TITLE

Maintenance of serum potassium levels ≥ 3.6 mEq/L vs ≥ 4.5 mEq/L after isolated elective coronary artery bypass grafting, and the incidence of new-onset atrial fibrillation: pilot and feasibility study results

Niall G Campbell MBBS BSc PhD, Elizabeth Allen MA MSc PhD, Hugh Montgomery MB BS BSc MD, Jon Aron MB BS BSc, Ruth R Canter BA MSc, Matthew Dodd BSc MSc, Julie Sanders BSc MSc PhD, Joanna Sturgess MSc, Diana Elbourne BSc MSc PHd, Ben O'Brien MD PhD

INTRODUCTION

Atrial fibrillation (AF) is the most frequent adverse event following cardiac surgery, affecting at least one in three patients and as many as 70% in some cohorts(1-3). Most episodes AF after cardiac surgery (AFACS) occur in the first 5 postoperative days (peaking mainly at 48-72 hours) (1,2), and are associated with increased morbidity, short- and long-term mortality, length of stay and hospital resource costs(1-3). These associations may be causal, given that some persist after adjustment for potential confounding factors(3,4). The incidence and therefore associated costs of AFACS are expected to increase as the surgical population ages(5). To date, the disciplined peri-operative use of beta-blockers is the only effective mitigating strategy identified(6).

Potassium plays an important role in cardiac electrophysiology(7). Serum potassium concentrations ($[K^+]$) are often below the normal range (typically defined as < 3.6mEq/L) after cardiac surgery(8) and marginally lower amongst those suffering atrial arrhythmias in

non-surgical cohorts(9). Potassium levels that lie entirely outside the normal range are associated with poorer outcomes in certain cardiovascular cohorts(10). Although it is commonly assumed that lower post-operative serum potassium levels predispose to AFACS, this remains unproven, and the effects of prophylactic potassium supplementation inadequately studied.

Internationally, many centres endeavor to maintain serum [K+] levels in a “high-normal” (4.5–5.5 mEq/L) range(11), with 65% of caregivers in Europe stipulating some form of ‘high-normal’ potassium target maintenance protocol in an effort to prevent AFACS (12,13). The fact that one-third do not, and that there is large regional variation, suggests that genuine equipoise exists as to whether such a strategy is effective. Indeed, the limited supportive data are largely derived from observational rather than interventional studies(1,14), and proof that maintaining a high-normal potassium level is beneficial in these circumstances, or that aggressive replenishment of potassium in these patients improves outcome, is lacking(15).

The strategy to routinely supplement potassium may cause harm or discomfort. Central venous administration (when oral intake is not possible in the early post-operative period) is time-consuming, and carries risk: rapid infusion can be fatal(16), and keeping central venous catheters in situ solely for this purpose increases infection risk. It is also expensive: given the large quantities used, the annual cost of intravenous potassium exceeds that of other drugs in many cardiac surgery units, and nursing time (drug checks, administration) inflates this further(17). Oral potassium supplementation commonly causes gastrointestinal side effects, and is often poorly tolerated as a result(18).

We intend to assess any impact of targeted maintenance of serum [K+] ≥ 3.6 mEq/L versus ≥ 4.5 mEq/L on incidence of AFACS after coronary artery bypass grafting (CABG) by

performing an individually randomized controlled non-inferiority trial. We describe here the findings of a pilot study, designed to assess the feasibility of performing such a trial.

METHODS

We sought to determine whether, over a 6-month period, it was feasible to recruit and randomize 160 patients undergoing CABG surgery to the pilot study, while maintaining a <10% potassium protocol violation rate and retaining 90% of patients for follow-up 28 days post-surgery. Additionally, we piloted data collection procedures for the proposed full trial. This study was registered on 22nd June 2017 with ClinicalTrials.gov (identifier: NCT03195647), conformed to the Declaration of Helsinki. Appropriate ethics committee approval was obtained (Health Research Authority REC number 17/LO/0318), and written informed consent was obtained from all patients.

Patients

The study was performed at two National Health Service (NHS) academic teaching hospitals in London, United Kingdom: the Barts Heart Centre (St Bartholomew's Hospital, Barts Health NHS Trust) and St George's University Hospitals NHS Foundation Trust. Eligible for inclusion were all patients aged $\geq$ 18 years who were undergoing elective isolated CABG surgery and were able to give informed written consent. Excluded were those with known previous AF or dialysis-dependent end-stage renal failure, those with current/previous use of medication for cardiac rhythm management, those already recruited to another clinical trial assessing post-operative interventions, and those with active infection/sepsis, high-degree atrio-ventricular block or serum [K+] > 5.5 mEq/L.

Research staff approached eligible patients via post, telephone or email to discuss the study prior to their scheduled pre-operative hospital appointment. It was expected that patients would be allowed 24 hours to consider whether or not to take part in the study in order for them to make an informed decision.

Randomization and Trial Conduct

On the day of, and prior to surgery, eligible consenting patients were randomly allocated in a 1:1 ratio using a secure online database (Sealed Envelope Ltd, London UK, https://sealedenvelope.com/) to receive potassium supplementation (if and as required) when serum [K+] either < 4.5 mEq/L ('tight control') or < 3.6 mEq/L ('relaxed control'), with the allocation stratified by site. The intervention period commenced when the patient was admitted to any post-operative care facility after surgery, according to local practice. The method of administration of potassium supplements (whether intravenous (IV) or oral potassium formulation, administration of potassium-rich nasogastric feeding regimens or recommending the consumption of potassium-rich foods) was according to clinician preference and existing site-specific standardized protocols. There was no restriction on procedures that occurred intra-operatively, including the technique of CABG, the use of cardioplegia or intraoperative potassium supplementation.

The trial intervention period ended 120 hours (5 days) after trial initiation, at discharge from hospital or with the occurrence of a clinically identified episode of AFACS, whichever occurred first. Following an episode of AFACS, there was no restriction on potassium supplementation and patients' treatment reverted entirely to local practice. In keeping with recognized international criteria, AFACS was defined as an episode lasting ≥ 30 seconds that was clinically detected and electrocardiographically confirmed (on either a 12-lead

electrocardiogram or telemetry)(19). Routine clinical monitoring was supplemented by continuous Holter monitoring (eMotion Faros 180, Technomed Ltd) for the first 120 post-operative hours in all patients or until discharge, whichever came first.

All other clinical practice (including blood tests or the use of magnesium supplementation, beta-blockers or anti- arrhythmic agents) was routine, and independent of trial allocation. In particular, serum [K+] was monitored at a frequency which accorded with existing protocols and clinician/nursing staff preference.

In line with the protocol, we piloted full data collection for the main trial. We collected data relating to pre-determined baseline demographic data, medical history and cardiac and imaging assessment, using these to calculate CHA_2D_2-VASc score (which predicts thromboembolic risk(20)). We documented medication at baseline and hospital discharge; duration of critical care and hospital stay; inpatient mortality; and adverse events. For each 24-hour study period (1 through 5), serum [K+] and potassium administration (dose and route) were collated.

Twenty-eight days after surgery, mortality was determined and efforts were made to contact patients surviving to hospital discharge to assess whether further episodes of heart rhythm problems had occurred. All patients were asked to complete a quality of life questionnaire (5-level Euroqol-5D (EQ-5D-5L)) prior to surgery and at 28-day follow-up, by telephone or by post. The protocol stated that continuous electrocardiographic recordings ('Holter monitoring') would be analyzed after day 5 by clinical staff blinded to group allocation.

Safety reporting

Safety reporting was compliant with Good Clinical Practice. The Data and Safety Monitoring

Committee consisted of a chair, senior statistician and one other senior clinician. It was independent of the investigators and of the Trial Steering Committee (TSC) but reported to the TSC and (via the TSC) to the Sponsor. It met prior to the start of the trial and monitored both safety and data (quality and completeness) on an ongoing basis. This was facilitated through the development of a trial-specific database and an adverse event database.

Primary outcome measures

The primary outcome for this pilot study was the performance on feasibility endpoints, specifically whether it was feasible to:

1. recruit 160 patients over a period of 6 months (an estimated 20% of those eligible);
2. randomize patients into two arms for potassium replacement if [K+] < 4.5 mEq/L versus < 3.6 mEq/L;
3. maintain a potassium supplementation protocol violation rate of no more than 10%[1] (see definitions below) and
4. maintain follow-up rates > 90% at 28 days after CABG.

Potassium supplementation protocol violations were defined as:

a) A patient in the relaxed control arm inappropriately receiving potassium supplementation when a reading was [K+] ≥ 3.6mEq/L

(b) A patient in the tight control arm inappropriately receiving potassium supplementation when a reading was [K+] ≥ 4.5 mEq/L

[1] Note that in the published protocol a number of additional indicators of interest were incorrectly listed as protocol violations. Failure of randomization, alteration in planned surgery, failure of the Holter monitoring process, lack of data completion. These have been assessed and are reported in this paper but are not treated as protocol violations in this sense.

(c) A patient in the relaxed control arm who inappropriately did not receive potassium supplementation when [K+] was measured at < 3.6mEq/L.

(d) A patient in the tight control arm who inappropriately did not receive potassium supplementation when [K+] was measured at < 4.5mEq/L.

Secondary endpoints

In line with the proposed endpoints for the full trial, the following secondary endpoints were recorded in the pilot trial: incidence of new-onset AFACS until day 5; critical care and hospital lengths of stay; incidence of all other arrhythmias until day 5 (120 hours), defined using standard diagnostic criteria; in-patient and 28-day mortality and EQ-5D-5L.

Power calculations and sample size

One hundred and sixty patients were to be recruited from two centres. As this was a pilot study to assess feasibility, power calculations were not appropriate. The sample size of 160 was based on assessing the feasibility of a recruitment rate of 20% of eligible patients over six months.

Analysis

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram reports recruitment, randomization, treatment, and retention(21) and all feasibility endpoints are reported by arm and overall. We present details of potassium supplementation and violation of the potassium supplementation protocols. Exploratory analysis of the proposed endpoints for a full trial is by intention-to-treat. As this was a pilot study, no interpretation is made of any effect sizes, and findings will primarily be used to help refine the design of the full trial.

Generalized linear models were used to estimate the effect of the intervention (relaxed versus tight control) on the prevalence of new-onset AFACS and all other arrhythmias up to 5 days post-surgery, in-patient mortality, and mortality up to 28 days post-surgery. Risk ratios and corresponding 95% confidence intervals were calculated. Hospital length of stay and EQ-5D-5L scores were analysed using linear regression models to estimate differences in means, with bootstrap 95% confidence intervals calculated using 2,000 replications of size 100. All analyses were repeated adjusting for the effects of age and gender. In addition, descriptive summaries of baseline and follow-up data were tabulated by arm, including information on missing data. Details on data collected through the Holter monitors were also summarised.

RESULTS

Primary outcome measures

We recruited 160 patients between 28 August 2017 and 24 April 2018 (Figure 1) equating to a recruitment rate of 20 patients per month over the two sites. Of 723 screened patients, 22% were recruited, 50% were eligible but not recruited and 27% were ineligible. The recruited population had a mean age of 66 years with 91% males. One hundred and twenty-eight (80%) self-reported as having white ethnicity. Randomization was acceptable and was successful in all patients (n=81 to the 'relaxed' arm, n=79 to the 'tight' arm). One patient was randomized in error to the tight arm; they had a prior incidence of AF (an exclusion criteria) but did not declare this at recruitment. Review of the medical notes subsequently identified this and they were withdrawn from the trial treatment. The patient was informed after surgery and agreed to data collection.

Recruitment, randomization and follow up feasibility outcomes are shown in Table 1. Follow-up from randomization to 28 days post-surgery was successful in 148 patients (92.5%). Of those randomized, three patients withdrew or were withdrawn prior to surgery (one in the tight arm and two in the relaxed arm). One patient who had surgery died (0.6%) prior to 28-day follow-up. Overall, 9 patients (5.7%) who had surgery were not followed-up at 28 days, including the patient who died.

Potassium measurements and protocol violations

There were 2886 potassium measurements undertaken in total (average 18.3 measurements per patient). Potassium was supplemented on a median of 1 (range 0-22) and 6 (range 0-20) times in the relaxed and tight arms respectively (Figure 2).

We observed 283/2886 (9.8%) potassium supplementation protocol violations: 188/1554 (12.1%) in the tight arm and 95/1332 (7.1%) in the relaxed arm, meeting the feasibility target. However, these violations were not restricted to the same patients and, overall, a high number of patients experienced a protocol violation at some point during the 120-hour study period. In the tight arm, 62 out of 80 patients (78%) were not given potassium on at least one occasion despite their serum potassium value being < 4.5 mEq/L. In the relaxed arm, 33 out of 77 patients (43%) were given potassium despite their potassium value being ≥ 3.6 mEq/L on at least on occasion. Closer examination of the data suggests that in the tight arm, the clinical team supplemented with potassium when serum measurements fell below 4.5 mEq/L, but not after every measurement. However, we could demonstrate clear separation in potassium levels between the arms (Figure 3).

Secondary outcomes

Results from the analysis of the secondary outcomes of the pilot trial are shown in Table 2. The study was not powered to detect similarities or differences between the arms. New-onset AFACS occurred in 58 patients (36.9%). The mean length of critical care stay was 2.5 days and the mean length of hospital stay was 9.2 days. The incidence of all other (non-AF) arrhythmias until day 5 defined using standard diagnostic criteria was 104/157 (66%). One patient died in hospital prior to discharge (0.6%) and there were no other deaths by 28-day follow-up.

Data collected and data completeness

All data collected are reported by arm in Appendix tables A1 and A2a-e. This includes the proportion missing for each question.

Holter data

Overall, the Holter data were incomplete: some patients did not have a Holter fitted at all (13/157, 8%); the company contracted to analyse the monitors did not supply data for all patients who had a monitor (7/144, 5%, missing); and some patients experienced disruption in Holter data, defined as interruptions to readings for more than one hour during the study period or repeated 30 mins breaks (28/137, 20%). Although Holter data were matched to individual patients using unique IDs, single cardiac events could not be definitively matched to reported events in the CRF. Furthermore, the Holter data were not validated - one cardiac physiologist reviewed the data and interpreted it, there was no second review, and we have no documentation of how the data were classified.

DISCUSSION

The primary outcome measure of this pilot study was the performance on feasibility endpoints.

We sought to achieve efficient, timely recruitment and investigated whether we were able to recruit 160 patients (20% of the estimated eligible population based on previous years' patient numbers) at the two investigating centres over a 6-month period. Within this window, 133 patients were recruited, and the study period was extended to a total of 8 months to enable recruitment of 160 patients (which equated to 24% of the actual eligible population). This two-month overrun was largely due to the impact of the well-publicized 2017/18 NHS hospital winter bed crisis during this time and seasonal dips in elective cardiac surgical activity, especially at one of the recruiting centres. Lessons learned from this experience will inform recruitment strategies for the future full-scale trial.

We demonstrated that recruitment, randomization and 28-day follow-up were all feasible and we had a protocol violation rate of < 10% demonstrating the feasibility of administering the potassium supplementation protocols.

According to our pre-specified endpoints, we therefore deemed that a full study was viable. A lower expected recruitment rate is required for planning in the future study and a greater number of recruitment centres will participate.

Secondary endpoints in the pilot study were collected in order to further inform the proposed main randomized controlled trial endpoints.

The incidence of new-onset AFACS until day 5 was 36.9%. The sample size calculation for the full trial is based on a baseline incidence of AFACS of 35%, a figure derived from previous large studies[1,20]. Our figure aligns with this baseline figure suggesting that the detection rates in our study are reliable.

A possible concern about the trial design prior to undertaking the study was that many patients in each group would not ever reach a serum potassium that would trigger supplementation, which might be perceived as invaldidating the randomisation process. However, it was reassuring to note a clear difference between the two arms in terms of the number of potassium doses required. Furthermore, the serum potassium levels were clearly separated between the tight and relaxed arms, showing that the protocol was able to achieve the effect it set out to deliver. However, three-quarters of patients in the tight group were not given potassium at least once when their potassium was 3.6-4.4 mEq/L. One possible explanation could be that clinician judgement was being exercised and the definition of a potassium protocol violation in this arm needs to be redefined for a future 'real-world' study. In the relaxed group, there was evidence of supplementation when serum potassium values were ≥3.6mEq/L. Further work will be done with participating clinical teams in the full trial to reinforce the need for adherence to the protocol and ensure that violations are minimized, whilst being conscious of and respectful of pragmatic clinical practice(22). Given the large number of 'violations' in the tight arm, it could also be considered whether a 'hard' cut off at 4.5mEq/L is appropriate.

Overall, there was a significant failure of the Holter monitoring process that only became apparent when the pilot study had completed recruitment. Not all patients had a Holter monitor applied, and the data that were obtained were incomplete and unvalidated. We have learned that for a future trial, more robust early-warning processes will need to be put in place to ensure that Holter monitor application and data analysis are adequate. These systems will need to operate throughout the study with the capacity for prompt feedback to centres that are not compliant with protocols. The Trial Management Group have opted to

work with a heart rhythm core laboratory for the full trial to enable a greater level of control and validation of Holter data analysis.

Some variables were poorly completed and are not going to be used in any planned analysis. We have revised the CRF for the full trial to reflect this.

One out of every ten patients recruited to the study was female. According to contemporary UK registry data, females account for about two out of ten of the CABG population(23). We will need to make a particular effort to ensure that the population of female patients in the full future trial better reflects real world cardiac surgical practice.

It was expected that patients would be allowed 24 hours to consider whether or not to take part in the study in order for them to make an informed decision. In practice, some patients were recruited < 24 hours before surgery if clinical teams were confident that the patients were making a fully informed decision. The pilot data, and further consultation with patients and public representatives, gave us confidence to lift the stipulated 24-hour restriction for the full trial enabling some patients to consent sooner than this if they wish to. As per GCP guidance, patients will never be pressured to participate but equally will be given the opportunity to participate in the study, even if their operation is scheduled to occur in less than 24 hours' time. During site training for the full trial, we will emphasize that potential patients should be approached at the earliest possible opportunity.

CONCLUSION

It is feasible to recruit and randomize patients to two different potassium supplementation protocols, with an acceptable rate of protocol violations. Lessons were learned to improve the conduct and data collection for the full Tight K multicentre randomized controlled trial

that will commence recruitment in 2020.

List of Abbreviations:

AF – Atrial Fibrillation

AFACS – Atrial Fibrillation After Cardiac Surgery

CABG – Coronary artery bypass grafting

CONSORT – Consolidated Standards of Reporting Trials

CRF – Case Report Form

K+ - Potassium

[K+] – Potassium concentration

NHS - National Health Service

TSC – Trial-Steering Committee

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Figure 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram of study recruitment, treatment and follow-up.

Figure 2: Number of times potassium was administered in each patient the Relaxed and Tight Arms.

Figure 3: Serum potassium levels in the Relaxed and Tight arms for 5 days post-surgery.

Table 1: Feasibility Outcomes. (CABG=Coronary artery bypass graft.)

Table 2: Outcome measures which will be assessed in future full Tight K study.

Table A1: Baseline characteristics (BMI: Body Mass Index, CCS: Canadian Cardiovascular Society, NYHA: New York Heart Association, TIA: Transient Ischemic Attack, MI: Myocardial Infaction, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Grafting, LVEF: Left Ventricular Ejection Fraction, COPD: Chronic Obstructive Airways Disease, eGFR: Estimated Glomerular Filtration Rate).

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