Effect of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and updated systematic review

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Abstract

Importance

Small trials suggest post-operative outcomes may be improved by the use of cardiac output monitoring to guide intra-venous fluid and inotropic drugs as part of a hemodynamic therapy algorithm.

Objective

To evaluate the clinical effectiveness of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm.

Design, Setting and Participants

Pragmatic, multi-center, randomized, observer-blinded trial of 734 high-risk patients aged over 50 years undergoing major gastrointestinal surgery, and an updated systematic review and meta-analysis.

Interventions

Cardiac output-guided, hemodynamic therapy algorithm for intra-venous fluid and inotrope (dopexamine) infusion during, and six hours following surgery, compared with usual care.

Main outcome measures

The primary outcome was a composite of pre-defined 30-day moderate or major complications and mortality. Secondary outcomes were morbidity on day 7, infection, critical care free days and all cause mortality at 30 days, all cause mortality at 180 days and length of hospital stay.

Results

Baseline patient characteristics, clinical care and volumes of intra-venous fluid were similar between groups. Care was non-compliant with the allocated treatment for fewer than 10% of patients in each group. The primary outcome was 36.6% for the intervention and 43.4% for usual care (RR 0.84 [0.71-1.01], ARR 6.8% [−0.3% to 13.9%]; p=0.07). There was no significant difference between groups for any secondary outcomes. Five intervention patients (1·4%) experienced cardiovascular serious adverse events within 24 hours compared with none in the usual care group. Findings of the meta-analysis suggest the intervention is associated with fewer complications (Intervention 488/1548 [31.5%] vs Controls 614/1476 [41.6%]; RR 0·77 [0·71-0·83]), and a non-significant reduction in hospital / 28 day / 30 day mortality (Intervention 159/3215 deaths [4.9%] vs Controls 206/3160 deaths [6·5%]; RR 0·82 [0·67-1·01]) and mortality at longest follow-up (Intervention 267/3215 deaths [8.3%] vs Controls 327/3160 deaths [10.3%]; RR 0·86 [0·74-1·00]).

Conclusions

In a randomized trial of high-risk patients undergoing major gastrointestinal surgery, use of a cardiac output-guided hemodynamic therapy algorithm compared with usual care did not reduce a composite outcome of complications and 30-day mortality. However, inclusion in an updated meta-analysis indicates that the intervention was associated with a clinically important reduction in complication rates.

Trial registration: http://www.controlled-trials.com/ISRCTN04386758

Short summary

Findings from small trials suggest post-operative outcomes may be improved by cardiac output-guided, hemodynamic therapy but this remains unconfirmed. In a multi-center randomized trial, we allocated 734 high-risk patients undergoing major gastrointestinal surgery to a hemodynamic therapy algorithm for intra-venous fluid and inotrope (dopexamine) infusion during and six hours following surgery, or usual care. The primary outcome of pre-defined moderate or major post-operative complications was met by 36.6% of intervention patients and 43.4% of usual care patients (RR 0.84 [0.71-1.01]; p=0.07). Whilst not statistically significant, these findings were consistent with those of a recent Cochrane systematic review. When the systematic review was updated to include our results, significantly fewer patients developed complications having received this intervention (RR 0·77 [0·71-0·83]). The combined findings of the randomized trial and systematic review suggest cardiac output-guided hemodynamic therapy may be associated with a clinically important reduction in complications after surgery.

Introduction

Estimates suggest that over 230 million patients undergo surgery worldwide each year with mortality reported between 1 and 4%.[1,2] Complications and deaths are most frequent among high-risk patients, those who are older or have co-morbid disease and undergo major gastrointestinal or vascular surgery. Importantly, patients who develop complications, but survive to leave hospital, suffer reduced long-term survival.[3,4]

It is accepted that intra-venous fluid and inotropic drugs have an important effect on patient outcomes, in particular following major gastrointestinal surgery. Yet, they are commonly prescribed to subjective criteria leading to wide variation in clinical practice.[5] One possible solution is the use of cardiac output monitoring to guide intra-venous fluid and inotropic drugs as part of a hemodynamic therapy algorithm. This approach has been shown to modify inflammatory pathways, and improve tissue perfusion and oxygenation.[6,7] Use of hemodynamic therapy algorithms has been recommended in a report commissioned by the Centers for Medicare and Medicaid Services in the USA,[8] and by the National Institute for Health and Care Excellence (NICE) in the UK.[9] A recent Cochrane review, however, has suggested that the treatment benefit may be more marginal than previously believed.[10] The current evidence consists primarily of small trials and is insufficient to resolve controversies regarding potential harm associated with fluid excess, myocardial injury and invasive forms of monitoring. As a result, this treatment has not been widely adopted into clinical practice.

In this context, we evaluated the clinical effectiveness of cardiac output monitoring to guide intra-venous fluid and inotropic drugs as part of a hemodynamic therapy algorithm in a large, pragmatic, multi-center randomized controlled trial in high-risk patients undergoing major

gastrointestinal surgery. We then conducted an updated systematic review incorporating the findings of this trial.

Methods

Trial design

OPTIMISE was a multi-center, randomized controlled trial conducted in seventeen acute hospitals in the National Health Service in the United Kingdom. Adult patients, aged 50 years or over undergoing major abdominal surgery involving the gastrointestinal tract of expected duration greater than 90 minutes, were eligible for recruitment provided they satisfied one of the following high-risk criteria: aged 65 years or over; presence of a defined risk factor for cardiac or respiratory disease (Exercise tolerance equivalent to six metabolic equivalents (METs) or less as defined by American College of Cardiology & American Heart Association guidelines;[11] ischemic heart disease; ejection fraction less than 30% (echocardiography); moderate or severe valvular heart disease; heart failure; chronic obstructive pulmonary disease; poor lung function demonstrated by spirometry; radiographically confirmed chronic lung disease; anaerobic threshold ≤14 ml min^{-1} kg^{-1} on sub-maximal exercise testing; heavy smoker; see appendix 3 of protocol, available in supplementary file); renal impairment (serum creatinine ≥1.5 mg dl^{-1}); diabetes mellitus; or emergency surgery. Exclusion criteria included refusal of consent, pregnancy, acute pulmonary edema (within prior seven days), acute myocardial ischemia (within prior 30 days) and patients undergoing surgery for palliative treatment only. Investigators were asked not to randomize patients where the clinician intended to use cardiac output monitoring for clinical reasons. OPTIMISE was approved by the East London & City Research Ethics Committee (09/H0703/23) and the Medical and Healthcare products Regulatory Agency and registered with Controlled Trials (ISRCTN04386758). Written informed consent was obtained from all patients prior to surgery. Site visits were performed by RP and AA for training and for source data verification. The trial protocol was made freely available on request and is available online at www.perioperativemedicine.net/OPTIMISE.

Randomization and procedures to minimize bias

Randomization was performed through a dedicated, secure, web-based system. Participants were allocated to treatment groups using a computer-generated, dynamic procedure (minimization) with a random component. Participants were allocated, with an 80% probability, to the group that minimized between group differences in trial site, urgency of surgery and surgical procedure category among all participants recruited to date (Protocol, available in supplementary file). This was a pragmatic effectiveness trial and it was not possible to blind all investigators to study group allocation. To minimize bias, investigators were instructed not to reveal study group allocation unnecessarily. Patients were followed up by another investigator who, wherever possible, was unaware of allocation. Investigators performing follow-up self-assessed the extent to which they remained blinded. Outcomes were verified according to pre-defined criteria by the principal investigator or designee at each site, who was always blinded to allocation. The decision to admit a trial patient to critical care was made by clinical staff and recorded prior to randomization and surgery, allowing comparison with actual location of post-operative care.

Clinical management

The intervention period commenced with induction of anesthesia and continued until six hours following completion of surgery.

All patients

Peri-operative treatment goals were flexibly defined for all patients to avoid both extremes of clinical practice and practice misalignment.[12] All patients received standard measures to maintain oxygenation ($SpO_2 \geq 94\%$), hemoglobin (>80 gl^{-1}), core temperature (37 °C) and heart rate (<100 beats min^{-1}). 5% dextrose was administered at 1 ml kg^{-1} hr^{-1} to satisfy maintenance fluid requirements. Additional fluid was administered at the discretion of the treating clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and

base excess. Mean arterial pressure was maintained between 60 and 100 mmHg using an alpha adrenoceptor agonist or vasodilator, as required. Post-operative analgesia was provided by epidural infusion (bupivacaine and fentanyl) or intra-venous infusion (morphine or fentanyl). With the exception of the interventions below, all other treatment decisions were at the discretion of, and taken by, senior clinicians.

Hemodynamic therapy algorithm group patients

Intervention group patients received intra-venous fluid and inotropes according to a cardiac output-guided, hemodynamic therapy algorithm (supplementary file). The algorithm was developed for OPTIMISE by an expert group. It was designed to be delivered in the operating room/post-anesthetic care unit by both medical and nursing staff, ensuring that critical care admission was not necessary for compliance. A cardiac output monitor was chosen which could be used in conscious (extubated) patients (LiDCOrapid, LiDCO Ltd, UK). This technology has been extensively evaluated and in clinical use for more than ten years.[13] The hemodynamic therapy algorithm was supported by high quality clinical and mechanistic evidence and had a good cardiovascular safety profile.[6,7,14-16] Intra-venous colloid solution was administered in 250ml boluses in order to achieve and maintain a maximal value of stroke volume; no attempt was made to standardize choice of colloid. Dopexamine was administered at a fixed, low dose of 0.5 $\mu g\ kg^{-1}\ min^{-1}$ either through a peripheral, or central venous catheter (Cephalon Ltd, Welwyn Garden City, UK). The choice and dose of inotrope was based on the findings of a previous meta-regression analysis.[15] The dose of dopexamine was reduced if the heart rate increased to 120% of baseline or 100 beats min^{-1} (whichever was greater) for more than 30 minutes despite adequate anesthesia and analgesia. If the heart rate did not decrease despite dose reduction, then the infusion was discontinued.

Usual care group patients

These patients received usual peri-operative care although the use of a dynamic central venous pressure target was recommended. Cardiac output monitoring was not used in the usual care group unless specifically requested by clinical staff because of patient deterioration.

Trial endpoints

The primary effect estimate was the relative risk of a composite of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery (Pulmonary embolism; myocardial ischemia or infarction; arrhythmia; cardiac or respiratory arrest; limb or digital ischemia; cardiogenic pulmonary edema; acute respiratory distress syndrome; gastrointestinal bleed; bowel infarction; anastomotic breakdown; paralytic ileus; acute psychosis; stroke; acute kidney injury; Infection, source uncertain; Urinary tract infection; Surgical site infection; Organ/space infection; Bloodstream infection; Nosocomial pneumonia; Post-operative hemorrhage; see appendix 1 of protocol, available in supplementary file). Secondary outcomes were: Post-Operative Morbidity Survey (POMS) defined morbidity on day 7;[17] infectious complications, critical care free days (number of days alive and not in critical care) and all cause mortality at 30 days following surgery; all cause mortality at 180 days following surgery; and acute hospital length of stay. Level of post-operative critical care was categorized according to standard criteria.[18] Patients were followed for 30 days by visit and through local computerized records while in hospital. All patients were contacted at 30 days either by telephone for those who had left hospital or by visit for those who had not. Where necessary, investigators contacted community physicians or other hospitals, by telephone and in writing, for outstanding information describing the primary outcome. All cause mortality at 180 days was assessed through the Office for National Statistics. Data entry was performed through a dedicated, secure, web-based system. Automated validation checks included plausibility ranges and cross checks between data fields. Further data checks were performed centrally and through source data verification.

Statistical analysis

Assuming a type I error rate of 5%, 345 patients per group (690 total) were required to detect, with 90% power, a reduction in the composite of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery from 50% in the usual care group to 37.5% in the hemodynamic therapy algorithm group (absolute risk reduction 12.5%; relative risk reduction 25%).[14] Allowing for a 3% one-way, cross-over rate due to use of cardiac output monitoring in the usual care group, this was increased to 367 per group (734 total). A planned interim analysis was performed at halfway. Pre-defined stopping guidelines permitted early termination of the trial for harm but not effectiveness.

Analyses were performed according to an a priori statistical analysis plan including all patients on an intention to treat basis. Categorical data were compared using Fisher's exact test. Differences in critical care free days and acute hospital length of stay were tested using the Wilcoxon rank-sum test. Kaplan-Meier curves were plotted for all cause mortality up to 180 days following surgery. Adjustment for baseline data was made using a logistic regression model including age, gender, urgency of surgery, surgical procedure category, ASA grade, planned location following surgery, renal impairment, diabetes mellitus, risk factors for cardiac or respiratory disease and random effect of site. Baseline variables were selected for inclusion in the adjusted analysis according to anticipated relationship with outcome, including all variables used in the minimization algorithm. Results for primary and secondary outcomes are reported as relative risks (RR) with 95% confidence intervals (CI). Results for the primary outcome are additionally reported as absolute risk reduction (ARR) with 95% CI. Results of the logistic regression model are reported as adjusted odds ratios (OR) with 95% CI, with unadjusted OR for comparison.

Pre-specified secondary analyses were: a modified intention to treat analysis excluding patients who did not undergo surgery; a compliance-adjusted analysis; and scenario-based sensitivity

analyses for missing primary outcomes. The modified intention to treat analysis excluded patients who did not undergo surgery. In the compliance-adjusted analysis, patients whose treatment did not comply with allocation were assumed to have the same outcome as if they had been assigned to the alternative treatment group.[19] This approach utilizes the underlying principle of randomization to assume that for each non-compliant patient there would be an equivalent patient in the alternative treatment group who would have been non-compliant had their allocations been reversed, and therefore, unlike a 'per protocol' or 'as treated' analysis, can give an unbiased estimate of the treatment effect among those patients that were compliant with their allocated treatment. The scenario-based sensitivity analyses considered two extreme scenarios for the outcomes of patients with missing data for the primary outcome variable: a best case analysis, assuming all missing outcomes in the intervention group were favorable and all missing outcomes in the usual care group were unfavorable; and a worst case analysis, assuming the reverse. Pre-specified sub-group analyses were performed: by urgency of surgery; by surgical procedure category; and by timing of recruitment (comparing the first ten patients recruited at each site with those recruited subsequently (sites recruiting fewer than ten patients were excluded). Continuous variables are presented as mean (SD) where normally distributed or median (quartiles) where not. Categorical variables are presented as n (%). Analyses were performed using Stata SE version 10.1. Significance was set at $p<0.05$ (two-tailed).

Systematic review

Using identical methods, we updated the previous Cochrane systematic review (SR) of published randomized trials of 'Peri-operative increase in global blood flow to explicit defined goals and outcomes following surgery' with the findings of the OPTIMISE Trial and other published trials identified by an updated search.[10] Extended methods are presented in the eAppendix. CENTRAL (Cochrane Library 2014), MEDLINE (1966 to February 2014) and EMBASE (1982 to February 2014) were searched for randomized trials involving adult patients (≥ 16 years) undergoing surgery in an operating room where the intervention met the following criteria: Peri-operative administration of fluids, with or without inotropes/vasoactive drugs, targeted to increase blood flow (relative to control) against explicit measured goals. 'Peri-operative' was defined as: initiated within 24 hours before surgery and lasting up to six hours after surgery. 'Explicit measured goals' were defined as: cardiac index, oxygen delivery, oxygen consumption, stroke volume, mixed venous oxygen saturation, oxygen extraction ratio or lactate. We selected the following key outcomes: number of patients with complications (primary outcome variable for the OPTIMISE trial), number of infections, length of postoperative hospital stay, mortality at longest follow-up (primary outcome variable of Cochrane SR) and 28 day or 30 day or hospital mortality (as reported by authors). Treatment effects were reported as relative risks (RR) with 95% CI for clinical variables or weighted mean differences (SD) for length of hospital stay. Analyses were performed using Review Manager (RevMan 5.2.8) using fixed effects models with random effects models for comparison.

Results

A total of 734 patients were enrolled between June 2010 and November 2012; 368 patients were allocated to the hemodynamic therapy algorithm, and 366 to usual care. In the usual care group, one patient who was enrolled in another trial was randomized in error and excluded before surgery (Figure 1). Baseline patient characteristics were similar between the groups (Table 1). Most patient types were well represented with the exception of those having emergency surgery (25 patients) and those having urological or gynecological surgery involving the gut (nine patients). Clinical care outside the trial intervention was also similar (Table 2), including critical care admission. Overall volumes of intra-venous fluid (colloid and crystalloid combined) administered during the intervention period were similar (intervention 4190 ml versus usual care 4024 ml). For usual care group patients, more intra-venous fluid was administered during than after surgery, while for intervention group patients similar volumes were administered during surgery and during the six hours following surgery. Intervention group patients received more colloid and less crystalloid than usual care group patients. With the exception of dopexamine, use of vasopressor and inotropic agents was similar between the groups. Fewer than 10% of patients in each group were non-compliant with their allocated treatment (eTable 1). This was achieved through the presence of trained investigators, where necessary, to observe, advise or deliver the intervention (eTable 2). Investigator self-assessment of blinding for determination of outcomes also indicated a high rate of compliance with trial procedures (Table 3).

The primary outcome, a composite of pre-defined moderate or major post-operative complications and mortality at 30 days following surgery, was met by 36.6% (134 of 366) of patients in the intervention group and by 43.4% (158 of 364) of patients in the usual care group (RR 0.84 [0.71-1.01], ARR 6.8% [−0.3% to 13.9%]; p=0.07) (Table 3). Following adjustment for baseline risk factors, the observed treatment effect remained non-significant with an adjusted OR of 0.73 [0.53-1.00];

p=0.05 (Wald chi-squared for model fit on 16 degrees of freedom 27.6, p=0.036; unadjusted OR 0.75 [0.56-1.01]; p=0.07). The pre-specified, modified, intention to treat analysis, in which three patients (all in the usual care group) who did not undergo surgery were excluded, had little effect on the primary outcome (RR 0.84 [0.70-1.00]; p=0.06). In the pre-specified, compliance-adjusted analysis conducted using established methodology,[19] the observed treatment effect was strengthened when the 65 patients whose care was non-compliant (eTable 1) were assumed to experience the same outcome as if they had been allocated to the alternative group (RR 0.80 [0.61-0.99]; p=0.037). Scenario-based sensitivity analyses demonstrated that the four patients with missing primary outcome data had minimal influence on treatment effect (RR 0.84 [0.70-1.00] to 0.85 [0.71-1.02]).

Five patients in the intervention group experienced serious adverse cardiac events within 24 hours of the end of the intervention period (two tachycardia, two myocardial infarction and one arrhythmia) compared with none in the usual care group (p=0.062). At 30 days following surgery, however, the incidence of cardiovascular events was similar between the groups (myocardial infarction, arrhythmia and cardiogenic pulmonary edema) (Table 3). There were no significant differences for any of the secondary outcomes: POMS defined morbidity on day 7; infectious complications, critical care free days and all cause mortality at 30 days following surgery (unadjusted OR 1.09 (0.48-2.45); adjusted OR 1.20 (0.51-2.82), p=0.68; Wald $\chi^2(16)$ for model fit 15.3, p=0.50); all cause mortality at 180 days following surgery (unadjusted OR 0.63 [0.39-1.04]; adjusted OR 0.61 [0.36-1.04], p=0.071; Wald $\chi^2(16)$ for model fit 41.8, p<0.001); and duration of acute hospital length of stay (Table 4, Figure 2). No interaction was found for urgency of surgery, the intervention was associated with a slight reduction in the primary outcome for the elective surgery sub-group. No interaction was found for surgical procedure category, the intervention was associated with a slight reduction in the primary outcome for patients undergoing small bowel +/- pancreas surgery. A significant interaction (p=0.019) was found for timing of recruitment, the intervention was

associated with a reduction in the primary outcome for patients recruited later (RR 0.59 [0.41-0.84] compared with earlier at each site (RR 1.51 [0.75-3.01] (eTable 3).

Systematic review and meta-analysis

The updated literature search identified seven additional trials including OPTIMISE, to provide a total of 38 trials that included 6595 participants with 23 trials including 3024 participants providing data describing our primary outcome (eFigure 1). Extended results are provided in the eAppendix. The addition of the findings of OPTIMISE and other recent trials does not substantially alter the findings of the recent Cochrane meta-analysis. Complications were less frequent amongst patients treated according to a hemodynamic therapy algorithm (Intervention 488/1548 [31.5%] vs Controls 614/1476 [41.6%]; RR 0·77 [0·71-0·83]) (Figure 3). The intervention was associated with a reduced incidence of post-operative infection (Intervention 182/836 patients [21·8%] vs Controls 201/790 patients [25.4%]; RR 0·81 [0·69-0.95]) and a reduced duration of hospital stay (mean reduction 0.79 days [0·96-0.62]) (eFigures 2 and 3). There was no significant reduction in hospital or 28 day or 30 day mortality (Intervention 159/3215 deaths [4.9%] vs Controls 206/3160 deaths [6·5%]; RR 0·82 [0·67-1·01]) and a non-significant reduction in mortality at longest follow-up (Intervention 267/3215 deaths [8.3%] vs Controls 327/3160 deaths [10.3%]; RR 0·86 [0·74-1·00]) (eFigures 4 and 5). These results were strengthened through the use of random effects models (eAppendix).

Discussion

The principal finding of the OPTIMISE trial was that in patients undergoing major abdominal surgery involving the gastrointestinal tract, when compared with usual care, use of this cardiac output-guided, hemodynamic therapy algorithm was not associated with a significant reduction in the composite primary outcome of moderate or major post-operative complications at 30 days following surgery. However, after incorporating the results of this large trial into an updated systematic review and meta-analysis, there was evidence that this intervention was associated with a clinically important reduction in the number of patients who develop complications after surgery. In the OPTIMISE trial, there was no difference in the secondary outcomes of POMS defined morbidity at day 7; infectious complications, critical care-free days or all cause mortality at 30 days; all cause mortality at 180 days; or acute hospital length of stay. However, the findings of the updated systematic review suggest this treatment approach is associated with a significant reduction in the number of patients who develop post-operative infection as well as in duration of hospital stay. The findings of the mortality analyses provide borderline evidence but remain consistent with benefit.

To the best of our knowledge, this is the largest trial of a peri-operative, cardiac output-guided, hemodynamic therapy algorithm, to date. OPTIMISE was designed to address several limitations in the previous trials.[20] The large sample size allowed for comparison of the cardiac output-guided hemodynamic therapy algorithm with usual peri-operative care, avoiding problems associated with alternative 'control' treatment algorithms which do not reflect typical practice.[12] A large number of algorithms for cardiac output guided hemodynamic therapy have been published describing a variety of options in terms of hemodynamic end-points, use of inotropic agents and cardiac output monitoring. We used an algorithm suited to the care of patients during and after major gastrointestinal surgery, that was supported by high quality clinical and mechanistic evidence and a

good cardiovascular safety profile.[6,7,10,14-16] The β_2-agonist dopexamine has mild inotropic and vasodilator effects and is the most widely studied agent in this context. The findings of a meta-regression analysis suggested that dopexamine infusion at low dose is associated with improved outcomes following major surgery.[15] Further modifications were made by an expert group to allow delivery in the operating room and post-anesthetic care unit by both medical and nursing staff and in particular to ensure admission to critical care was not necessary for compliance with the intervention. Importantly, the high rate of compliance with the hemodynamic therapy algorithm used in this trial suggests this treatment approach is feasible for use in routine clinical practice. A widely used cardiac output monitoring technology was employed (although our findings are not specific to this device). In keeping with the pragmatic nature of the trial, no attempt was made to standardize the choice of colloid in either group. Recent evidence has suggested an increased incidence of acute kidney injury in critically ill patients receiving starch-based, colloid solutions.[21,22] While we do not have individual patient data describing the use of starch, a post-hoc survey of investigators suggested few patients received this. A recent systematic review identified no evidence of acute kidney injury associated with the use of starch solutions in surgical patients.[23]

A potential weakness of OPTIMISE may be the use of a primary outcome that was a composite of moderate or major post-operative complications and mortality. The components of this outcome measure may reflect benefit, no effect or harm associated with the intervention. We controlled for bias by assessing and grading this outcome according to pre-defined criteria and, although it is not possible to blind all clinical staff administering complex interventions, our data suggest excellent compliance with blinding for patient outcome assessment. Finally, the event rate in the usual care group was slightly lower than expected and cross-over in terms of cardiac output monitoring in the usual care group was more frequent than predicted. These factors reduced the power of the trial, perhaps resulting in a failure to achieve statistical significance for the primary outcome. Although emergency surgery was one of our inclusion criteria, we were only able to recruit a small number of

these patients. The approach to recruiting elective and emergency patients is quite different and the design of future trials should take this into account. Whilst additional research staff were often present during the trial, anesthesia and critical care staff would be able to deliver such algorithms of care with minimal training. Myocardial injury is the most important adverse effect of hemodynamic therapy algorithms; there was a low rate of cardiovascular serious adverse events within 24 hours of the intervention and the incidence of cardiovascular events was similar between the groups at 30 days following surgery. The trial findings also suggests that cardiac output-guided fluid therapy need not result in excessive fluid administration but may lead to a more individualized approach to achieving the correct dose of fluid, as and when required. A pre-specified analysis of timing of recruitment suggested that a learning curve may have existed, consistent both with an expectation for trials of complex interventions and from previous experience from implementation in this field, and this warrants consideration in future research in this area.[24] The systematic review is the most up-to-date and robust summary of the literature, but also has limitations. Most of the component trials are small single centre trials that lack statistical power and may have an elevated risk of bias; there is evidence of small studies effects. Addition of the OPTIMISE trial findings improves the quality of this evidence synthesis, but the reporting of outcomes remains inconsistent between trials, with diverse criteria for complications reported over a variety of time frames. More than half the included studies were published more than ten years ago and may not be representative of current practice.

Conclusion

In a randomized trial of high-risk patients undergoing major gastrointestinal surgery, the use of a cardiac output-guided hemodynamic therapy algorithm did not reduce a composite outcome of complications and 30-day mortality when compared with usual care. However, inclusion in an

updated meta-analysis indicates that the intervention was associated with a clinically important reduction in complication rates.

Author contributions

Prof Pearse had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. RP has received equipment loans from LiDCO Ltd, a research grant from Circassia Holdings Ltd. and has performed consultancy work for Edwards Lifesciences, Covidien and Massimo Inc. CH and RP are named inventors on a lapsed patent application relating to the peri-operative use of dopexamine. MG has received an honorarium from LiDCO Ltd for organizing a teaching workshop. All other authors declare they have no conflicts of interest. MPWG has received unrestricted grant funding from Deltex Medical Ltd, and fees for lecturing from Fresenius Kabi and Edwards Lifesciences.

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Role of the funder

The funding bodies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript and decision to submit the manuscript for publication.

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Figure 1. CONSORT flow diagram

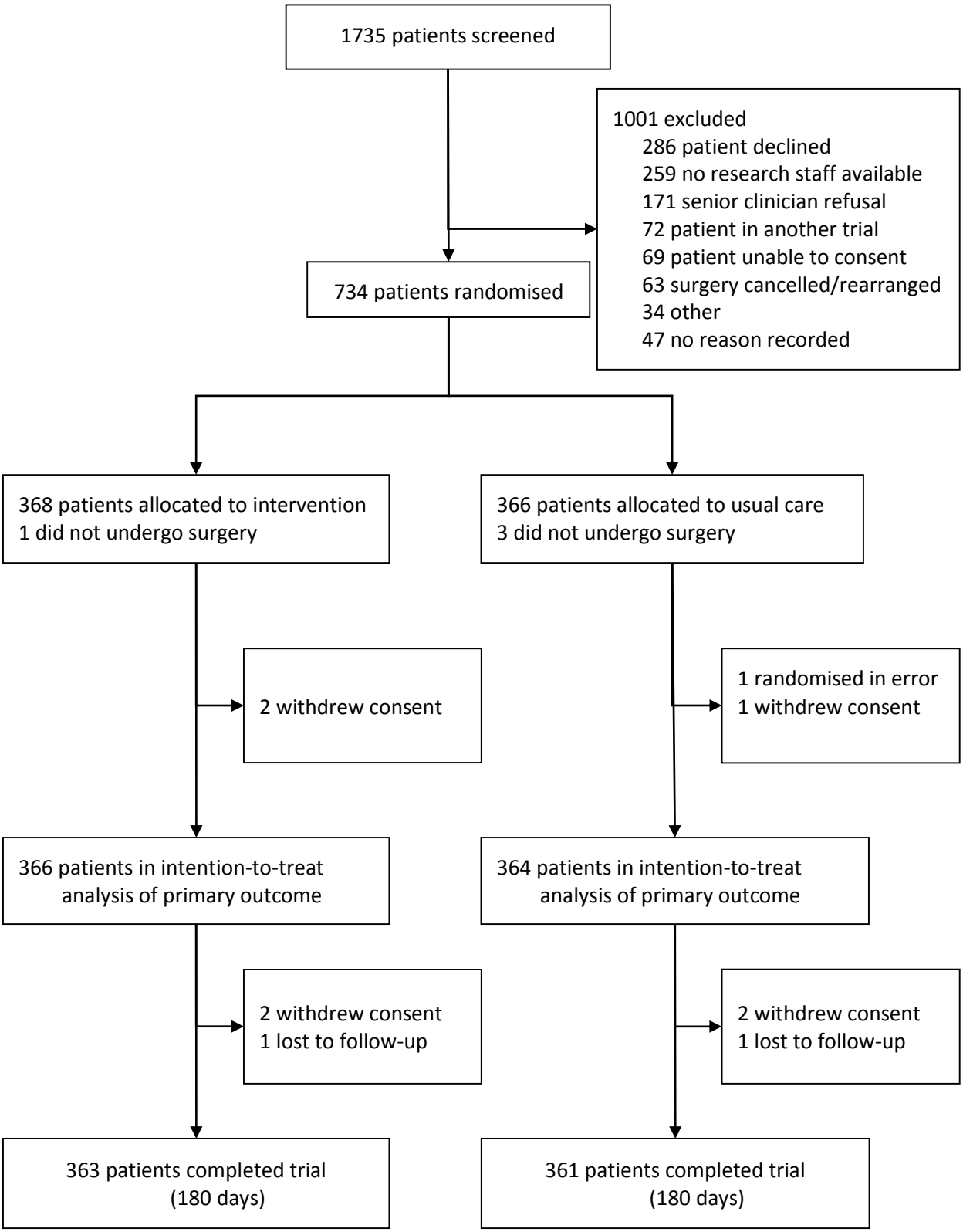

Figure 2. Kaplan-Meier cumulative incidence plots for mortality by treatment allocation to 180 days from start of surgery

Log rank test p-value: 0.093.

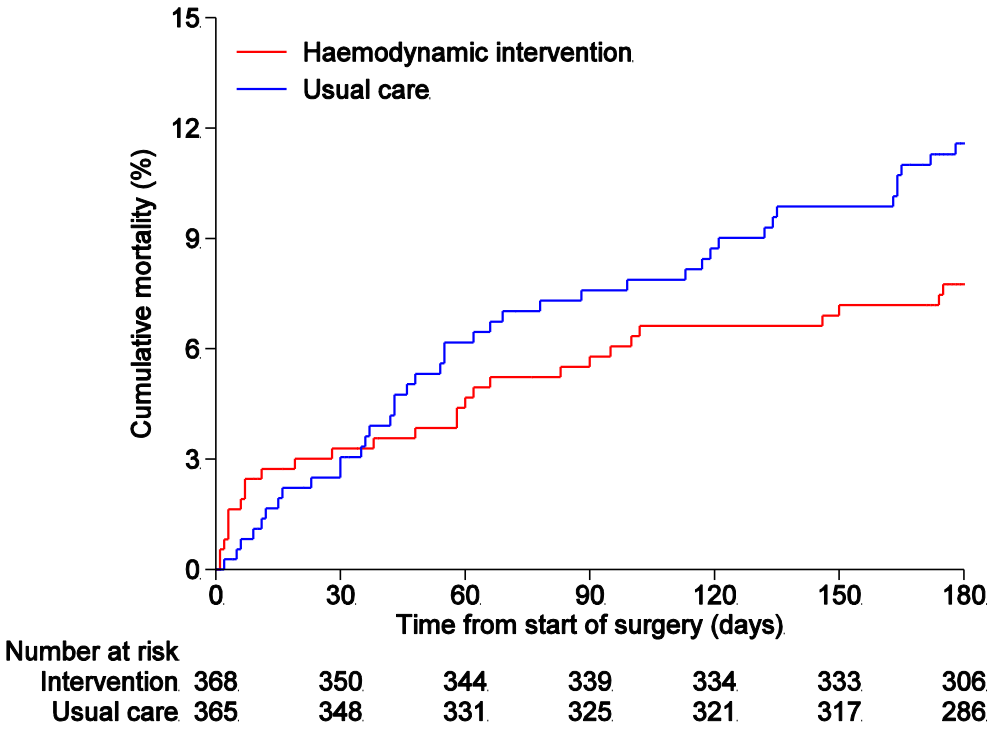

Figure 3. Forest plot of meta-analysis for number of patients developing complications after surgery. *New trials identified in updated literature search. Size of data markers corresponds to weighting for each component trial.

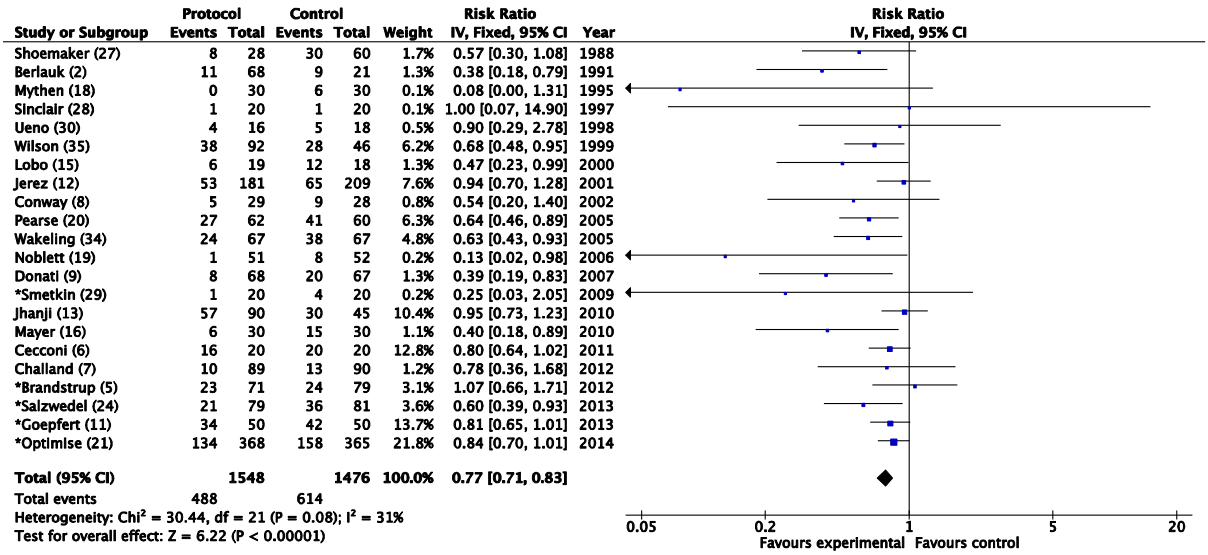

Table 1: Baseline patient characteristics

Data presented as mean (SD) or n (%). Does not include one usual care patient randomized in error.

*** Eligibility criterion**

† Minimization criterion

‡ Patients may have more than one risk factor

	Cardiac output-guided hemodynamic therapy algorithm (n=368)	**Usual care (n=365)**
Age (years)	71.3 (8.4)	72.2 (8.6)
Age*		
50-64 years	68 (18.5)	57 (15.6)
≥ 65 years	300 (81.5)	308 (84.4)
Sex		
Male	237 (64.4)	229 (62.7)
Female	131 (35.6)	136 (37.3)
Urgency of surgery*†		
Elective	356 (96.7)	352 (96.4)
Emergency	12 (3.3)	13 (3.6)
Baseline risk factors*‡		
Renal impairment	26 (7.1)	12 (3.3)
Diabetes mellitus	57 (15.5)	65 (17.8)
Pre-defined risk factor for cardiac or respiratory disease	117 (31.8)	118 (32.3)
Planned surgical procedure category†		
Upper gastrointestinal	110 (29·9)	114 (31·2)
Lower gastrointestinal	167 (45·4)	163 (44·7)
Small bowel +/- pancreas	86 (23·4)	84 (23·0)
Urological or gynecological surgery involving gut	5 (1·4)	4 (1·1)
ASA grade		
1	21 (5.7)	24 (6.6)
2	200 (54.5)	174 (48.1)
3	143 (39.0)	155 (42.8)
4	3 (0.8)	9 (2.5)
Planned location following surgery		
Critical care unit (level 3)	275 (74.7)	276 (75.6)
Critical care unit (level 2)	33 (9.0)	33 (9.0)
Post-surgical recovery unit	4 (1.1)	7 (1.9)
Ward	56 (15.2)	49 (13.4)

Table 2: Clinical management of patients during intervention period (during surgery and six hours following surgery)

Data presented as mean (SD), median (IQR) or n (%). Does not include one usual care patient randomized in error and four patients (three usual care patients and one hemodynamic therapy) who did not undergo surgery.

*** Two patients (one in each group) missing data on anesthetic technique**

† Two patients (both usual care) missing data on fluids both during surgery and during six hours following surgery; one patient (hemodynamic therapy algorithm) missing data on fluids during six hours following surgery; one patient (hemodynamic therapy algorithm) missing data on fluids during surgery; one patient (usual care) missing data on crystalloid during six hours following surgery; one patient (hemodynamic therapy algorithm) missing data on blood products during six hours following surgery

§Two patients (one in each group) missing data on vasopressor or inotrope agents both bolus and infusion; one patient (usual care) missing data on vasopressor or inotrope infusion

	Cardiac output-guided hemodynamic therapy algorithm (n=367)	**Usual care (n=362)**
Duration of surgery (minutes)	270 (200-350)	260 (195-360)
Anesthetic technique*		
General anesthetic only	107 (29.2)	105 (29.1)
General anesthetic plus epidural	259 (70.8)	256 (70.9)
Intravenous crystalloid (ml)†		
During surgery	1000 (459-2000)	2000 (1283-3000)
During six hours following surgery	506 (410-660)	600 (450-800)
Intravenous colloid (ml)†		
During surgery	1250 (1000-2000)	500 (0-1000)
During six hours following surgery	500 (250-1000)	0 (0-500)
Blood products (ml)†		
During surgery	141 (723)	95 (542)
During six hours following surgery	80 (555)	10 (66)
Bolus vasopressor or inotrope agent used during intervention period§	301 (82.2)	270 (74.8)
Infusion of vasopressor or inotrope (other than dopexamine) used during intervention period§	103 (28.1)	108 (30.0)
Actual location of care following surgery		
Critical care unit (level 3)	258 (70.3)	246 (68.0)
Critical care unit (level 2)	42 (11.4)	40 (11.0)
Post-surgical recovery unit	10 (2.7)	9 (2.5)
Ward	57 (15.5)	67 (18.5)

Table 3: Results for primary outcome

All data presented as n (%). Superficial and deep surgical site infection presented as single data point. The pre-defined complication 'Other infections of the urinary tract' did not occur in any patient. Does not include one usual care patient randomized in error and three patients (one usual care patient and two hemodynamic therapy) who withdrew consent. *Six patients (three hemodynamic therapy, three usual care) missing data on self-assessment of blinding of outcome assessment. †Includes three patients (two hemodynamic therapy, one usual care) who died within 30 days

	Cardiac output-guided hemodynamic therapy algorithm (n=366)	Usual care (n=364)	Relative risk (95% CI)	p-value
Composite				
Pre-defined moderate or major post-operative complications and mortality at 30 days following surgery	134 (36.6)	158 (43.4)	0.84 (0.71-1.01)	0.07
Individual elements				
Mortality	12 (3.3)	11 (3.0)		
Pulmonary embolism	4 (1.1)	1 (0.3)		
Myocardial ischemia or infarction	10 (2.7)	8 (2.2)		
Arrhythmia	39 (10.7)	40 (11.0)		
Cardiac or respiratory arrest	16 (4.4)	14 (3.8)		
Limb or digital ischemia	2 (0.5)	1 (0.3)		
Cardiogenic pulmonary edema	1 (0.3)	2 (0.5)		
Acute respiratory distress syndrome	3 (0.8)	4 (1.1)		
Gastrointestinal bleed	13 (3.6)	8 (2.2)		
Bowel infarction	2 (0.5)	5 (1.4)		
Anastomotic breakdown	12 (3.3)	16 (4.4)		
Paralytic ileus	20 (5.5)	27 (7.4)		
Acute psychosis	3 (0.8)	8 (2.2)		
Stroke	1 (0.3)	0 (0)		
Acute kidney injury	17 (4.6)	17 (4.7)		
Infection, source uncertain	11 (3.0)	9 (2.5)		
Urinary tract infection	9 (2.5)	9 (2.5)		
Surgical site infection	22 (6.0)	39 (10.7)		
Organ/space infection	20 (5.5)	36 (9.9)		
Bloodstream infection	6 (1.6)	15 (4.1)		
Nosocomial pneumonia	36 (9.8)	39 (10.7)		
Post-operative hemorrhage	6 (1.6)	4 (1.1)		
Self-assessment of blinding for outcome assessment*				
Assessor suitably blinded	342 (94.2)	349 (96.7)		
Assessor may have known allocation	9 (2.5)	6 (1.7)		
Assessor knew allocation†	12 (3.3)	6 (1.7)		

Table 4: Results for secondary outcomes

Odds ratios for all cause mortality at 30 days following surgery: unadjusted 1.09 (0.48-2.45); adjusted 1.20 (0.51-2.82); p=0.68

Odds ratios for all cause mortality at 180 days following surgery: unadjusted 0.63 (0.39-1.04); adjusted 0.61 (0.36-1.04); p=0.071

Data presented as median (quartiles) or n (%)

***For patients alive and in hospital on day 7 following start of surgery**

	Cardiac output-guided, hemodynamic therapy algorithm	Usual care	Relative risk (95% CI)	p-value
Post-Operative Morbidity Survey defined morbidity at 7 days following surgery*	182 (66.2) (n=275)	195 (67.9) (n=287)	0.97 (0.87-1.09)	0.72
Infectious complications at 30 days following surgery	87 (23.8) (n=366)	108 (29.7) (n=364)	0.80 (0.63-1.02)	0.08
Critical care free days at 30 days following surgery	27 (26-29) (n=366)	28 (25-29) (n=364)	--	0.98
All cause mortality at 30 days following surgery	12 (3.3) (n=366)	11 (3.0) (n=364)	1.08 (0.48-2.43)	1.00
All cause mortality at 180 days following surgery	28 (7.7) (n=363)	42 (11.6) (n=361)	0.66 (0.42-1.05)	0.08
Duration of post-operative hospital stay (days)	10 (7-14) (n=359)	11 (7-17) (n=356)	--	0.05
Survivors	10 (7-14) (n=343)	11 (7-17) (n=343)		
Non-survivors	7 (3-33) (n=16)	16 (9-36) (n=13)		