attempting to address this important issue. The recently completed SHOCK (SHould we revascularize Occluded coronaries for Cardiogenic shock) trial has taken 5 years to enroll the 328 patients required for its planned statistical power[5]. Tardy recruitment is also a feature of the ongoing HEROICS (How Effective are Revascularization Options in Cardiogenic Shock)[6] and TACTICS (Thrombolysis And Counterpulsation To Improve Cardiogenic shock Survival) studies (M. Ohman personal communication). What are the possible reasons for this common phenomenon?

Time delay is critical to any infarct intervention study. This is particularly relevant in the presence of shock which, clinically, is recognized to evolve frequently into an irreversible condition regardless of apparently successful intervention. This delay is unavoidable when patients present to a hospital without facilities for invasive investigation or revascularization, and transfer of such patients to a tertiary care centre has then to be considered. Decision making in this clinical setting has to take account of many practical problems; however, the necessary addition of ethical factors associated with consent and enrolment into a randomized trial brings these dilemmas into sharp focus.

Another factor relevant to recruitment is the preference of the referring physician who may decline to enter patients into such a study. The many reasons for this are understandable. There may be a reluctance to subject a critically ill patient (and their relatives) to an aggressive treatment strategy, possibly involving inter-hospital transfer, with little anticipated likelihood of modifying the outcome. The 50% chance that the patient will be randomized to a conservative arm anyway, might appear to justify this approach. Alternatively the physician, relatives or patient might not wish to agree to an option which excludes any possible (albeit unproven) therapeutic manoeuvre, that may be life-saving, thus making
After patient randomization, how is the question of crossover to be tackled? Trials in infarct intervention frequently allow the possibility of moving from the conservative to the active treatment arm in the event of subsequent clinical deterioration. The presence of cardiogenic shock, however, makes this approach unrealistic as the clinical condition of the patient is already severely compromised. Thus, in practical terms, crossover has either to be restricted to rigid, predefined criteria or ideally discouraged altogether. Such a protocol design may be seen as unattractive and patient recruitment subsequently suffers.

The pooled results of retrospective, uncontrolled series may give grounds for optimism but such data, by selecting patients most likely to do well, do not help us make decisions in every day clinical practice. At present, the most promising glimmer of hope is the SHOCK trial, the preliminary results of which are due to be presented in the near future. This should answer the question as to whether an aggressive (and expensive) strategy of urgent revascularization in shocked patients is justified. Failing that, the results may still provide some insights into the clinical characteristics of those patients more likely to benefit from emergency intervention.

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References