The impact of continuous haemofiltration with high-volume fluid exchange during cardiopulmonary bypass surgery on the recovery of patients with impaired renal function: a pilot randomised trial

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Scientific summary

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Background

Coronary artery bypass graft (CABG) surgery is predominantly performed on-pump by using the heart and lung machine commonly termed cardiopulmonary bypass (CPB). Patients undergoing on-pump cardiac surgery have an increased risk of developing major organ dysfunction. The traditional risk factors for developing postoperative complications include advanced age, pre-operative left ventricular dysfunction, perioperative low cardiac output, pre-operative renal impairment, duration of CPB and aortic cross-clamp time.

For patients with pre-operative moderate renal impairment, on-pump surgery also poses major challenges such as the further deterioration of kidney function. It is estimated that up to 20% of patients undergoing cardiac surgery have a pre-existing renal insufficiency (increased creatinine > 132 µmol/l). In this patient group, on-pump CABG can be associated with a decline in renal function. Several strategies have been developed to manage perioperative kidney impairment. Strategies such as extracorporeal leucodepletion and haemofiltration during CPB appear to show some promise, although the extent of clinical efficacy is not clear.

Although there is evidence from a variety of sources that early filtration soon after on-pump surgery is beneficial for patients who have pre-operative renal impairment, there is not much work on the prognostic impact of intraoperative haemofiltration (haemofiltration applied during on-pump surgery) on these patients. There is currently no evidence to suggest that haemofiltration when applied to patients during the period of the operation may have an impact on the postoperative cost of care and renal impairment.

We hypothesised that the initiation of intraoperative haemofiltration during on-pump CABG surgery for patients with pre-operative impaired renal function may reduce the progression of renal impairment and overall length of intensive care unit (ICU) stay. We therefore sought to conduct a pilot randomised clinical trial on the use of intraoperative haemofiltration to assess the issues that might impact on conducting a definitive multicentre trial. In addition, we sought to assess the safety of this procedure and the suitability and reliability of selected outcome measures, and to evaluate whether or not intraoperative haemofiltration had a significant clinical or cost impact.

Objectives

As no large randomised trial has involved this kind of study before, the study design was limited by the absence of past trial data that could be used as a reference. In order to overcome these limitations, we at first made a decision to conduct a pilot trial with an embedded feasibility study to explore the following objectives:

1. To assess the feasibility of randomising 60 on-pump CABG surgery patients with impaired kidney function in 6 months within a single centre for intraoperative haemofiltration; that is, to investigate the likely recruitment rates and issues that may impact on recruitment into the study.
2. To assess the suitability and reliability of the chosen outcome measures.
3. To investigate the likelihood of recruitment into the main definitive study and explore issues that may impact on recruitment, such as staffing, barriers to recruitment, and suitability and reliability of the outcome measures selected.

The feasibility outcomes of the pilot trial included the assessment of the ratio of patients screened as eligible versus the number randomised, the incidence of crossover between the randomised treatment groups, and the accuracy of data collection assessed by a 20% source data verification check. In addition, this pilot study sought to identify the likely barriers to effective recruitment into a main definitive trial, and whether or not the outcome measures and data collection methods were appropriate and reliable. The pilot trial compared the patterns of the clinical outcomes for on-pump CABG surgery with or without the use of intraoperative haemofiltration to assess suitability for and applicability to a larger randomised trial.

Methods

This single-centre pilot randomised trial was carried out at the Liverpool Heart and Chest Hospital NHS Foundation Trust between November 2010 and March 2012. Institutional, Ethics and National Competent Authority [Medicines and Healthcare products Regulatory Agency (MHRA)] approvals were obtained prior to commencement of recruitment. Patients were recruited if they were undergoing CABG surgery and had a known impaired kidney function indicated by an estimated glomerular filtration rate (eGFR) ranging between 60 and 15 ml/minute adjusted for 1.73 m^2 of body surface area, in accordance with the US National Kidney Foundation guidelines. Consenting men and women with impaired kidney function were included if they were $\geq$ 18 years old and were scheduled to undergo elective on-pump CABG.

Patients were excluded if they were undergoing surgery on the great vessels (aortic surgery) or valve surgery, had significant impaired liver function [serum bilirubin > 60 µmol/l or international normalised ratio (INR) > 2 without anticoagulation], were further down the line of renal failure (i.e. eGFR < 15 ml/minute) or already required dialysis. In addition, they were excluded if they could not give informed consent, had any known malignancy or were known to be pregnant.

Patients who were scheduled to undergo elective/urgent on-pump CABG surgery and who fulfilled the inclusion and exclusion criteria and gave informed consent to participate in the study were randomised into one or the other of the two study groups on the day prior to surgery as follows:

1. On-pump CABG surgery patients with eGFR < 60 ml/minute receiving haemofiltration during cardiopulmonary bypass (experimental group).
2. On-pump CABG surgery patients with eGFR < 60 ml/minute not receiving haemofiltration during cardiopulmonary bypass (control group).

Treatment assignment was done online and was based on the block randomisation method using randomly varying block sizes of 2, 4 and 6 to ensure numerical balance between the groups. In the experimental group, patients were given zero-balance ultrafiltration (Z-BUF) during CPB.

In-hospital follow-up was continued until hospital discharge or up to 30 days of postoperative hospital stay. Patients were then followed up from discharge until the 6-week postdischarge follow-up visit. All information was collected in structured case record forms (CRFs). Data were entered into a secure password-protected bespoke database. Prospective monitoring of adverse and clinical events started at randomisation and continued until hospital discharge. Costs associated with each of the two pilot arms, postoperative renal replacement therapy, ICU stay, hospital ward stay and medications were estimated up until hospital discharge. Serious adverse and clinical events monitoring started at randomisation and continued until the 6-week postdischarge follow-up visit.

Outcome measures included the frequency of duration of ICU stay > 3 days and overall length of stay in ICU (days) for patients with renal impairment. Other clinical outcome measures included length of CPB and cross-clamp time, duration of mechanical ventilation and time to tracheal extubation, duration of hospital

stay, need for postoperative continuous venovenous haemofiltration (CVVH) in the ICU, eGFR at 6-week follow-up, and frequency of perioperative incidences of bleeding, sepsis, death, arrhythmias, stroke and myocardial infarction.

Secondary health economics outcomes were defined as resource utilisation and key cost indicators associated with each of the two pilot arms, specifically for ICU and hospital stay, postoperative renal replacement therapy, mechanical ventilation and medications, estimated up until hospital discharge or up to 30 consecutive days of hospital stay.

Results

The pilot trial was conducted over a period of 15 months (21 November 2010 to 30 March 2012). A total of 1276 patients were screened for eligibility, of whom 952 were excluded because their eGFR was ≥ 60 ml/minute. A further 137 were excluded for the following reasons, despite having eGFR < 60 ml/minute: undergoing off-pump surgery ($n = 103$) or had planned combined valve replacement or other complex surgeries ($n = 34$). One hundred and seven out of 187 patients undergoing isolated on-pump CABG with an eGFR of < 60 ml/minute met the inclusion criteria. Thirty-seven out of the 107 eligible patients consented and were successfully randomised into the trial arms. This number proved to be far short of the original recruitment target of 60 patients. The ratio of randomised to screened eligible patients was 3.5 : 10 (35%). A total of 26 eligible patients declined to participate, while 124 patients were lost to recruitment owing to other reasons.

The main barriers to recruitment were as follows:

1. In our centre up to 50% of coronary surgery is performed off-pump, a figure that is one of the highest in the UK, and this trial was recruiting on-pump CABG patients only. Our figure demonstrates that 103 patients with pre-operative renal impairment underwent off-pump CABG during the time frame of the trial.
2. Recruitment was restricted to the research nurses' working week of Monday to Friday, 0900 to 1700 hours. Consequently, 36 patients who were potentially eligible for the trial could not be recruited outside of these hours.
3. Issues were encountered through the screening process for identifying prospective eligible patients. Patients had to have had an eGFR of < 60 ml/minute in order to be eligible. For urgent or interhospital transfer cases the eGFR values were often not documented in the case notes/clinical database or blood samples were not taken until later on the day before surgery. This was particularly common in patients admitted as urgent cases. Consequently, 30 patients who were eligible for the trial were not recruited.
4. Seasonal outbreaks of influenza pandemic and other infectious diseases occurred. In the winter of 2010–11, an outbreak of pandemic influenza led to the closure of all elective cardiac surgery from December 2011 to February 2012. In addition, an outbreak of norovirus within one surgical ward in January 2012 significantly reducing planned cardiac surgical activities for 2 weeks and only urgent cases were considered for operations.
5. There were two protocol deviations and four crossovers. In three cases this was because of a necessary change in clinical strategy intraoperatively. Of the remaining cases, in two there were communication errors and in the last case it was noted that eGFR had recovered to normal post randomisation compared with the value at the initial screening.

Treatment fidelity for intraoperative haemofiltration was followed in all cases where the intervention was received in accordance with standard protocol for Z-BUF, regardless of whether or not the patients were crossovers.

Twenty-seven per cent of the randomised participants were female, equally spread between the two study groups. Demographic factors such as age, ethnicity, family history of ischaemic heart disease, hypertension, hypercholesterolaemia, smoking, diabetes, and baseline eGFR and EuroSCORE were comparable between the two groups.

Data collection process was sufficiently robust, with few errors detected. Some outcome measures were also more reliable than others; for example, the outcome measure of length of ICU stay was deemed to be more informative than the categorical variable of frequency of duration of ICU stay > 3 days. The composite outcomes variable was also found to be less informative and therefore we propose that a broader outcome measure of the number of hospital complications would be more useful in a larger trial.

The application of intraoperative haemofiltration was associated with a trend towards reduced length of ICU stay, particularly for patients with diabetes. The cumulative number of patients being discharged from the ICU at any given time between the two treatment groups was presented using a Kaplan–Meier plot as an illustration. The pattern was similar in the earlier periods of ICU stay of up to 50 hours. The period exceeding 50 hours indicated that fewer patients in the no-intraoperative haemofiltration group were leaving ICU compared with those who received intraoperative haemofiltration for anything up to 150 hours.

Adverse events were few in both groups and not in excess of expected postoperative complications following major cardiac surgery in the study population.

Conclusions

The data from this pilot trial are suggestive that although there are likely barriers to recruitment these are not insurmountable with adequate resources. In addition, there is potential for significant benefits of using intraoperative haemofiltration to be realised in a larger randomised trial. If the use of intraoperative haemofiltration was routinely applied to all patients with impaired renal function undergoing on-pump CABG, in cost terms alone there would be a potential saving in excess of £150,000 per year in a unit as large as ours. This could extrapolate to an overall significant national health economy saving. However, evidence from this pilot trial is not definitive, hence it warrants further investigation in a large randomised trial with greater patient numbers. Such a trial should explore further efficacy and cost implications of intraoperative haemofiltration at both the national and the international scale.

Trial registration

This trial is registered as ISRCTN49513454.

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