TITLE: EFFECT OF GOAL-DIRECTED HEMODYNAMIC THERAPY ON POSTOPERATIVE COMPLICATIONS: A MULTICENTER RANDOMIZED CONTROLLED TRIAL (FEDORA TRIAL).

ARTICLE TYPE: Original investigation

AUTHORS AND AFFILIATIONS:

José María Calvo-Vecino, Prof.* (1); Javier Ripollés-Melchor, MD* (1); Monty G Mythen, Prof. (2); Rubén Casans-Francés, P.D. (3); Andrej Balik, MD (3); Juan Pérez Artacho, MD (5); Eugenio Martínez-Hurtado, MD (1); Ana Serrano Romero, P.D. (5); Cristina Fernández Pérez, Prof. (6); and Soledad Asuero de Lis, Prof. (5)

1: Complutense University of Madrid, and Department of Anaesthesia, Hospital Universitario Infanta Leonor, Madrid, Spain. Evidence Anaesthesia Review Group (EAR)

2: University College London Hospitals National Institute of Health Research Biomedical Research Centre, UK

3: University of Zaragoza, Department of Anaesthesia, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain. Evidence Anesthesia Review Group (EAR)

4: Department of Anaesthesia; Hospital de Torrevieja, Torrevieja, Spain. 4: Department of Anaesthesia; Hospital de Vinalopó, Vinolopó, Spain.6: Department of Anaesthesia; Hospital Universitario Ramón y Cajal, Madrid, Spain. 7: Complutense University of Madrid, and Department of Public Health, Hospital Clínico San Carlos, Madrid, Spain.

***Corresponding authors**:

- Javier Ripollés-Melchor; Infanta Leonor University Hospital, Madrid, Spain. Gran Vía del Este 80, 28031, Madrid. ripo542@gmail.com, +34 620965143

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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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FEDORA trial Investigators Group: Ana Tirado Errazquin, MD; Cristina Gil Lapetra, MD; Rut Salvachua Fernández, MD; Ane Abad Motos, MD; Elena Garrido Reche, Phd ; Victor Carrero López, PhD; Javier Cambronero Santos, MD (Hospital Universitario Infanta Leonor, Madrid, Spain), Cristina Medraño Viñas, MD; Raúl Villaba, MD; Pilar Cobeta, MD; Eva Ureta, MD; María Montiel, MD; Nuria Mané, MD; Nilda Martínez Castro, PhD (Hospital Universitario Ramón y Cajal, Madrid, Spain), Eva Alarcón Aramburo, MD; Gema Aleson Horno, PhD; Rebeca Alonso Salas, MD; Carmen Bona García, MD; Marta L Ferrer Ferrer, MD; Marta Franco Abad, PhD; Ana C García Lecina, PhD; Julia Guillén Antón, MD; Guillermo Hojas Gascón, MD; Clara Marín Zaldivar, MD; Javier Peligero Deza, MD; Leticia Pérez Pascual, PhD; Tomás Ruiz Garcés, PhD; Ana T Roberto Alcácer, MD (Hospital

Clínico Universitario Lozano Blesa, Zaragoza, Spain), Marek Badura, MD; Eduardo Terrer Galera, MD (Hospital de Torrevieja, Torrevieja, Spain), Antonio Fernández Casares, MD and Maria Carmen Martínez Fernández, MD (Hospital de Vinalopó, Vinalopó, Spain) participated as study investigators.

Ángel Espinosa, MD (Orebro University Hospital, Orebro, Sweden), Alfredo Abad-Gurumeta, PhD (Hospital Universitario La Paz, Madrid, Spain) and Aarne Feldheiser, PhD (Campus Charité Mitte and Campus Virchow-Klinikum, Charité-University Medicine Berlin, Germany) served as scientific advisors. Francisco López Timoneda, Prof (Hospital Universitario Clínico San Carlos, Madrid, Spain); Alix Zuleta-Alarcón, PhD and Sergio Bergese, Prof (The Ohio State University Hospital, Columbus, USA) critically reviewed the study proposal.

ABBREVIATED TITLE

FEDORA trial: ODM-guided GDHT in major surgery.

CONFLICTS OF INTEREST

JMCV received honoraria and travel funding for lectures from Merck Sharp &Dohme, Deltex Medical and Fresenius Kabi.

JRM received travel funding from Deltex Medical and honoraria for lectures from Fresenius Kabi, Edwards Lifesciences, Deltex Medical and Merck Sharp & Dohme.

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AB, JPA, ASR, EMH, CFP and SAL claim no conflict of interest.

ABSTRACT

Background: The aim of this study was to evaluate postoperative complications in patients having major elective surgery using Oesophageal Doppler Monitor (ODM) guided Goal-Directed Hemodynamic Therapy (GDHT), in which administration of fluids, inotropes, and vasopressors was guided by stroke volume (SV), mean arterial pressure (MAP), and cardiac index (CI).

Methods: This was a prospective, multicentre, randomized, parallel-group, controlled patient- and observer-blind trial (ISRCTN93543537) conducted in adults scheduled for major elective surgery. Randomization and allocation were carried out by central computer system. In the control group, intraoperative fluids were given based on traditional principles. In the GDHT group, the intraoperative goals were to maintain a maximal SV, with MAP > 70mmHg, and CI $\geq$ 2.5 $L*min^{-1}*m^{-2}$. The primary outcome was percentage of patients with postoperative complications during the first 180 days after surgery.

Results: 450 patients were randomized to the GDHT group (n=224) or to the control group (n=226). Data from 428 patients were analysed. The percentage of patients with complications was significantly lower in the GDHT group (15% vs.27.6% p=0.001). There were also fewer specific complications (acute kidney disease, pulmonary oedema, respiratory distress syndrome, wound infections etc), and the length of hospital stay was shorter in the GDHT group.

Conclusions: ODM-guided GDHT using SV, CI and MAP decreased postoperative complications in patients having major surgery.

INTRODUCTION

Approximately 240 million anaesthesia procedures are performed annually worldwide[1]. Of these, approximately 10% are in high-risk patients. Although there is no consensus on the definition of "high-risk" patients[2], this group of patients probably accounts for more than 80% of perioperative deaths[3]. Moderate-risk surgery is much more common and constitutes about 40% of total surgical procedures. Nearly 30% of moderate-risk surgical patients experience minor postoperative complications, most often affecting gastrointestinal tract, and including delayed enteral feeding, paralytic ileus, nausea or vomiting, and wound complications[4]. Even minor complications prolong hospital stay[5] and increase healthcare costs[6], and, more importantly, can reduce long-term survival[7]. The European Surgical Outcomes Study (EUSOS) in patients having non-cardiac surgery concluded that in-hospital mortality rate was high (4%) and varies substantially among European countries[8]. There were also large differences in post-surgery mortality among hospitals within each country, suggesting that there is a potential to improve survival after surgery[9 10]. Many postoperative complications are thought to be related to tissue hypoperfusion and an imbalance between oxygen delivery and consumption[11]. Perioperative fluid management strongly influences patient outcomes[12–14]. Paradoxically, despite existence of national guidelines[15 16] and international recommendations[17–20], there remains wide variability in hemodynamic monitoring[21] and type and volume of administered fluids[22 23].

Goal-directed hemodynamic therapy (GDHT) is a method aiming at optimal dosing and timing of fluids, inotropes, and vasopressors through monitoring of cardiac output (CO) and other hemodynamic parameters. Various studies suggested that GDHT helps prevent organ hypoperfusion and fluid overload, thereby reducing the rate of postoperative complications[24]. However, the OPTIMISE trial[12] and other recent

studies[25–27] suggested that the benefits associated with GDHT may be lower than previously reported, and that GDHT may even worsen patient outcomes if combined with a liberal maintenance regimen[28]. In particular, the usefulness of Oesophageal Doppler monitoring to guide GDHT has recently been questioned[29 30].

We carried out a controlled randomized clinical trial to study the effect of ODM-guided administration of intravenous fluids and vasopressor and inotropic drugs on postoperative complications after major surgery. Specifically, we tested the hypothesis that Doppler guided management reduces postoperative complications.

METHODS

This was a randomized controlled clinical trial performed at 5 centres in Spain between 2011 and 2014. Patients were recruited at Hospital Universitario Infanta Leonor, Madrid; Hospital Universitario Ramón y Cajal, Madrid; Hospital Clínico Universitario Lozano Blesa, Zaragoza; Hospital de Vinalopó, Alicante; and Hospital de Torrevieja, Alicante. Unidad Española de Evaluaciones Sanitarias (Agencia Laín Entralgo, Madrid, Spain) supported this study, approved by the Ethics Committee of the Hospital Universitario Gregorio Marañón, Madrid (HUIL 2011-02-22), and registered by the principal investigator (JMCV) in the primary clinical trial registry ISRCTN (ISRCTN93543537). The Ethics Committee at each centre approved the study protocol; the trial was conducted according to the original protocol, which remained unchanged throughout the duration of the trial. The full study protocol (in Spanish) is available upon request, and the summarized English version can be accessed at http://www.eargroup.es/.

The manufacturer of the ODM system used for CO monitoring (Deltex Medical Ltd., Chichester, United Kingdom) provided training to all investigators before the start of the clinical trial. Written informed consent was obtained from all patients prior to surgery. Principal investigators (JMC and SAL) performed site visits for source data verification.

Study population

Eligible patients were subjects of 18 years of age or older and scheduled for major abdominal, urological, gynaecological, or orthopaedic surgery under general anaesthesia, using laparoscopic or open approaches. Surgery was considered major if it fulfilled at least one of the following criteria: expected duration ≥2 hours, estimated

blood loss greater than 15% of blood volume, transfusion requirements of at least 2 packs of red blood cells. Exclusion criteria were emergency surgery, American Society of Anaesthesiology (ASA) patient classification status[31] exceeding III, contraindications for ODM monitoring, or aortic pathology that could lead to misinterpretation of hemodynamic variables (i.e., intra-aortic balloon pumping, or aneurysms of the thoracic aorta). The principal investigator at each site evaluated eligibility, obtained informed consent, and enrolled participants.

Study design

This was a randomized, controlled, multicentre, parallel-arm, patient- and observer-blind superiority trial. Randomization was performed through a secure web-based system provided by 'Agencia Laín Entralgo' (Madrid, Spain). Eligible participants were randomized 1:1 ratio to the intervention or control groups. Allocation details were concealed in sequentially numbered, opaque, sealed and stapled envelopes. The envelopes were opened by the investigator on the day of surgery, when patients were randomized. Patients and physicians who collected data and evaluated patients during the postoperative period were blinded to the treatment allocation. However, it was impossible to blind the researchers who performed hemodynamic monitoring.

All patients received balanced anaesthesia, intravenous anaesthetic induction, and neuromuscular relaxants; for pragmatic reasons, their administration was made at the discretion of the anaesthesiologist. Bispectral Index monitoring system (BIS, Medtronic, Dublin, Ireland) was used to monitor the depth of anaesthesia. Sevoflurane was used for anaesthesia maintenance, with the target range of BIS values between 40-60. Epidural anaesthesia, central venous catheter placement and invasive radial arterial

blood pressure monitoring were performed per preference of the anaesthesiologist. All patients had basic anaesthetic monitoring with five-lead-electrocardiogram, pulse oximetry, and oscillometric blood pressure; at least one peripheral intravenous line was established. All patients received standard measures to maintain oxygen saturation by pulse oximetry ≥ 94%, normothermia, and heart rate (<100 beats min^{-1}). Ventilation with inspired oxygen fraction of 60% was mechanically controlled to maintain $P_{arterial}\ CO_2$ between 35 and 45 mmHg, with a positive end-expiratory pressure of 4-6 mmHg and tidal volume of 6-8 ml kg^{-1}.

In both groups, blood loss was compensated for by infusion of colloid in a 1:1 ratio. Packed red cells were transfused when haemoglobin level was < 10 g dl^{-1} in patients with cardiac comorbidities, or below 7 g dl^{-1} in those without cardiac comorbidities).

Control group

During the intraoperative period, patients randomized to the control group received a continuous infusion of balanced crystalloid fluids (Ringer lactate) at an infusion rate of 3-5 ml kg^{-1} h^{-1} in case of laparoscopic surgery, and 5-7 ml kg^{-1} h^{-1} in case of open surgery. They were also allowed to receive colloid solution (hydroxyethyl starch [HES] 6% 130/0.4, Voluven®, Fresenius Kabi, Germany), vasopressors and inotropes based on the judgment of the anaesthesiologist in charge. Intraoperative treatment goals in the control arm were flexible to avoid both extremes of clinical practice and practice misalignment[32].

GDHT group

Patients in the intervention group were given intravenous fluids, vasopressors, and inotropes according to a hemodynamic algorithm as shown in Figure 1. Intraoperative hemodynamic monitoring was conducted using oesophageal Doppler (CardioQ, EDM; Deltex Medical, Inc., Chichester, UK). The hemodynamic protocol was initiated after insertion of the probe. At the beginning of surgery, patients received an initial hemodynamic assessment based on stroke volume (SV), cardiac index (CI) and mean arterial pressure (MAP). First, preload was optimized by crystalloid loading to achieve and maintain a maximal SV. In addition to routine fluid management, the patients were given 250 ml boluses of crystalloid solution. If the SV increased by 10% or more, the fluid challenge was repeated. If, after two crystalloid boluses, the patient required more fluids to optimize SV, colloid (HES) boluses were given. The fluid challenges of 250 ml were repeated until the SV failed to rise by 10%. At this point, the patient's individual preload was considered optimized, and SV was determined and used as the hemodynamic goal until the end of surgery. No further colloid fluid boluses were given until a 10% decrease in SV occurred. In patients with no response to fluid challenge, inotropes were given to reach a minimum CI (2.5 l min^{-1} m^{-2}), which served as a safety parameter to prevent low CO. If SV was optimized and CI was within the target range but MAP was below 65 mmHg, vasopressors were given. Every 5 minutes, patients were reassessed to maintain the values within the desired range, and hemodynamic data were recorded. The hemodynamic protocol started immediately after probe placement, and continued until the end of the surgery. At the end of surgery total catecholamine administration, estimated blood loss, urine output, and infused fluid volume were recorded.

End points

The primary end point was the percentage of patients who developed pre-defined postoperative complications in the 180 days after surgery, including complications that occurred before hospital discharge and those that happened after discharge and required ambulatory or in-hospital care. Data were obtained from patient history and by telephone follow-up at 180 days after surgery. Initial definition of postoperative complications was based on the guidelines of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) published in 2011[33]. However, after the standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine (EPCO) guidelines[34] were updated in 2014, the definition of postoperative complications in the study were updated to align with the new standards[35], a change that was made before unblinding and data analysis.

Secondary end points were: length of hospital stay (defined as the number of days spent in the hospital from the day of surgery to hospital discharge or death), length of stay in the intensive care unit, re-interventions, time to onset of oral tolerance and time to ambulation, and all-cause mortality at 180 days following surgery.

Sociodemographic and clinical data, ASA physical status[31], comorbidities, and preoperative haemoglobin were recorded at baseline. Functional status was described via metabolic energy equivalents (METS)[36].

Data were recorded in case report forms at each site by blinded investigators; postoperative data were obtained from clinical records completed by surgeons and anaesthesiologists responsible for patient care (blinded to the allocation). Data were uploaded in the database created for the study; this database could be accessed only by the trial principal investigator and the statistician (JMCV, CFP), who analysed the data.

Data validation was conducted by the principal investigator and an external advisor (AAG). The study was performed and is reported in accordance with the CONSORT guidelines[35].

Statistical analysis

Sample size calculation was based on a meta-analysis of randomized clinical trials of ODM in colorectal resection, which reported a 30% incidence of complications in the ODM group, compared to 49% in the control group[37]. One hundred five patients per arm would be needed to detect a 19% difference in the incidence of complications between GDHT and control with a power of 80% and an alpha error of 0.05. We thus planned to recruit equal number of patients for each type of surgery (abdominal, urological, gynaecological, or orthopaedic), resulting in a total of 840 patients. Due to low recruitment, we decided to exclude “post hoc” the Orthopaedic subgroup for analysis of complications and their severity.

The analysis was carried out on a modified intention to treat basis (all randomized patients who received the study treatment). Qualitative variables were described using frequency distribution, and quantitative variables were described by mean and standard deviation (SD) in case of normal distribution or median and interquartile range (IQR) in case of asymmetric distribution.

Potential confounders were selected to adjust the primary effect of the study. The primary outcome was expressed as percentage of patients with postoperative complications in each group. Odds ratios and 95% confidence intervals (95% CI), both univariate and adjusted to a logistic model with bootstrap estimate, were calculated. Each complication was classified as type 0, 1, 2 or 3 depending on its severity according

to the EPCO guidelines[34], describing the severity reached as mean and standard deviation and analyzed by Student's T test. Quantitative secondary objectives were assessed using Mann-Whitney nonparametric test. For all statistical tests, the significance level was set to 0.05. Calculations were performed using JMP 13.1 and R 3.3.2 statistical packages. An interim analysis was performed at the halfway point. No adjustments in statistical power or alpha error were made.

RESULTS

A total of 450 patients were enrolled, and 428 were randomized between 2011 and 2014. Two hundred twenty-four patients were allocated to the GDHT algorithm, and 226 to the standard care. Twenty-two patients did not receive study treatment and were not included in the analysis (Figure 2). There were no cases of lost-to-follow-up. The resolution of the Committee on Pharmacovigilance Risk Assessment (PRAC) of the European Medicines Agency (EMA) / 606.303 of October 2013[38], recommended not to use 6% HES in septic, burned and critically ill patients, as well as in clinical trials and in situations of hypovolemia[39]. The confusion generated by the restrictions in the use of HES led to a major decrease in recruitment, since HES was the only colloid permitted by the study protocol. Because of the drop in recruitment we were forced to stop the trial in 2014. Thus, only 214 patients per arm (GDHT or control, with the 4 types of surgery pooled together) were included.

Baseline patient characteristics were similar between the groups (Table 1), although there were more patients with diabetes mellitus, chronic obstructive pulmonary disease, and chronic alcohol consumption in the GDHT arm (Table 1). There were more patients with ASA physiological status III in the GDHT group. Mean surgery duration was similar between the two groups. Most of the study patients were undergoing major gastrointestinal surgery, while the number of those undergoing orthopaedic surgery was relatively small. Distribution of patients between the surgery categories and approaches was similar in the two arms (Table 2).

Only one patient suffered nasal trauma with epistaxis caused by nasal insertion of the oesophageal probe.

The percentage of patients who experienced complications was lower in the GDHT group than in control group [14.95% vs. 27.6%, p=0.001, Odds Ratio = 0.46 (95% CI: 0.29-0.75; relative risk reduction = 45.7%, Figure 3], as well as the severity of complications were also lower (Figure 4). There were significant fewer patients with acute kidney injury (AKI), acute respiratory distress syndrome, acute pulmonary oedema, pneumonia, and superficial and deep surgical site infection in the GDHT group. No significant differences in other analysed complications were observed. Notably, we found no significant difference in the incidence of anastomotic breakdown between the groups [3 (1.4%) patients in the GDHT group versus 8 (3.7%) patients in the control group]. The "post hoc" exclusion of the orthopaedic subgroup did not modify the analysis results (Figure 3 and 4).

Analysis of secondary outcomes revealed a significant reduction in length of hospital stay (p=0.002), length of UCI stay (p<0.001), length of complication-related hospital stay (p=0.01), time to onset of oral tolerance (p<0.001) and time to ambulation (p<0.001) in the GDHT group (Figure 5). There was no significant difference in the percentage of patients that were re-operated [13 (6%) patients in the GDHT group versus 25 (11.6%) patients in the control group], or in all-cause mortality at 180 days of follow-up [10 (4.6%) patients in the GDHT group versus 9 (4.25%) patients in the control group]. Blood losses and overall volume of intra-venous colloid and crystalloid fluids infused during the intraoperative period was similar the GDHT and control groups. Volume of fluids administered postoperatively, as well as use of vasoactive drugs (norepinephrine and dobutamine) was comparable between the groups (Figure 5 and Table 2).

DISCUSSION

Use of a hemodynamic optimization algorithm for management of low-moderate risk patients having major abdominal surgery significantly reduced postoperative complications in the 180 days after surgery. There was a decrease in AKI, acute respiratory distress syndrome, acute pulmonary oedema, pneumonia, and superficial and deep surgical site infection. Moreover, length of hospital stay was shortened, although no differences in mortality at 180 days after surgery were found.

Hemodynamic monitoring and responsive fluid administration are supposed to allow for early detection of warning signs and for prompt problem rectification thus preventing organ damage related to inadequate oxygen supply. Adjustments in the administration of fluids and drugs must be performed in a timely manner to avoid both insufficient organ perfusion and fluid overload[40]. Numerous trials and meta-analyses showed that a goal-directed approach of haemodynamic optimisation reduces postoperative complications and mortality in high-risk surgical patients[12 41 42], regardless of the choice of monitoring method or target variables[43–45]. However, a recent meta-analysis and several trials[26 30 46], suggested that the GDHT benefits might be less pronounced than previously believed, especially in low-moderate risk patients. Thus, the question of whether GDHT improves postoperative outcomes is still under debate[47–49]. In addition, it should be noted that previous studies[12 28] analyzed moderate or severe complications, while low-severity complications were not considered. In our study, although we also found a statistically significant decrease in moderate-severe complications, most of the complications that occurred were low-severity.

Several reasons could explain the observed discrepancies between different trials. One of them is ample differences in trial design, patient populations, hemodynamic protocols in the intervention groups and standard of care in the control groups. The

other reason in many cases is low sample size and insufficient statistical power to demonstrate the differences. Thus, for instance, in studies by Pearse et al. and Pestaña et al., the researchers found a decrease in the complication incidence in the GDHT group, but it was not statistically significant[12 25].

In our study, there were significantly fewer patients with AKI in the intervention group, despite similar net amounts of perioperative fluids, both crystalloid and colloid, and no differences in the number of patients intraoperatively treated with vasopressors and inotropes. Several studies showed that GDHT decreases the incidence of postoperative AKI[50], including when, as in our study, the amounts of perioperative fluids administered to intervention and control arms were similar[51]. This suggests that the benefits of GDHT could be attributed not only to providing additional fluids where required, but also to guided and responsive fluid usage and to avoiding unnecessary fluid delivery when hemodynamic objectives are met[52].

While there is a general agreement that GDHT is beneficial in high-risk surgical patients[41 53] the use of GDHT in surgical patients with low-moderate risk is still controversial[14 54]. SV optimization could lead to fluid overload[28] (24), especially in cases with a liberal fluid maintenance[46]. A systematic review[55] and recent randomized controlled trials demonstrated that liberal administration of fluid and salt could be deleterious compared to a more restrictive regimen[56 57]. Many centres now recommend a baseline intraoperative crystalloid regimen of 1.5ml kg^{-1} h^{-1} [17]. Against this background, our trial could be criticized for an excessively liberal standard fluid regimen. Indeed, we used a fluid maintenance currently considered liberal[28], however, it was more restrictive than what was considered liberal when the study was initiated (perioperative infusion greater than 5 litres/24 hours)[28 46]. Although GDHT allows for personalized titration of

intraoperative intravenous fluids, it is possible that aiming at a neutral perioperative fluid balance is adequate for patients with sufficient physiological reserve to correct minor disturbances in homeostasis.

Although retrospective studies with a similar algorithm have been conducted in the past[58], this is, to our knowledge, the first randomized controlled clinical trial where vasopressor and inotropic treatment were incorporated as security measures to treat episodes of hypotension or low CI in patients with optimized SV. Our results are consistent with previous studies in which the CI was used as a target (54) or as a safety measure[44]. A recent review and meta-analysis also concluded that outcomes were improved when vasopressors and inotropes were incorporated in the hemodynamic algorithm[59]. SV hemodynamic optimization proved superior to CI optimization when haemorrhagic shock was induced in experimental animals[60].

Infectious complications were significantly reduced in the GDHT group. These findings are consistent with a recent meta-analysis demonstrating that GDHT reduced surgical site infections and pneumonia[61]. Despite fewer patients with complications mortality was similar at 180 days. Nonetheless, it is possible that a longer-term follow-up would help to reveal an effect on post-surgery deaths[53].

The strengths of the study include its randomized and controlled nature and large sample size. To our knowledge, this is one of the largest controlled clinical trials on ODM-guided GDHT. Our pragmatic approach increases its external validity by approximating routine clinical practice.

Our study has also limitations. First, the person performing intraoperative hemodynamic monitoring was not blinded. To compensate for this, blinded researchers performed data collection and followed the patients after the surgery. Second, although the

outcomes were properly pre-defined, it is possible that some subjectively perceived postoperative complications might have been underestimated due to intrinsically less accurate analysis. Third, the postoperative fluid management in the ICU was not standardized. Although overall postoperative fluid volumes infused were similar, we do not have details about exact timing of fluid administration cannot exclude the possibility that poor postoperative fluid management skewed the effects of intraoperative fluid optimization. Forth, the discharge criteria were not predefined in our study, which can limit the interpretation of length of stay parameters. Undoubtedly, length of hospital stay is an important factor for the patient and for the healthcare system. However, it is obvious that it is affected by many aspects besides postoperative complications, including patients' preoperative fitness and health, but also the social, structural, and logistical aspects of each individual patient and each health care system. Finally, although recruiting large groups of patients undergoing different types of surgery was initially planned, the actual patient population was largely composed of abdominal surgery patients, with only few subjects undergoing orthopaedic surgery. Thus, to clarify the effect of GDHT in urological, gynaecological, and orthopaedic surgery patients, further studies are warranted.

CONCLUSIONS

The use of ODM-guided hemodynamic algorithm reduced the incidence of postoperative complications and length of hospital stay in adult patients having major surgery. However, mortality at 180 days was not affected.

AUTHORS' CONTRIBUTIONS

JMCV participated in the study design and data acquisition, analysis and interpretation, critically revised the manuscript for important intellectual content, and supervised the research. JRM participated in design of the study and data acquisition, analysis and interpretation, supervised the research, and drafted the manuscript. SAL participated in the study design and data acquisition and critically revised the manuscript for important intellectual content. MM participated in the data interpretation, critically revised the manuscript for important intellectual content and supervised the research. RCF and CFP participated in data acquisition and statistical analysis and critically revised the manuscript for important intellectual content. EMH, AB, ASR and JPA participated in data acquisition and interpretation, and revised the manuscript critically for important intellectual content data. All authors read and approved the final manuscript.

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Ángel Espinosa, MD (Orebro University Hospital, Orebro, Sweden), Alfredo Abad-Gurumeta, PhD (Hospital Universitario La Paz, Madrid, Spain) and Aarne Feldheiser, PhD (Campus Charité Mitte and Campus Virchow-Klinikum, Charité-University Medicine Berlin, Germany) served as scientific advisors. Francisco López Timoneda, Prof (Hospital Universitario Clínico San Carlos, Madrid, Spain); Alix Zuleta-Alarcón, PhD and Sergio

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AB, JPA, ASR, EMH, CFP and SAL claim no conflict of interest.

TABLES AND FIGURES

Table 1. Baseline and demographic characteristics

Table 2. Type of surgery and perioperative clinical management characteristics

Figure 1. Haemodynamic algorithm in Goal-Directed Hemodynamic Therapy group. CO: Cardiac output, SV: Stroke volume, SVV: Stroke volume variation, CI: cardiac index, MAP: mean arterial pressure.

Figure 2. Consort Flow diagram

Figure 3: Analysis of postoperative complications

Figure 4. Grade of severity of postoperative complications according to European Perioperative Clinical Outcome guidelines

Figure 5. Secondary outcomes

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