A Randomised feasibility study to assess a novel strategy to rationalise fluid in patients after cardiac surgery

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Abstract

Background: After cardiac surgery, patients receive large amounts of fluid in the Intensive Care Unit (ICU). We plan to conduct a multi-centre randomised controlled trial, of a conservative fluid regime, in patients after cardiac surgery, and have reported results of a feasibility study that evaluated efficacy and safety of the proposed regime.

Methods: After ethical approval, a single-centre, prospectively randomised interventional study was undertaken. Participants were randomised to either usual care, or to a protocolised algorithm, utilising stroke volume variation, to guide fluid administration to patients who were deemed to have inadequate cardiac output and were likely to be volume responsive. The study protocol lasted from ICU admission to de-sedation or 24 h, whichever occurred first.

Results: We randomised 144 subjects over 9 months. Less bolus fluid and less total overall fluid volume was administered in the intervention group (median (IQR) 1620 ml (500–3410) and 2525 ml (1440–5250; P<0.001), compared with the usual care group (2050 ml (910–4280) and 2980 ml (2070–6580; P=0.001), from ICU admission to extubation. There was no significant difference in incidence of acute kidney injury or the average amount of fluid administered to the usual care group at the beginning compared with the end of the study.

Conclusion: It is both possible and safe to achieve a significant reduction in the amount of fluid administered to patients, allocated to a conservative fluid protocol. These results suggest that a planned multi-centre study is both justified and feasible. Clinical trial registration: Australia New Zealand Clinical Trials Registry www.anzctr.org.au (ACTRN12612000754842).

Key words: acute kidney injury; cardiac output; cardiac surgery; haemodynamics; intensive care units

Demand for cardiac surgery has increased with improved results and decreased mortality in recent yrs.1 The incidence of post-operative morbidity and frequency of complications is still significant, with patients requiring a prolonged stay in either the intensive care unit (ICU) or the postoperative ward.2 3 After cardiac surgery, fluid resuscitation with large amounts of fluid in the ICU is common,4 and the optimal use of fluids is unclear. Numerous studies in general surgical populations, have demonstrated a positive outcome in some patient groups, if a more conservative fluid administration regime is used.5 6 The mechanisms for the positive effects seen, include a reduction in tissue oedema and better wound healing,7 while an accumulated...
Editor’s key points

- The impact of conservative postoperative fluid management strategies on outcomes after cardiac surgery is unknown.
- A feasibility study to evaluate safety and efficacy of a goal-directed fluid management algorithm was conducted.
- The intervention group received less fluid in the first 24 h after surgery than the usual care group with no evidence of increased morbidity.
- A large multi-centre study is required to demonstrate whether goal-directed therapy can influence patient outcomes in cardiac surgery.

positive fluid balance has been associated with poor lung, renal and gastrointestinal function and an increased risk of morbidity and mortality. Fluid volume strategies have been investigated in other ICU populations such as those with acute respiratory distress syndrome or sepsis, however widespread practice variation exists. To date there have been no reported studies of perioperative fluid management strategies, in patients undergoing cardiac surgery. A prior multi-centre study by our group, determined that on average patients received 2250 ml for volume expansion in the first 24 h postoperatively (interquartile range (IQR) 1250–3500 ml). We planned to undertake a randomised controlled trial (RCT) of a fluid regime involving a novel use of advanced haemodynamic monitoring, compared with usual care, in an attempt to reduce the amount of fluid patients receive postoperatively, and to see whether this influences length of stay. Before undertaking the RCT, we completed a feasibility study to determine whether the fluid management strategy was practicable, feasible, and safe and would answer the research question. This single centre, prospectively randomised interventional study was aimed to test the safety and would answer the research question. This single centre, prospectively randomised interventional study was aimed to test the safety and efficacy of a goal-directed fluid management algorithm was conducted.

Methods

A single centre, prospectively randomised, open label interventional study was undertaken in a large metropolitan hospital. The study was approved by the Regional Ethics Committee (12/NTA/2). Written informed consent was obtained by research staff from all study participants, before enrolment. The study was registered prospectively with the Australia and New Zealand Clinical Trials Registry (ACTRN12612000754842).

Study participants

All patients aged ≥16 yrs were eligible for inclusion in this study, if undergoing cardiac surgery, involving full median sternotomy and use of cardiopulmonary bypass. Patients were excluded if they were undergoing an emergency procedure, had a preoperative intra-aortic balloon pump (IABP), pre-existing atrial fibrillation (AF), or end-stage renal failure. In addition, if patients were in AF, had an IABP or an open chest on return to the ICU postoperatively, they were not randomised (secondary exclusion criteria). These exclusion criteria were necessary, to ensure validity of measured stroke volume variation (SVV).

Randomisation

On return to the ICU after surgery, patients were screened for the absence of secondary exclusion criteria and randomised 1:1 in blocks of 8, with the sequence generated by an independent statistician. Subject allocation was stratified by the presence or absence, on admission to ICU, of a pulmonary artery catheter (PAC), previously inserted in theatre. Allocation concealment was maintained until the time of randomisation by using opaque, sealed, sequentially numbered envelopes, prepared by a person not involved with the study.

Study treatments

On return to the ICU, participants were again screened by the research nurses and if deemed still eligible for randomisation, allocation was revealed and allocated therapy commenced. Participants were randomised to either usual care or to a protocolised strategy for fluid administration, from admission to ICU until 24 h, or de-sedation if earlier.

Intervention group

A protocolised strategy for administering bolus fluid postoperatively was developed for use by nursing and medical staff (Fig. 1). The strategy required patients to have both an inadequate cardiac output (as assessed either by measurement of cardiac index, where available, or by clinical signs where no PAC was present) and likely to be fluid responsive, before administration of a fluid bolus, as determined by an elevated SVV. The FloTrac sensor and EV1000 clinical platform (Edwards Lifesciences, Irvine, CA) were used to assess SVV, however, bedside clinicians were blinded to other data available for the EV1000, including cardiac output. Other treatment options are suggested in the protocol if fluid responsiveness is not apparent, however the decision as to which therapy was used was at the discretion of the treating clinician.

Usual care group

Standing orders in this ICU allow the bedside nurse to routinely deliver up to 2000 mls of crystalloid fluids at their discretion, for perceived haemodynamic inadequacy, based on their clinical judgement, mean arterial pressure and central venous pressure measurements.

Data collection, measurements and outcomes

The main outcome for this study, was the difference in fluid administered to subjects in each group, from the time of admission to ICU, to 24 h, or de-sedation, whichever occurred first. Data was collected by both the bedside nurse and research nurses, in the ICU, to capture bolus fluid administered and total fluid administered during the study period. Urine and creatinine data were also collected, to calculate incidence of acute kidney injury, as determined by the Kidney Disease: improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group guidelines. Patient characteristics, co-morbid conditions and operative details were recorded, and length of stay and use of inotropic or vasopressor medications in the ICU. Continuous data from bedside haemodynamic monitors were downloaded into Excel (Microsoft, Redman WA USA) spreadsheets for analysis. All patients were contacted 90 days after randomisation, to determine...
mortality and incidence of requirement for renal replacement therapy.

Sample size

Data from an audit of fluid administration in our unit, showed that the usual care group, would receive a mean of 3920 ml (sd 1790 ml) in the initial 24 h after surgery, 3010 mls of which would be given within the first 6 h. Given a minimal, clinically important reduction in volume of fluid administered of 1000 mls, using Fleiss’ formula, we calculated that 138 subjects would be needed to have a 90% power to detect a difference of 1000 mls, between the usual care and intervention groups at an alpha of 0.05. We planned to randomise 144 patients to allow for possible withdrawals.

Statistical analysis

Data were analysed according to the intention-to-treat principle. Continuous data were tested for normality using histograms. Between-group comparisons for continuous data were performed by means of Student’s t test or the Mann-Whitney U test and for categorical data with the use of the χ² test. We considered a P value <0.05 to indicate statistical significance. Data were entered into Excel spread sheets, and then extracted into STATA (StataCorp. 2011. Stata Statistical Software: Release 12. (Stata-Corp LP: College Station, TX USA), for analysis.

Results

Subject characteristics

Over the period January–October 2013, 151 patients were enrolled into the study, of which 144 were randomised (Fig. 2). Seven previously enrolled patients were excluded, either before surgery (two were operated on elsewhere, because of theatre availability and one withdrew consent), or on return to the ICU when rescreened before randomisation (three returned with an IABP and one with an open chest). Of those randomised, 74 were allocated to usual care and 70 to intervention. Baseline characteristics of study participants are described in Table 1.

Fluid therapy

A significant reduction in the amount of bolus fluids administered to participants in the intervention group was seen at both extubation (median (IQR) 1620 ml (500–3410), compared with 2520 ml (1440–5250), P<0.001) and at 24 h (median (IQR) 2760 ml (1690–4500), compared with 3750 ml (2250–5550), P=0.02), when compared with the usual care group. There were also significant reductions in the total amount of fluids administered and the overall fluid balance in the intervention group, when compared with the usual care group (Table 2). There was no significant difference seen between the groups with type of fluids used (Fig. 3).
Renal function

There was no significant difference in the occurrence of renal dysfunction between groups as measured by KDIGO and based on either change in creatinine or urine output (Table 2).

Other clinical outcomes

There was not a significant decreased ICU length of stay, or reduced length of ventilation hours, but there was a significant increase in ventilation free hours in the intervention group (Table 2). Less diuretic was administered to the intervention group. No significant differences were seen in the use of vasactive drugs, or the incidence of new onset atrial fibrillation.

One subject in the cohort died. This patient had been allocated to standard care and died between day 28 and day 90 postoperatively. There was a low rate of protocol violations with 16 recorded out of a total of 1495 boluses given.

Hawthorne effect

We tested for any evidence of a Hawthorne effect, by comparing the volume of fluid received in sequential quintiles in the usual care group, over the entire study period. No significant difference

### Table 1 Baseline subject characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Usual Care</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56 (48)</td>
<td>61 (52)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (67)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>51 (47)</td>
<td>58 (53)</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>11 (69)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>7 (78)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (38)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Age, yrs mean (range)</td>
<td>61.2 (18–86)</td>
<td>65.4 (38–86)</td>
</tr>
<tr>
<td>BMI kg m⁻², mean (sd)</td>
<td>29.1 (5.5)</td>
<td>28.5 (4.7)</td>
</tr>
<tr>
<td>Euroscore II, mean (sd)</td>
<td>2 (2.1)</td>
<td>2.7 (3.7)</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated CABG</td>
<td>37 (45)</td>
<td>46 (55)</td>
</tr>
<tr>
<td>Valve surgery</td>
<td>27 (62)</td>
<td>17 (38)</td>
</tr>
<tr>
<td>CABG+Valve</td>
<td>9 (56)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Other cardiac surgery</td>
<td>2 (67)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Bypass time, mins mean (sd)</td>
<td>112 (54)</td>
<td>106 (44)</td>
</tr>
<tr>
<td>Cross clamp time, mins mean (sd)</td>
<td>76 (41)</td>
<td>73 (33)</td>
</tr>
</tbody>
</table>
was found in volume of fluids administered to the usual care group, when the first quintile of subjects was compared with the last (Fig. 4).

**Decision making**

The most common primary indication cited for bolus fluid administration, was hypotension, in both the usual care and the intervention group. Other reasons differed between the two study groups, with low urine output and low cardiac output/index being cited next in the usual care group, while low central venous pressure was more common than low urine output, and low cardiac output/index in the intervention group (Table 3).

**Discussion**

This feasibility study assessed a protocolised strategy to guide bolus fluid administration after cardiac surgery. We found that
There are few published studies using goal-directed haemodynamic strategy could achieve a significant reduction in fluid administration, without an increase in cardiac surgery associated acute kidney injury and no significant Hawthorne effect in the control arm, despite the unblinded nature of the study.

To our knowledge, this is the first study to utilise a protocolised strategy incorporating SVV, to rationalise bolus fluid administration after cardiac surgery, by limiting fluid administration to patients who have a perceived inadequate cardiac output and who are likely to be fluid responsive (i.e. likely to increase their cardiac output after administration of the fluid bolus). A recent meta-analysis of goal-directed therapy in cardiovascular outcomes but specifically excluded studies that enrolled cardiac surgical patients, to minimise heterogeneity. There are few published studies using goal-directed haemodynamic manipulation in cardiac surgical patients, and all aimed to significantly increase cardiac output, through the administration of fluids and/or inotropes. Previous studies have utilised flow-based goals, such as cardiac index or stroke volume index to guide fluid administration, in patients undergoing cardiac surgery. One study found a reduction in hospital length of stay, in patients allocated to an algorithm guided by oesophageal Doppler flow measurements. Another study found a reduced hospital length of stay when patients, after cardiac surgery, were treated according to a protocol designed to maintain $\text{SvO}_2 \geq 70\%$ and serum lactate concentration $\leq 2.0 \text{ mM}$. However patients in the intervention group received more crystalloid and colloid fluid replacement than patients in the usual care group ($2270 \text{ ml compared with } 1970 \text{ ml and } 922 \text{ ml compared with } 802 \text{ ml}$) respectively. A third study assessed the utility of goal-directed therapy, using FloTrac cardiac index monitoring in 27 patients with moderate to high risk (EuroSCORE$\geq 3$) and found no reduction in ventilation hours, ICU and hospital length of stay. However the amount of extra fluid administered to the EGDT group, was significantly higher than the usual care group ($330 \text{ ml compared with } 80 \text{ ml}$). These studies suggest a reduction in the incidence of postoperative complications, when a goal-directed approach is used in patients undergoing cardiac surgery.

In contrast to the above, our study shows that it is possible to utilise advanced haemodynamic monitoring as part of a strategy, to administer less fluid to patients after cardiac surgery, by ensuring that the patients who receive fluid are most likely to benefit from it. Our trial demonstrates importantly, that fluid administration guided by haemodynamic monitoring does not necessarily result in larger volumes of fluid being administered, and concurs with others, who have concluded that this might result in an individualised approach to fluid administration. This study was not designed to demonstrate differences in clinical outcomes. Whether differences become significant in a larger patient group, will be studied as part of our proposed multi-centre Phase IIb trial of this intervention. A recent study in 734 patients, undergoing major abdominal surgery, evaluated the effectiveness of cardiac output monitoring to guide administration of fluid and inotropes as part of a haemodynamic algorithm. This study showed that overall volumes of colloid and crystalloid fluid, administered during the intervention period, were similar ($4190 \text{ ml and } 4020 \text{ ml}$ respectively). However in the usual care group more fluid was administered during than after surgery, while for the intervention group similar amounts were administered during surgery and during the 6 h after surgery. Use of inotropic and vasopressor agents, was similar between groups. Although the study did not demonstrate any significant reduction in primary outcome, when the results of this trial were incorporated into an updated systematic review and meta-analysis, there was evidence that this intervention was associated with a reduction in the number of patients who developed complications, after surgery and in the duration of hospital length of stay. Importantly this study demonstrated a high rate of protocol adherence to the therapy algorithm, demonstrating feasibility of this approach in routine clinical practice.

**Study strengths and limitations**

A pragmatic study design was used, to ensure timely completion and enrolment, aiding in generalisability of study results, as all patients presenting for cardiac surgery were screened for enrolment and invited to participate. Only 15% of patients approached declined to participate and there was no loss to follow-up, which demonstrates acceptability of the study to patients. This resulted in a satisfactory recruitment rate, ensuring timely completion in 9 months. The low rate of exclusion (4.8%) at the secondary screening time on return to ICU, shows that the inclusion and exclusion criteria were able to identify suitable participants and minimise drop out.

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**Table 3 Primary Indication for fluid administration**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Usual Care (n=74, n (%)</th>
<th>Intervention (n=70, n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>646 (80)</td>
<td>481 (79)</td>
</tr>
<tr>
<td>Low Central Venous Pressure</td>
<td>20 (2)</td>
<td>31 (5)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5 (1)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Low Cardiac Output/Index</td>
<td>42 (5)</td>
<td>25 (4)</td>
</tr>
<tr>
<td>Respiratory swing</td>
<td>4 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Low urine output</td>
<td>49 (6)</td>
<td>23 (4)</td>
</tr>
<tr>
<td>Low haemoglobin</td>
<td>14 (2)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>7 (1)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (2)</td>
<td>17 (3)</td>
</tr>
</tbody>
</table>

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**Fig 4 Analysis of volume of fluid administered to usual care group over course of study. All participants in the standard care group were sequentially divided into five groups from beginning of study to end of study (i.e. approximately 15 participants per group) to compare the amount of fluid given in participants enrolled at different timepoints over the whole study enrolment period. This figure shows the median and interquartile range for each of the 5 groups. Median (IQR) 1st quintile: 4500 ml (2000-6000) vs 5th quintile: 2400 ml (1250-6000). P=0.32.**
The protocol was developed ‘in-house’, by clinicians skilled in the care of patients after cardiac surgery and was easily instituted at the bedside by nursing staff and involved common agreement on haemodynamic parameters. Alongside utilising objective measures, such as the pulmonary artery catheter where available, to guide determination of cardiac output, it also allowed measures routinely used at the bedside, such as urine output, capillary refill and skin turgor, to be used in the assessment of haemodynamic status, reflecting everyday practice.

Limitations of both the EV1000 and SVV are recognized, including restrictions regarding ventilation strategy, arrhythmias and intra-aortic balloon counterpulsation. Obviously in the cardiac surgical population this is an issue, however as a result of the enrolment criteria and the secondary exclusion point, all subjects were enrolled appropriately. It does limit the generalisability of these results, in patients in whom these methods could not be reliably used.

Our findings are from a single-centre and only assess fluid administered postoperatively on return to the ICU from theatre. We did not attempt to influence or assess the type or amount of fluid replacement that occurred in the operating room, as our study solely focused on bolus fluid administration in the ICU.

In summary this study demonstrated the feasibility of a conservative fluid management strategy based on non-invasive haemodynamic monitoring. Large studies are required to demonstrate possible reduction in ventilation time, ICU length of stay, and acute kidney injury in those treated with the fluid management strategy. For future research in this area, including an appropriately powered randomised controlled trial, consideration must be given to addressing important safety endpoints, such as renal dysfunction, by adequate monitoring of the incidence of renal failure and the use of a data safety monitoring board.

Authors’ contributions
R.L.P. contributed to the study design, obtaining funding, patient recruitment, site training, data collection, data analysis, and manuscript preparation. S.P.M. contributed to the study design, patient recruitment, data analysis, and manuscript preparation. E.G., L.W.M. and K.L.C. contributed to the study design, patient recruitment, data collection and manuscript preparation. All of the authors read and approved the final manuscript.

Acknowledgements
We would like to sincerely thank the staff of the CVICU and the anaesthetic technicians, Auckland City Hospital, who provided care to the patients and assisted with data collection and delivery of the study intervention. We would also like to thank the patients, who so generously agreed to participate in this study.

Declaration of interest
None declared.

Funding
This work was supported by: the Health Research Council of New Zealand by way of a Feasibility Study award (HRC13/756) (RLP). Research in the CVICU is supported in part by an unrestricted grant from Fisher and Paykel Healthcare, New Zealand. Edwards Lifesciences provided the consumables for this study without charge and loaned the monitors for the life of the study. These sponsors had no input into the study design and no access to trial data. All analyses, reporting and decisions to publish have been made independent of the sponsors.

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Handling editor: H. C. Hemmings