Perioperative Goal-Directed Hemodynamic Optimization Using Noninvasive Cardiac Output Monitoring in Major Abdominal Surgery: A Prospective, Randomized, Multicenter, Pragmatic Trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery)

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BACKGROUND: In this study, our objective was to determine whether a perioperative hemodynamic protocol based on noninvasive cardiac output monitoring decreases the incidence of postoperative complications and hospital length of stay in major abdominal surgery patients requiring intensive care unit admission. Secondary objectives were the time to peristalsis recovery and the incidence of wound infection, anastomotic leaks, and mortality.

METHODS: A randomized clinical trial was conducted in 6 tertiary hospitals. One hundred forty-two adult patients scheduled for open colorectal surgery, gastrectomy, or small bowel resection were enrolled. A hemodynamic protocol including fluid administration and vasoactive drugs based on arterial blood pressure, cardiac index, and stroke volume response was compared with standard practice. Patients were followed until hospital discharge (determined by a surgeon blinded to the study) or death. In contrast to previous studies, we designed a pragmatic trial (as opposed to explanatory trials) to mimic real practice and obtain maximal external validity for the study.

RESULTS: Fluid administration was similar except for the number of colloid boluses (2.4 ± 1.8 [treated] vs 1.3 ± 1.4 [control]; $P < 0.001$) and packed red blood cell units (0.6 ± 1.3 [treated] vs 0.2 ± 0.6 [control]; $P = 0.019$). Dobutamine was used in 25% (intraoperatively) and 19.4% (postoperatively) of the treated patients versus 1.4% and 0% in the control group ($P < 0.001$). We have observed a reduction in reoperations in the treated group (5.6% vs 15.7%; $P = 0.049$). However, no significant differences were observed in overall complications (40% vs 41%; relative risk 0.99 [0.67–1.44]; $P = 0.397$), length of stay (11.5 [8–15] vs 10.5 [8–16]; $P = 0.874$), time to first flatus (62 hours [40–76] vs 72 hours [48–96]; $P = 0.180$), wound infection (7 vs 14; $P = 0.085$), anastomotic leaks (2 vs 5; $P = 0.23$), or mortality (4.2% vs 5.7%; $P = 0.67$).

CONCLUSIONS: The results of our pragmatic study indicate that a perioperative hemodynamic protocol guided by a noninvasive cardiac output monitor was not associated with a decrease in the incidence of overall complications or length of stay in major abdominal surgery. (Anesth Analg 2014;XXX:00–00)

Fast-track surgery is a multimodal approach involving surgeons, anesthesiologists, nurses, and physical therapists that focuses on enhancing recovery and reducing morbidity by implementing evidence in different fields of perioperative care.[1] Many aspects of surgical care, including anesthesia, analgesia, reduction of surgical stress, temperature control, nutrition, minimally invasive surgery, and others, have shown to improve outcome[1] and are included in the Enhanced Recovery after Surgery

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(ERAS) pathway. Perioperative fluid management, individualized goal-directed therapy (GDT), and cardiovascular optimization have received increased interest recently. The choice between liberal versus restrictive perioperative fluid therapy[2–7] and the type of fluid used[3,8] have been debated. Liberal and restrictive intravascular volume regimens are not well-defined, so patients can be assigned to different groups depending on the study design.[6] The use of GDT for intravascular volume replacement has been proposed with inconclusive results.[9–12] Some studies have included the use of vasoactive drugs in the hemodynamic protocol mostly showing beneficial effects.[13–20] Cardiovascular optimization has been achieved using different hemodynamic goals.[9–15,17–21] Most of these studies have been performed during the intraoperative period,[9–12,15,17] and only a few have analyzed the immediate postoperative[16,18] or perioperative (including surgery and the first postoperative 24 hours) periods.[13,14,19,20] All these studies share the need for invasive monitoring: esophageal probe,[9,11] arterial catheter,[10,12,15–18] or a pulmonary artery catheter.[13,14,19,20] Several meta-analyses have concluded that hemodynamic optimization improves outcome in high-risk surgical patients,[8,22,23] and all forms of monitoring appear to be effective. However, most of the studies are single-center, unblinded, include a small number of patients, and the presence of significant heterogeneity and inconsistency limits the strength of the evidence. Besides, the lack of benefits observed in some studies including a large multicenter trial casts doubts on the generalization of this approach.[1,14,16]

The NICOM™ (Cheetah Medical, Washington, DE) is a noninvasive cardiac output monitoring device based on chest bioreactance that has been validated in clinical practice.[24,25] The NICOM requires the connection of 4 double-electrode stickers symmetrically placed on the thorax. The upper electrode pair delivers a small alternating current, and the lower pair analyzes the variation in the frequency spectra of the delivered current (bioreactance). The time delay between the applied current and the measured voltage ("phase shift") is correlated with cardiac stroke volume and allows the monitoring of cardiac output.

We analyzed in a randomized controlled trial whether a perioperative GDT based on noninvasive hemodynamic monitoring aiming at the optimization of arterial blood pressure and cardiac output is associated with a decrease in hospital length of stay (LOS) and the incidence of postoperative complications in major abdominal surgery patients requiring postoperative intensive care unit (ICU) admission compared with standard practice. Our secondary objectives were the time to peristalsis recovery (first flatus) and the incidence of wound infection, anastomotic leaks, and hospital mortality.

METHODS

This randomized, multicenter clinical trial (clinicaltrials.gov Identifier: NCT01217151) was conducted in 6 tertiary hospitals (5 in Spain and 1 in Israel) between January 2011 and August 2012. During the study, none of the hospitals was following the ERAS pathway. The study was approved by the local ethics committee of each participating center, and all patients gave their signed informed consent. Patients were followed until hospital discharge (determined by a surgeon not involved in the study) or death.

Study Participants

Adult patients scheduled for open colorectal surgery, gastrectomy, or small bowel resection were eligible for the study. Patients were excluded if not requiring ICU admission or in case of laparoscopic or emergency surgery, abdominal procedures not related to the above mentioned, intra-abdominal infection, life expectancy <60 days, and disseminated malignancy. ICU admission was decided based on local standard protocols.

Study Design

Patients were screened for eligibility by a member of the research team. Patients meeting inclusion criteria were randomized (ratio 1:1, stratified by center) and assigned to GDT or control groups by computer-generated random sequence. The assignment of study groups was placed in serially numbered opaque envelopes. Patient characteristics and clinical data, including ASA physical status and the Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (P-POSSUM)[26] to adjust surgical risk, were recorded. The use of bowel clearance procedures and the amount of fluids administered in the 12-hour period before surgery were also registered.

In the control group, hemodynamic management was performed according to the institution's standard of care, using fluids and vasoactive drugs at the discretion of the anesthesiologist, and the ICU specialist. In the GDT group, hemodynamic management followed a protocol aiming at maintaining both a mean arterial blood pressure (MAP) ≥65 mm Hg and a cardiac index (CI) ≥2.5 L/min/m^2 (intra- and postoperatively; Fig. 1). Measurement of noninvasive cardiac output was initiated before the induction of anesthesia. For intravascular volume replacement, crystalloids (lactated Ringer's solution or saline 0.9%) were infused following standard procedures according to the anesthesiologist or ICU specialist. Both the MAP and the CI were assessed every 5 minutes, and volume boluses (250 mL colloid in 10 minutes, starch or gelatin following local practice) and/or vasoactive drugs (dobutamine, norepinephrine) were added as necessary to achieve the hemodynamic goals. The protocol was instituted after the induction of anesthesia and continued for 24 hours after ICU admission.

In all cases, the anesthetic procedure, including the placement of an epidural catheter, was decided by the responsible anesthesiologist. Packed red blood cells were administered at the discretion of the anesthesiologist (our perioperative care protocol only suggested to use a hemoglobin level of 7 g/dL as a threshold for healthy patients and 9 g/dL in patients with pulmonary or cardiac disease). Patients' lungs were ventilated (F_{IO_2} ≥0.5) with a tidal volume of 8 mL/kg (ideal body weight) and an initial respiratory rate of 12 breaths/min adjusted to achieve an end-tidal CO_2 between 30 and 40 mm Hg. Pain control was achieved according to local standard procedures: epidural catheter (if present) or patient-controlled analgesia devices with morphine (if included in local protocols).

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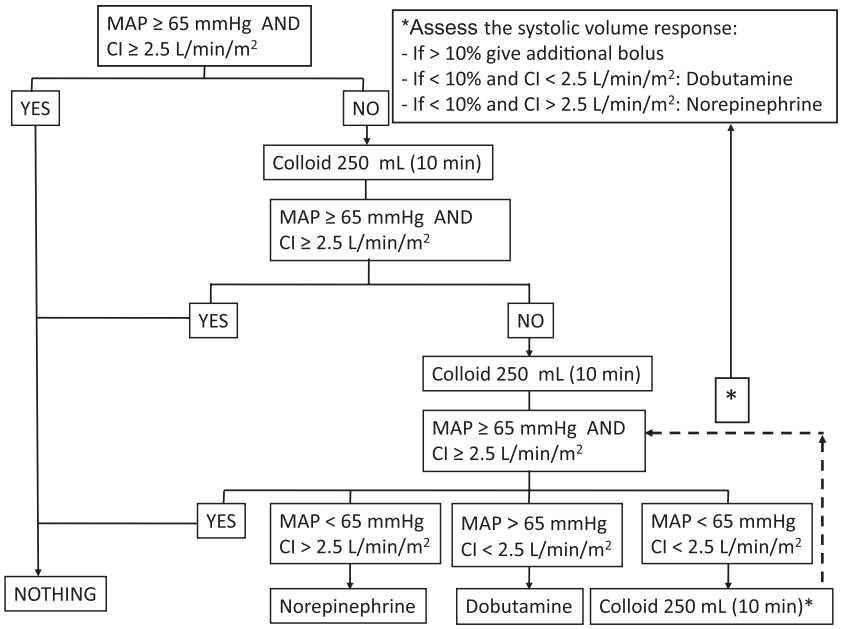

Figure 1. Goal-directed therapy protocol. MAP = mean arterial blood pressure (mm Hg). CI = cardiac index (L/min/m²).

Intraoperative data included the duration of the procedure, fluid input and output (diuresis, hemorrhage), the use of vasoactive drugs, and the occurrence of prespecified complications. Fluid balances were defined.

On admission to the ICU, MAP, heart rate, temperature, hemoglobin, and lactate were recorded. The duration of mechanical ventilation (MV, hours) and ICU stay (days) included the sum of all periods of MV and ICU stay during hospital admission.

Outcome

Hospital LOS was defined as the number of days from the day of surgery to hospital discharge or death. Discharge was decided by surgeons blinded to study group allocation. Morbidity was expressed as the sum of all prespecified complications. Renal failure was defined as at least a doubling of serum creatinine or oliguria (<500 mL/24 hours). Pulmonary edema or circulatory failure (sustained low cardiac output and hypotension) not related to infection was considered cardiac failure. Infections were defined according to standard criteria (see text, Supplemental Digital Content 1, http://links.lww.com/AA/A911). Secondary variables included the time to first flatus (considering time zero the end of surgery), the presence of wound infection or anastomotic leaks, and any cause mortality.

Data were recorded on a case report file by the principal investigator at each center and included in a database created for this study. Data were obtained from the clinical files completed by the surgeons responsible of the patient (blinded to the study). Validation of the data (conformity between the case report file and the database, screening for internal coherence of recorded values, detection of abnormalities, and discrepancies according to the plan of controls previously prepared) was performed by the principal investigator.

Sample Size

Based on previous literature, we estimated that any complication may appear in 65% of cases (Supplemental Digital Content 2, http://links.lww.com/AA/A912), and we considered a reduction from 65% to 40% clinically relevant. Assuming a 2-sided type I error rate of 5% and a power of 80%, we calculated that a sample size of 140 patients would be required to detect a reduction in the proportion of patients developing complications from 65% in the control group to 40% in the GDT group (χ^2 test). With respect to hospital LOS, a sample size of 70 in each group would have an 80% power to detect a probability of 0.637 that an observation in group GDT was less than an observation in the control group using a Wilcoxon (Mann-Whitney) rank-sum test with a 0.05 two-sided significance level.[27]

Statistical Analysis

Qualitative data are described as absolute and relative frequencies and quantitative data by mean ± standard deviation (SD) or median (25th and 75th percentile). A Cochran and Mantel-Haenszel statistics test stratified by center was used to compare the GDT and control groups in terms of incidence of complications. For qualitative data, differences between groups were tested by the Pearson χ^2 test and for quantitative data by the Student *t* test or the Mann-Whitney rank-sum test if the distribution of the variable departed from normality. In the case of LOS, WMWodds was also calculated from the receiver operating characteristic model area under the curve.[27,28] Adjusted regression models using predefined variables (P-POSSUM and fluid balance) were performed by interaction contrasts. Statistical significance was defined as a *P* value ≤0.05. Statistical analysis was performed with the Stata 12 (StataCorp LP, College Station, TX).

RESULTS

One hundred forty-two patients (control 70, GDT 72) were included in the study between January 2011 and August 2012 (Fig. 2). No difference between groups was observed in patient characteristics, comorbidity, bowel clearance, surgical procedure, or perioperative use of epidural catheters (Table 1). Nine patients in the GDT group did not complete

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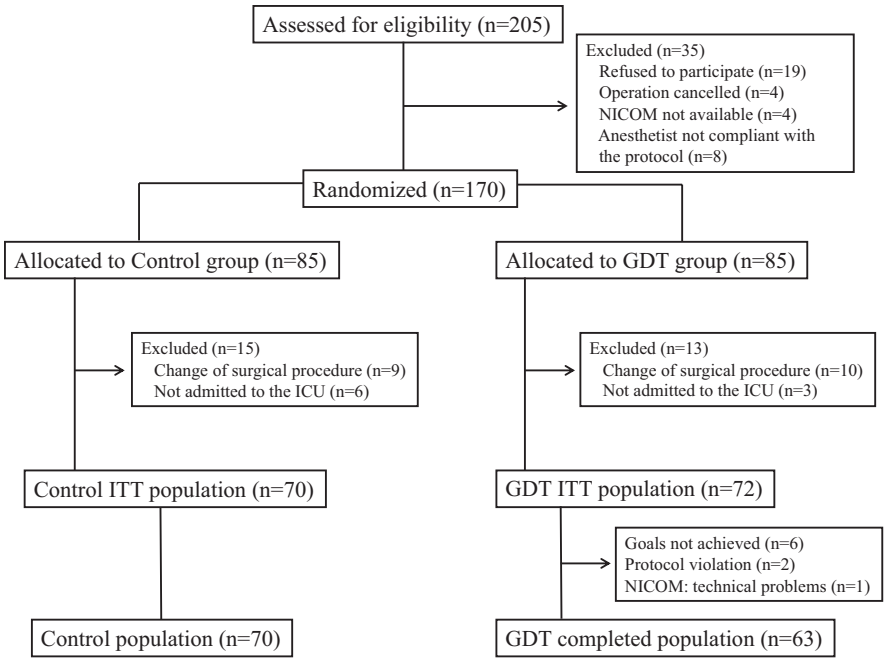

Figure 2. Flow of participants. GDT = Goal-directed therapy. ITT = Intention-to-treat.

the protocol. In 1 case, it was due to technical problems with the NICOM after induction of anesthesia. In the remaining 8 cases, dobutamine was not used, despite being indicated (protocol violation, 2 cases), or the hemodynamic goals could not be reached during the intra- or postoperative periods, despite the use of dobutamine (6 cases).

Table 1. Patient Characteristics, Type of Surgery, Preoperative Morbidity, and Perioperative Use of Epidural Catheter

	Control (*n* = 70)	GDT (*n* = 72)	*P*
Age	74 (64 to 79)	73.5 (63.5 to 80)	0.984
Weight	73 (63 to 83)	73.5 (62.5 to 82.5)	0.928
BMI	26 (24 to 30)	27 (24 to 30)	0.923
P-POSSUM	35 (28 to 58)	38 (26.5 to 58.5)	0.591
Preoperative hemoglobin (g/dL)	11.8 (10.6 to 13)	12.1 (11.3 to 13.7)	0.129
Gender (female)	30 (42.9)	32 (44.4)	0.849
Cancer	61 (87.1)	62 (86.1)	0.857
Renal insufficiency	6 (8.6)	11 (5.3)	0.218
Chronic obstructive pulmonary disease	14 (20)	15 (20.8)	0.902
Hypertension	39 (55.7)	45 (62.5)	0.411
Ischemic heart disease	10 (14.3)	16 (22.2)	0.221
Peripheral vascular disease	5 (7.1)	4 (5.6)	0.698
Congestive heart failure	7 (10)	7 (9.7)	0.956
Cerebrovascular disease	6 (8.6)	6 (8.3)	0.959
Arrhythmia	18 (25.7)	15 (20.8)	0.491
Diabetes mellitus	21 (30)	19 (26.4)	0.632
Liver cirrhosis	3 (4.3)	1 (1.4)	0.297
Previous abdominal surgery	36 (51.4)	39 (54.2)	0.744
Bowel clearance procedure	51 (72.9)	57 (79.2)	0.378
Surgical anastomosis	66 (94.3)	67 (93.1)	0.764
Colonic surgery	50 (71.4)	54 (75)	0.631
Abdominal perineal resection	3 (4.3)	2 (2.8)	0.626
Gastric surgery	11 (15.7)	11 (15.3)	0.943
Other surgical procedure	6 (8.6)	5 (6.9)	0.717
ASA physical status			
I	2 (2.9)	2 (2.8)	0.977
II	34 (48.6)	31 (43.1)	0.510
III	34 (48.6)	37 (51.4)	0.737
IV	0 (0)	2 (2.8)	0.160
No epidural	55 (78.6)	56 (77.8)	0.909
Lumbar epidural	14 (20)	13 (18.1)	0.768
Thoracic epidural	1 (1.4)	3 (4.2)	0.324

Quantitative data are expressed as median (25th–75th percentile). For qualitative data, percentages are expressed in brackets.
GDT = goal-directed therapy. BMI = body mass index. P-POSSUM = Portsmouth Physiological and Operative Severity Score for the enumeration of mortality and morbidity. ASA = American Society of Anesthesiologists physical status.

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Table 2. Surgical Time and Perioperative Fluid Balances

	Control (*n* = 70)	GDT (*n* = 72)	*P*
Surgical time (min)	180 (135 to 240)	184.5 (132.5 to 240)	0.969
Vol 12-h presurgery (mL)	200 (0 to 300)	200 (0 to 500)	0.383
Vol 12-h presurgery (mL/kg/h)	0.2 (0 to 0.3)	0.2 (0 to 0.5)	0.336
Presurgical fluid deficit	−720 (−900 to −520)	−660 (−920 to −420)	0.416
Vol OR (mL)	2325 (1600 to 3000)	2500 (1625 to 3000)	0.462
Vol OR (mL/kg/h)	9.8 (8 to 12)	10 (8 to 14.5)	0.341
Diuresis OR (mL)	310 (200 to 500)	237.5 (150 to 540)	0.414
Diuresis OR (mL/kg/h)	1.2 (0.8 to 2.1)	1.2 (0.8 to 2)	0.605
Hemorrhage OR (mL)	250 (200 to 400)	300 (200 to 500)	0.220
Hemorrhage OR (mL/kg)	3 (2.1 to 5.6)	4 (2 to 7.1)	0.404
Packed red blood cells OR (units)	0 (0 to 0)	0 (0 to 1)	0.019
Fresh frozen plasma OR (units)	0 (0 to 0)	0 (0 to 0)	0.162
Colloid boluses	1 (0 to 2)	2 (1 to 3)	<0.001
Balance presurgery/OR (mL)	965 (480 to 1570)	1092.5 (432.5 to 1825)	0.460
Balance presurgery/OR (mL/kg)	13.3 (6.4 to 19.7)	15.7 (5.4 to 25.1)	0.461
Total balance (mL)	−312.5 (−850 to 35)	−262.5 (−867.5 to 360)	0.334
Total balance (mL/kg)	−4.3 (−12.2 to 0.4)	−3.6 (−13 to 4.8)	0.406
Vol ICU 24 h (mL)	3100 (2750 to 3800)	3200 (2650 to 3875)	0.757
Vol ICU 24 h (mL/kg)	42.1 (37.3 to 54.5)	41.3 (32.5 to 53.6)	0.656

Data are expressed as median (25th–75th percentile).

GDT = goal-directed therapy. Vol = volume infused. OR = operating room. ICU = intensive care unit. Presurgical fluid deficit = fluids administered 12 hours before surgery minus 1 mL/kg/h. Balance presurgery/OR = presurgical deficit + fluids infused in the OR (including boluses) minus diuresis minus hemorrhage. Total balance = balance presurgery/OR minus estimated intraoperative insensitive losses (6 mL/kg/h).

Table 3. Use of Vasoactive Drugs and Complications in the Intraoperative Period, Hemodynamic Variables, Temperature, Lactate, and Hemoglobin Obtained on Admission to the Operating Room (OR) or the Intensive Care Unit (ICU)

	Control (*n* = 70)	GDT (*n* = 72)	*P*
Dobutamine OR	1 (1.4)	18 (25)	<0.001
Noradrenaline OR	4 (5.7)	5 (6.9)	0.764
Ephedrine OR	22 (31.4)	25 (34.7)	0.677
Bowel perforation	1 (1.4)	1 (1.4)	0.984
Arrhythmia OR	2 (2.9)	2 (2.8)	0.977
Hemorrhage >10 mL/kg	4 (5.7)	6 (8.3)	0.542
MAP OR	96 ± 16	100 ± 15	0.084
HR OR	80 ± 12	75 ± 12	0.016
MAP ICU	91 ± 15	93 ± 14	0.353
HR ICU	79 ± 15	76 ± 14	0.181
Temperature ICU (°C)	35.4 ± 0.7	35.4 ± 0.7	0.883
Lactate ICU (mmol/L)*	1.2 (0.9 to 1.7)	1.2 (0.8 to 1.6)	0.526
Hemoglobin ICU (g/dL)*	10.7 (9.8 to 11.6)	10.9 (10 to 12.2)	0.287

For qualitative data, percentages are expressed in brackets. Quantitative data are expressed as mean ± SD except for (*), expressed as median (25th–75th percentile).

GDT = goal-directed therapy. MAP = mean arterial blood pressure. HR = heart rate.

Preoperative and Intraoperative Periods

Fluid administration in the perioperative period and estimated losses and balances are shown in Table 2. No differences were observed between groups, except in the number of colloid boluses (2.4 ± 1.8 [GDT] vs 1.3 ± 1.4 [control]; $P < 0.001$) and packed red blood cell units (0.6 ± 1.3 [GDT] vs 0.2 ± 0.6 [control]; $P = 0.019$). In the GDT group, dobutamine was used in 25% (18 of 72) of the cases versus 1.4% (1 of 70) in the control group ($P < 0.001$). No differences were observed concerning the use of other vasoactive drugs, intraoperative complications, hemodynamic variables, temperature, lactate, and hemoglobin obtained on admission to the operating room or the ICU, except a slight increase in heart rate in the control group at operating room admission (Table 3).

Postoperative Period

ICU LOS and the duration of MV were similar in both groups (Table 4). Dobutamine was used in the first postoperative day in 19.4% (14 of 72) of the GDT patients versus none in the control group ($P < 0.001$).

Primary and Secondary Variables

No significant differences were observed in overall complications (40% GDT vs 41% in the control group; $P = 0.397$, relative risk 0.99 [0.67–1.44]), LOS (11.5 vs 10.5; $P = 0.874$; WMWodds 1.03 [0.70–1.52]), time to first flatus (62 vs 72 hours; $P = 0.180$), wound infection (7 vs 14; $P = 0.085$), anastomotic leaks (2 vs 5; $P = 0.23$), or mortality (4.2% vs 5.7%; $P = 0.67$). The incidence of postoperative complications was similar between groups, except for reoperation (11 of 70 [15.7%] in the control group versus 4 of 72 [5.6%] in the GDT group; $P = 0.049$). In 4 patients (control), the causes for reoperation were multiple. Three of these patients had hemorrhages associated with suture failure and/or evisceration. Despite an apparent reduction in all variables, there were no significant differences for any end point (Table 5). No detrimental

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Table 4. Postoperative Variables

	Control (n = 70)	GDT (n = 72)	P
ICU LOS (d)	1 (1 to 2)	1 (1 to 2)	0.6
Dobutamine first day	0	14 (19.4)	<0.001
Noradrenaline first day	6 (8.6)	6 (8.3)	0.959
Intraabdominal infection	10 (14.3)	6 (8.3)	0.262
Respiratory infection	4 (5.7)	2 (2.8)	0.384
Urine infection	6 (8.6)	3 (4.2)	0.281
Catheter infection	5 (7.1)	4 (5.6)	0.698
MV >24 h	5 (7.1)	4 (5.6)	0.698
Vasopressors	10 (14.3)	9 (12.5)	0.755
Acute myocardial infarction	0	0	—
Stroke	0	0	—
Arrhythmia not present preoperatively	3 (4.3)	2 (2.8)	0.626
Cardiac failure	1 (1.4)	2 (2.8)	0.576
Reoperation	11 (15.7)	4 (5.6)	0.049
Reoperation: suture failure	5 (7.1)	2 (2.8)	0.230
Reoperation: hemorrhage	6 (8.6)	1 (1.4)	0.048
Reoperation: evisceration	4 (5.7)	1 (1.4)	0.162
Paralytic ileus	3 (4.3)	2 (2.8)	0.626
Acute renal failure	9 (12.9)	8 (11.1)	0.749

Quantitative data are expressed as median (25th–75th percentile). For qualitative data, percentages are expressed in brackets. In 4 of 11 patients in the control group, the causes for reoperation were multiple.
GDT = goal-directed therapy. ICU = intensive care unit. LOS = length of stay. MV = mechanical ventilation.

Table 5. Study Variables

	Control	GDT	Risk ratio	P
Complications	29 (41)	29 (40)	0.99 (0.67 to 1.44)	0.397
No. complications per patient	0 (0 to 2)	0 (0 to 1)		0.467
Hospital LOS	10.5 (8 to 16)	11.5 (8 to 15)		0.874
Time to first flatus (h)	72 (48 to 96)	61.5 (40 to 76)		0.180
Wound infection	14 (20)	7 (9.7)	0.46 (0.19 to 1.13)	0.085
Anastomotic leak	5 (7.1)	2 (2.8)	0.43 (0.08 to 2.13)	0.230
Hospital mortality	4 (5.7)	3 (4.2)	0.72 (0.17 to 3.04)	0.670

Quantitative data are expressed as median (25th–75th percentile). For qualitative data, percentages are expressed in brackets.
GDT = goal-directed therapy. LOS = length of stay.

effects (tachycardia, pulmonary edema) were attributed to the protocol in any case.

The interaction tests did not show any difference between categorized P-POSSUM (<30 vs 31–60 vs >60) or total fluid balance (≤–10 vs –10 to +10 vs >10 mL/kg). Thus, neither the surgical risk nor fluid administration had a different effect in response to the hemodynamic protocol.

DISCUSSION

The implementation of a hemodynamic protocol based on continuous noninvasive monitoring of cardiac output in major abdominal surgery was not related to a reduction in overall complications. We have observed a reduction in reoperations in the treated group. No benefits were observed in LOS, peristalsis recovery, anastomotic leaks, or mortality. The current study adds to previous knowledge in 2 main aspects. First, it was a multicenter international study and the decision for hospital discharge was made by blinded surgeons; therefore, the results are more generalizable. Second, we used a completely noninvasive monitoring technique to measure cardiac output.

Our findings are not as conclusive as a number of previous studies,[9,10,13,15,17–21] and there are several possible explanations for this. The 2 main reasons are methodological and could not be predicted before the study. Although the incidence of surgical site infection and mortality was similar to previous large studies,[29,30] the rate of complications was less than expected (41% vs 65%) and coincided with the aim of the study for the GDT group. This fact is probably related to the high ICU admission rate of scheduled surgical patients in Spanish hospitals[31] that probably leads to the admittance of some low-risk patients due to the absence of intermediate care units. However, the post hoc analysis did not show a different effect of the hemodynamic protocol in the higher risk population (P-POSSUM >60) with respect to the lower risk patients, although post hoc observations should be considered cautiously. In addition, morbidity and hospital LOS showed a high interhospital variability, with a complication rate varying between 25% and 73% and median LOS between 7.5 and 16 days. Three surgical procedures were included in the analysis. Therefore, some degree of heterogeneity can be expected, but most of the cases (75%) were colonic interventions, equally distributed between groups. Laparoscopic procedures were excluded to improve the generalizability of the results. Previous studies, with fewer participants and including more heterogeneous populations (vascular, pancreatic, and urologic procedures), have shown positive results.[10,15,17–20] Because the hemodynamic protocol (GDT group) and anesthetic recommendations (all patients) were the same for all hospitals, we speculate that the "surgeon" factor in terms of skill (as shown by the great variability in the rate of complications across centers)

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and local protocols for hospital discharge probably plays a major role, especially in non-ERAS institutions. This variability accounts for the lack of significance, despite the apparent beneficial effects for some variables.

An inadequate GDT protocol focusing on MAP, CI, and stroke volume response might also have been the cause for the lack of benefits. A minimal perfusion pressure, represented by MAP, has to be provided. However, changes in MAP (MAP = cardiac output × vascular resistance) do not accurately reflect changes in perfusion. Absolute values of cardiac output (a surrogate of perfusion) are also not easy to interpret, so we included in the protocol the change in stroke volume in response to fluid challenge after the initial 2 fluid challenges to overcome the preoperative fluid deficit and anesthetic-induced vasodilation. This approach is based on previous protocols associated with improved outcome.[9,15,17] We also speculate that the targeted CI should be different during anesthesia and in the postoperative period. However, to our knowledge, this hypothesis has not been tested, although it deserves to be explored. An alternative approach could be the use of individual baseline CI (before anesthesia) as a reference, instead of a fixed value (2.5 L/min/m^2) that depends on the accuracy of the monitor and might be suboptimal in noncalibrated devices. This strategy might be easily performed with this noninvasive technology but, to our knowledge, has not been studied. Finally, the NICOM does not measure CI but makes an estimation based on chest bioreactance. Other commonly accepted devices such as the esophageal Doppler or FloTrac also do not measure cardiac output. The change in stroke volume in response to fluid challenge was included in the protocol to overcome this potential inconvenience. A lack of reliability of the NICOM seems unlikely because this device has been validated in postsurgical patients. Using continuous thermodilution as a reference method, NICOM and Vigileo devices presented similar monitoring capabilities in cardiac surgery patients.[24] Similarly, in 1 study, NICOM was comparable with pulse contour analysis calibrated by thermodilution (PiCCO) during a recruitment maneuver and positive end-expiratory pressure changes.[25] However, the authors of a recent study concluded that NICOM cannot predict fluid responsiveness in a medical ICU setting.[32] The reliability of bioimpedance (based on the amplitude instead of the delay of the signal analyzed by bioreactance) is influenced by peripheral vascular resistance[33] and changes in lung fluid.[34] Because bioreactance is closely related to bioimpedance, the reason for their findings was probably related to the fact that most of their patients presented with septic shock and required vasopressors and MV (likely associated with increased lung fluid). This is not usually the case in scheduled surgery, but the role of NICOM in this setting requires further studies.

The major strength of the present study is the multicenter, international design and the blinding of the surgeons that decided hospital discharge. Hemodynamic management in the control group followed standard practice, which implies that a high variability of fluid administration was expected among hospitals, and even within every institution, depending on the attending physician. This "uncontrolled" approach (effectiveness or pragmatic trial as opposed to efficacy or explanatory trial) mimicked real practice and was intended to obtain the maximal external validity for the study because, if the GDT approach improved outcome, its use could be generalized. However, obtaining positive results with such a study design is less likely than when 2 protocols are compared in a single-center study (high internal validity, but difficult to extrapolate to a general population). There are examples showing a lack of positive results in multicenter studies. Despite using a protocol that had shown improved outcome in a previous study,[19] Sandham et al.[14] found no benefit to therapy directed by pulmonary artery catheter over standard practice in high-risk surgical patients in a large multicenter study. Similarly, in contrast to previous studies, combined epidural and general anesthesia did not decrease morbidity in high-risk patients, except for a reduction in respiratory failure.[35] A review of hemodynamic monitoring found 7 of 8 multicenter studies to have negative results and nearly half of the 27 single-center studies to have a positive result.[36] Regarding LOS, had specific criteria for hospital discharge been indicated in the protocol, the surgeons making the decision might have been influenced by the criteria and changed their normal practice.

Although the mean number of complications per patient was lower in the GDT group (0.8 ± 1.4 vs 1.3 ± 2.2), the difference was not significant. The major benefit of the GDT approach was the potential reduction in the number of reoperations. The reason for these findings remains speculative. Hemodynamic optimization has been related to an improvement in perianastomotic microcirculation,[21] which might reduce the incidence of suture failure and could improve healing of the abdominal wall. According to our results, GDT might be of value when combined with other recommendations related to improved outcome in the perioperative period such as the ERAS perioperative bundle. Similarly, in septic shock patients, the compliance with individual guidelines that had proved beneficial in randomized controlled trials was not associated with a significant improvement in outcome. However, survival was significantly related to the number of fulfilled therapeutic guidelines included in a sepsis bundle.[37] A Cochrane review focusing on the ERAS pathway observed that the compliance with, at least, 7 ERAS items (of 17) was associated with a reduction in overall complications and hospital LOS.[38] None of the hospitals included in our study followed the ERAS protocols. Although this fact might be seen as a limitation, it reflects worldwide common practice.

The theoretical benefits of GDT are related to fluid replacement and/or the use of vasoactive drugs. With respect to fluid management, experimental data render conflicting results. In anesthetized pigs, mixed venous oxygen saturation-guided colloid replacement improved the perianastomotic microcirculation.[21] However, in a similar model, it was shown that flow autoregulation in the splanchnic bed maintains constant perfusion, despite variations in circulating volume.[39] Similar to a previous study,[17] we observed that crystalloid infusion and fluid balance were similar in both groups. There were differences in the number of colloid boluses and transfusion, but these were not clinically relevant. According to the post hoc analysis, positive perioperative fluid balance was not detrimental. The major difference was in the use of dobutamine, not associated with

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harmful effects, and we speculate if its administration to more patients could have improved the results.

CONCLUSIONS

The use of a hemodynamic protocol based on the data obtained from a noninvasive cardiac output monitor was associated with the increased use of dobutamine in scheduled major abdominal surgery. The amount of fluids and fluid balance were similar in both groups, except for slightly but significantly more colloid boluses and blood concentrates infused in the treated group. Both groups were comparable in baseline characteristics. In our pragmatic study, compliance with this protocol was not associated with a decrease in LOS or the number of overall postoperative complications, except for a potential reduction in the need for reoperation. A nonsignificant reduction in the time to first flatus was observed in the treated patients. According to our data, we consider that the implementation of a hemodynamic GDT in major surgery might be recommended but should be included in a perioperative bundle because it probably does not achieve the expected improvement per se in outcome according to previous single-center studies. The confirmation of major benefits related to GDT in abdominal surgery requires further assessment in larger multicenter trials.

DISCLOSURES

Name: David Pestaña, PhD.
Contribution: This author designed the study, was the local coordinator of the study, collected data, and drafted the manuscript.
Attestation: This author had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, is the archival author, and approved the final manuscript.
Name: Elena Espinosa, PhD.
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Attestation: Dr. Espinosa approved the final manuscript.
Name: Arieh Eden, MD.
Contribution: This author collected data and helped to draft the manuscript.
Attestation: Dr. Eden approved the final manuscript.
Name: Diana Nájera, MD.
Contribution: This author recruited patients, collected data, and helped to perform the informatics database.
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Attestation: Dr. Pizov approved the final manuscript.
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