Research Article

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http://www.imedpub.com/

Colorectal Cancer: Open Access
ISSN 2471-9943

2017
Vol.3 No.2:10

DOI: 10.21767/2471-9943.100040

Impact of a Goal Directed Fluid Therapy on Length of Hospital Stay and Costs of Hepatobiliary Pancreatic Surgery. A Prospective Observational Study

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Received: June 13, 2017; **Accepted:** June 20, 2017; **Published:** June 24, 2017

Citation: Naccarato A, Tribuzi S, Marco C, Valerio M, Giulia T, et al. (2017) Impact of a Goal Directed Fluid Therapy on Length of Hospital Stay and Costs of Hepatobiliary Pancreatic Surgery. A Prospective Observational Study. Colorec Cancer. 3:2.

Abstract

Background: The effectiveness of Goal Directed Fluid Therapy (GDFT) algorithms in improving postoperative outcomes has been extensively suggested in literature. Nevertheless, there is a lack of strong evidence regarding both the clinical impact and the cost-effectiveness of the GDFT protocols. The aim of this study is to evaluate the costs of patients undergoing hepatobiliopancreatic surgery when a GDFT fluid-therapy protocol is applied.

Methods: All consecutive ASA I-III patients undergoing hepatobiliopancreatic surgery were included in this prospective observational study. Depending on device availability patients were handled either by standard fluid treatment (Standard group) or fluid therapy guided by Vigileo monitor derived hemodynamic variables (Vigileo GDFT group). Postoperative length of stay and economic costs were analyzed.

Results: One hundred fortyseven consecutive patients were included, 71 in the Vigileo GDFT group and 76 in the Standard group. The total hospital length of stay was 13(9-20) days for the Vigileo GDFT group and 14(8-21) days for the Standard group (p=0.58); no statistically significant differences between the two groups emerged regarding costs and postoperative complications.

Conclusions: Application of a GDFT algorithm did not have impact on the total length of hospital stay and the global costs, which were mainly influenced by the number of complications.

Keywords: GDFT; Fluid therapy; Postoperative complications; Length of hospital stay; Costs

Introduction

Major abdominal surgery is associated with a significant systemic inflammatory response and a proportional increase in the demand for oxygen on behalf of the organs and tissues. If this demand does not correspond with an increase of the cardiac output, there can be organ failure, complications and death, especially in high-risk patients [1-3]. Over 25 years ago, Shoemaker was the first to prove a significant reduction in morbidity and mortality in patients undergoing major abdominal surgery through the application of a Goal Directed Fluid Therapy (GDFT) [4]. GDFT is a generic term that refers to the management of fluids and hemodynamics based on parameters, such as stroke volume, cardiac output and/or the transport of oxygen, combined with the clinical evaluation of vital signs, during and immediately following surgery. This approach reduces the systemic inflammatory response and increases tissue perfusion and oxygenation [5]. Its effectiveness in terms of clinical outcome (complications and length of hospital stay) in high-risk surgical patients has been extensively shown in literature [6-8] and it is currently recommended by the National Health Service in the United Kingdom [9], by the French Society of Anesthesiology [10] and the Enhanced Recovery After Surgery (ERAS) society in Europe [11]. However, the evidence showing the clinical effectiveness of GDFT derives from small randomized studies and includes forms of invasive monitoring. Furthermore, the OPTIMISE [12] study and a recent Cochrane study [13] have proved the benefits in terms of reduction of complications and mortality deriving from such treatment are more marginal than was previously thought. On the other hand, only a few studies have taken into consideration the cost-effectiveness of GDFT showing an actual reduction of costs but with multiple limitations linked to the variability of the kind of device used, the fluid therapy applied in the Standard groups, and the postoperative period considered for the evaluation of the outcome [14,15].

The objective of this study is to evaluate the length of hospital stay and costs of patients undergoing major abdominal surgery in which a GDFT protocol based on a mini-invasive hemodynamic monitoring system (Vigileo) is used for the management of fluid-therapy as opposed to a standard fluid therapy protocol. The hypothesis is that the use of a GDFT protocol based on a Vigileo system can reduce the length of hospital stay in patients undergoing hepatobiliopancreatic surgery.

Materials and Methods

This prospective observational study was approved by the Ethical Committee of the Regina Elena National Cancer Institute, Rome (Italy) with registration number 89/10, amendment 1. The procedures followed were in agreement with the Helsinki Declaration 1975, revised in Hong Kong 1989. After having obtained written informed consent, patients ASA I-III candidates for hepatobiliopancreatic surgery which met the inclusion criteria, were enrolled in the study. Patients under 18 years of age and patients with hemodynamically significant aortic valve disease and cardiac rhythm disorders were excluded from the study.

Depending on device availability, patients were handled either by a mini-invasive hemodynamic monitoring system for a goal directed fluid therapy (Vigileo-GDFT group) or receiving a fluid therapy (Standard group) according to a standardized protocol.

The same team carried out the surgical procedures for both groups and all patients underwent general anesthesia according to a standard protocol. Patients were premedicated with midazolam 0.01 mg/Kg IV. A general anesthesia was induced with fentanyl 2-5 mcg/Kg, propofol 1.5-2 mg/Kg, cisatracurium 0.07 mg/kg IV. After orotracheal intubation, anesthesia was maintained with a mix of Sevoflurane/O_2/air. A continuous infusion of cisatracurium 0.06-0.12 mg/Kg/h was also carried out and additional bolus of fentanyl was administered according to the anesthetic needs and the hemodynamic changes.

All patients were subjected to standard monitoring: continuous electrocardiography, heat rate (HR), invasive arterial blood pressure (ABP) measurement (with a radial artery catheter), pulse oxymetry (SpO_2), body temperature, hourly diuresis, inhaled and exhaled gas.

A FloTrac/Vigileo system (Edwards Lifesciences, Irvine CA, USA, software version 1.14) was applied to the Vigileo-GDFT group to obtain a continuous monitoring of the Cardiac Index (CI), Stroke Volume Index (SVI), and Stroke Volume Variation (SVV). The CI was maintained at values more than/equal to 2.5 L/min/m^2. A fluid-therapy protocol was used which included a basal infusion of crystalloids at 4 ml/Kg/h and bolus of colloids (250 mL of Hydroxyethyl Starch 130/0.4, HES, in 15 minutes) if CI < 2.5 l/min/m^2, SVI<35 ml/m^2 and SVV>13%. In the case of CI<2.5 l/min/m^2 and SVI<35 ml/m^2 with SVV<13% an infusion of dobutamine (3-10 mcg/Kg/min) was carried out.

In the Standard group, a regime of fluid-therapy through a basal infusion of crystalloids varying between 4 to 7 mL/Kg/h was maintained. Mean arterial pressure (MAP) was maintained between values of 65 and 95 mmHg. Colloid boluses (HES) of 250 mL were administered in 15 minutes if MAP was ≤ 70% the pre-induction value or if diuresis was ≤ 1 mL/Kg/h with a CVP<8 mmHg; when the MAP was ≤ 70% the pre-induction value or if diuresis was ≤ 1 mL/Kg/h despite fluid resuscitation an infusion of inotropic agents (dobutamine 3-10 mcg/Kg/min) was carried out. In both groups, patients were transfused with concentrated red cells for hemoglobin values <8 g/dl (<9 g/dl in patients with congestive heart failure or coronary heart disease).

At the end of surgery, patients were extubated in the operating theater and transported to the intensive care unit (ICU), where depending on their clinical conditions whether stable and normal, returned to their original hospital ward. In the postoperative period, the same standardized regimen of fluid therapy was applied to both groups: total parenteral nutrition (TPN) up to 3000 mL/day was administered and gradually converted into enteral nutrition (EN) after 5-7 days, starting 10 mL/h to achieve the dose of 60 mL/h, until mouth feeding resumed.

In both groups at the end of surgery, data were collected about the total amount of fluids administered, their breakdown (crystalloid/colloid), the total number of colloid boluses administered, the use of inotropic agents and units of red blood cells transfused.

In both groups, the incidence of major abdominal and systemic complications was evaluated, by personnel who were not involved in the intraoperative management of patients. The major abdominal complications considered were anastomotic leakage, enteric fistulas, perforation, abdominal abscesses (confirmed by computerized tomography); systemic complications were divided into cardiac (electrocardiographic signs or laboratory data of myocardial infarction, angina or arrhythmia), hepatic (persistent alteration in hepatic function tests including bilirubin, prothrombin time, ammonia concentration, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase), respiratory (x-ray findings of airspace or interstitial opacity, lobar consolidation, or pleural effusions; severe respiratory failure requiring respiratory support) and renal (oliguria with urine output <0.5 mL/kg/h for more than 4 hours, creatinine increase >30% of preoperative values, dialysis). Furthermore, the incidence of readmission to the ICU was also assessed.

The total length of hospital stays and costs were evaluated for both groups and 4 categories were identified: 1) pharmaceuticals and consumer goods, 2) costs of hospitalization, including medical and non-medical personnel and calculated as 'ordinary' or 'extraordinary' hospitalization (Intensive Care), 3) costs of surgical procedures and possible further surgeries, 4) cost of diagnostic exams, calculated according to the Regional expense lists (Price list of the Lazio Region).

A dedicated software (Supporting Costs evaluation in Major abdominal surgery, SCM) which enables one to register, conserve and analyze clinical data and costs of patients undergoing major abdominal surgery, was used to extract and analyze the data regarding the patients enrolled in the study.

Staistical analysis

Continuous variables with normal and with non-normal distribution (hospital length of stay and costs) were compared with Student's t-test and Mann-Whitney U test respectively. Data are expressed as mean (SD) or median (1st-3rd quartiles). Chi-square or Fisher exact tests was used for categorical variables. A P value <0.05 was considered significant. We used software version 21 of statistical package for social science (SPSS version 21, Chicago, IL, USA).

Results

One hundred fortyseven consecutive patients who underwent hepatobiliopancreatic surgery at our Institute between 2011 and 2013 were included in the study. Of these, 71 were underwent a GFDT protocol based on a mini-invasive hemodynamic monitoring system (Vigileo-GDFT group) and 76 underwent a standard fluid-therapy protocol (Standard group). The demographics and perioperative data are showed in **Table 1**.

Table 1 Demographics and perioperative data. *p<0.05. BMI: Body Mass Index; ASA: American Society of Anesthesiologists; COPD: Chronic Obstructive Pulmonary Disease.

	All patients		Pancreas Standard (n=23) Vigileo GDFT (n=21)		Liver Standard (n=53) Liver Vigileo GDFT (n=50)	
	Standard (n=6)	Vigileo GDFT (n=71)	Standard (n=23)	Vigileo GDFT (n=21)	Standard (n=53)	Vigileo GDFT (n=50)
Age, mean (sd)	64.5 (11.3)	63.6 (10.8)	65.7 (8.4)	64.7 (9.2)	64 (12.4)	62.2 (11.5)
Sex, m/f	44/32	42/29	17/6	13/8	27/26	29/21
BMI, mean (sd)	25.8 (4.3)	25.9 (4.9)	28 (5.2)	24 (4.5)*	24.8 (3.5)	26.6 (4.9)
ASA, I/II/III	3/47/26	3/46/22	0/14/9	0/17/4	3/33/17	3/29/18
Comorbidity, n (%):						
hypertension	46 (60.5%)	46 (64.8%)	18 (40%)	11 (25%)	28 (27.2%)	35 (34%)
COPD	17 (22.4%)	22 (31%)	6 (13.6%)	7 (15.9%)	11 (10.7%)	15 (14.6%)
diabetes	27 (35.5%)	26 (36.6%)	11 (25%)	8 (18.2%)	16 (15.5%)	18 (17.5%)
metastatic	20 (26.3%)	5 (7%)*	5 (11.4%)	1 (2.3%)	15 (14.6%)	4 (3.9%)*
cardiac failure	18 (23.7%)	16 (22.5%)	6 (13.6%)	5 (11.4%)	12 (11.7%)	11 (10.7%)
neurologic	2 (2.6%)	3 (4.2%)	1 (2.3%)	0	1 (1%)	3 (2.9%)

The length of hospital stay of the Vigileo-GDFT group was 13 (9-20) days (median, 1st-3rd quartile); the Standard group was 14 (8-21) days (median, 1st-3rd quartile) (P=0.58); the length of ordinary hospital stay of the Vigileo-GDFT group was 12 (9-19), and 12 (8-20) days for the Standard group (P=0.87). The length of stay in Intensive Care was 0 (0-1) for the Vigileo-GDFT group, and 0 (0-2) for the Standard group (P=0.23). In the Vigileo-GDFT group, the costs relating to pharmaceuticals, surgical procedures, hospitalization and diagnostic testing were 55 € (6.5-401); 1517 € (1042-2275); 5700 € (3040-9405); 2019 € (1201-3068), respectively. In the Standard group, they were 46 € (31-181); 1706 € (1138-2275); 4940 € (3420-7980); 1868 € (1335-2803), respectively. No statistically significant differences emerged regarding the four cost categories considered **(Table 2).** Nonsurgical complications (cardiac, respiratory, hepatic and renal) are showed in **Table 2**, without any statistically significant difference between the two groups.

Table 2 Main Postoperative Data: Hepatobiliopancreatic surgery.

	Standard (n=76)	Vigileo GDFT (n=71)	*P*-Value
Minimum one complication, n(%)	25 (32.9)	17 (23.9)	0.23

>1 complication, n (%)	12 (15.8)	10 (14.1)	0.77
Surgical complication amongst the complications, n (%)	16(21.1)	12(21.1)	0.66
Non-Surgical complication amongst the complications, n (%)	23(30)	20(28)	0.53
Cardiac	3(13)	4(20)	0.54
Respiratory	4(20)	4(20)	0.43
Hepatic	2(8.7)	1(5)	0.65
Renal	2(8.7)	2(10)	0.74
Total days of hospital stay, median (1st-3rd quartile)	14 (8-21)	13 (9-20)	0.58
Ordinary days of hospital stay, median (1st-3rd quartile)	12 (8-20)	12 (9-19)	0.87
Days of intensive care, median (1st-3rd quartile)	0 (0-2)	0 (0-1)	0.23
Cost of pharmaceuticals (€), median (1st-3rd quartile)	55 (6.5-401)	46 (31-181)	0.15
Cost of surgery (€), median (1st-3rd quartile)	1517 (1042-2275)	1706 (1138- 2275)	0.53
Cost of hospitalization stay (€), median (1st-3rd quartile)	5700 (3040-9405)	4940 (3420-7980)	0.44
Cost of testing (€), median (1st-3rd quartile)	2019 (1201-3068)	1868 (1335-2803)	0.58

Therefore, an analysis was carried for subgroups regarding the single surgeries: hepatic and pancreatic. No statistically significant differences emerged in the endpoints considered. **(Tables 3 and 4).**

Table 3 Main Postoperative Data: Hepatic Surgery.

	Standard (n=53)	**Vigileo GDFT (n=50)**	***P*-Value**
Minimum one complication, n (%)	13 (24.5)	8 (16)	0.28
>1 complication, n (%)	6 (11.3)	5 (10)	0.83
Surgical complication amongst the complications (Clavien-Dindo ≥ 3), n (%)	8 (15.1)	7 (14)	0.87
Total days of hospital stay, median (1st-3rd quartile)	10 (7-15)	10 (8-13.5)	0.72
Total days of ordinary stay, median (1st-3rd quartile)	9 (7-15)	10 /7-13)	0.7
Days of intensive care, median (1st-3rd quartile)	0 (0-1.5)	0 (0-0.25)	0.9
Cost of pharmaceuticals (€), median (1st-3rd quartile)	64.5(25.5-64.5)	35.5 (28.7- 67.7)	0.3
Cost of surgeries (€), median (1st-3rd quartile)	1138(916-1896)	1422(948-1990)	0.5
Cost of hospital stay (€), median (1st-3rd quartile)	3800 (3040- 6080)	3990 (3325-5700)	0.74
Cost of testing (€), median (1st-3rd quartile)	1468 (1082-2233)	1489 (1201-1976)	0.72

Table 4 Main Postoperative Data: Pancreatic surgery.

	Standard (n=23)	**Vigileo GDFT (n=21)**	***P*-Value**
Minimum one complication, n (%)	12 (52.2)	9 (42.9)	0.53
>1 complication, n (%)	6 (26.1)	5 (23.8)	0.86
Surgical complication amongst the complications (Clavien-Dindo ≥ 3), n (%)	8 (34.8)	5 (23.8)	0.42
Total days of hospital stay, median (1st-3rd quartile)	22 (16-59)	19 (16-36)	0.18
Total days of ordinary stay, median (1st-3rd quartile)	21 (15-27)	19 (14.5-30.5)	0.4
Days of intensive care, median (1st-3rd quartile)	2 (0-4)	0 (0-1.5)	0.09

Cost of pharmaceuticals (€), median (1st-3rd quartile)	15 (0-982)	61 (46-596)	0.34
Cost of surgeries (€), median (1st-3rd quartile)	2275 (1517-2654)	2086 (1706-2465)	0.89
Cost of hospital stay (€), median (1st-3rd quartile)	9120 (6840-16340)	7220 (6270-11590)	0.13
Cost of testing (€), median (1st-3rd quartile)	3070 (2336-4861)	2669 (2304-4307)	0.18

The total amount of fluids intraoperatively administered was 8784 ± 1103 ml in the Standard group and 5140 ± 1218 mL in the Vigileo-GDFT group (p<0.001). Dosage of dobutamine was statistically significant higher in the Vigileo-GDFT group: 5 ± 1.1 in the Standard group and 9 ±0.9 mcg/Kg/min in the Vigileo – GDFT group (p<0.001). No statistically significant differences emerged regarding units of red blood cells transfused **(Table 5).**

Table 5 Fluids amount, red blood cells transfused, inotropes and vasopressors.

	Standard group (n=76)	**GDFT group (n=71)**	***P*-value**
Crystalloid volume replacement (ml), mean (sd)	6587(1004)	3895(987)	<0.001
Colloid volume replacement (ml), mean (sd)	1927 (316)	1245 (283)	<0.001
Total volume replacement (ml), mean (sd)	8784 (1103)	5140 (1218)	<0.001
Red blood cells transfused (Unit)	3	2	0.43
Dobutamine (mcg/kg/min), mean (sd)	5 (1.1)	9 (0.9)	<0.001
Norepinephrine (mcg/kg/min), mean (sd)	0.08 (0.02)	0.06 (0.01)	0.4

In accordance with the Clavien-Dindo Classification [16] 71.42% (105/147) of the patients did not exhibit any postoperative complications; 42 patients (28.57%) experienced grade I-V postoperative complications without any statistically significant difference between the two groups. Twenty eight patients (19.04%) experienced postoperative complications of Clavien-Dindo grade ≥ 3 and needed surgical reintervention. Relative costs are showed in **Table 6**.

Table 6 Complications costs. Hepatobiliopancreatic surgery.

	NO Surgical complications (n=119)	**WITH surgical complications (n=28)**	**P-Value**
Cost of pharmaceuticals (€), median (1st-3rd quartile)	7 (0-43)	401 (145-1431)	0.024
Cost of surgeries (€), median (1st-3rd quartile)	1454 (948-1896)	2496 (2085-3649)	<0.001
Cost of hospital stay (€), median (1st-3rd quartile)	4180 (3040-6460)	11400 (8265-20900)	<0.001
Cost of testing (€), median (1st-3rd quartile)	1602 (1201-2402)	4078 (2994-6605)	<0.001

Discussion

In our study we attempted to assess whether the application of a GDFT protocol guided by minimally invasive Vigileo monitoring system can induce an advantage in terms of costs in the context of major abdominal surgery. For this purpose, we prospectively compared two groups of patients undergoing hepatobiliopancreatic surgery. Data of patients receiving a goal directed fluid therapy protocol, according to the availability of the Vigileo device, were compared with those of patients who received fluid therapy according to a standardized protocol. Our results have not been able to confirm our hypothesis. They showed that the application of a GDFT protocol did not provide benefits in terms of clinical outcome (length of hospital stay) and costs.

An optimal intraoperative fluid administration plays a crucial role for major abdominal surgery, avoiding both over-hydratation with edema and under-hydratation and tissue hypoxia. This surgery generates mechanical and inflammatory stimuli associated to an increased stress response, an increased oxygen demand, an increased rate of complications and death. Despite the importance of an appropriate fluid balance, studies on GDFT remain inconclusive.

Randomized clinical studies and meta-analyses published in the first decade of the 21st century have highlighted the importance of the application of an intraoperative GDFT protocol aimed to reduce postoperative complications and the length of stay for major abdominal surgery [17,18].

Berger et al. in a systematic review identified goals for perioperative fluid administration targeting of which appeared to be associated with less postoperative complications and shorter intensive care unit/ length of hospital stay. Perioperative mortality remained unaffected [19]. Guest et al. studied the impact of GDFT within the perioperative period showing a minimum potential cost saving of 31% [15], and, in a retrospective study, Benes and colleagues evaluated the economic implications of intraoperative fluid optimization

guided by stroke volume variation based on previously published clinical results. They concluded that the use of stroke volume variation and Vigileo/FloTrac system showed not only a substantial improvement in morbidity, but was associated with an economic benefit. The occurrence of any complication, irrespective of study group allocation increased the costs of postoperative care [20].

Conversely the recent analysis conducted in the OPTIMISE study on high-risk patients undergoing major gastrointestinal surgery showed that, the use of a therapeutic algorithm of cardiac output-guided hemodynamic compared to a treatment commonly used in clinical practice, does not reduce complications and mortality within 30 days. Furthermore, a recent meta-analysis [21] of 23 clinical studies has shown that GDFT is not superior to a standard fluid-therapy regime in patients undergoing major abdominal surgery so much for the clinical outcomes considered: length of hospital stays, morbidity, postoperative ileus, mortality within 30 days.

Nevertheless, recent studies have failed to demonstrate the effectiveness of a GDFT within the context of the ERAS protocol. The optimal perioperative fluid management is an important component of the ERAS protocols, in this context fluid management is considered within a continuum through the different preoperative, intraoperative, and postoperative phases [22,23]. Srinivasa et al. have randomized 85 patients within the context of an ERAS GDT/no GDT protocol. At the end of the procedure there were no statistically significant differences between the two groups regarding complications and length of hospital stay [24].

Our results could partly be explained considering the population involved in the study: we defined ASA 3 patients as high-risk patients. They were 48/147 (32.62%) in total, the majority of the patients treated instead belonged to a low-medium risk class. Goal- directed fluid therapy may be more important in a high-risk surgery population than in a relatively healthy population: Jammer et al. investigated if high-risk surgical patients could benefit from SVV-guided fluid therapy, but the question remained open because a majority of their patients was excluded from the trial due to methodological limitations (a laparoscopic technique was preferred in high risk patients) [25]. Finally, studies in the field of ERAS application protocol showed that the ERAS patient arrives in the operating room without a significant deficit of fluids; this condition aids in the intraoperative management of fluid-therapy. Therefore, the effectiveness of GDFT seems to be less evident within an ERAS program. Our results seem to further reduce the impact of a GDFT cardiac output guided algorithm on the clinical and economic outcomes considered and we could speculate that patients at low or moderate risk with a proper preoperative fluid balance do not derive additional benefit from the use of a mini-invasive hemodynamic monitoring system.

Furthermore, the incidence of postoperative complications did not seem to be influenced by the type of fluid-therapy applied. In particular, 42 patients (28.37%) developed complications in the postoperative period considered (28 days); 17 patients of the Vigileo GDFT group and 25 patients from the Standard GDFT group. No significant statistical difference was observed between the two study groups. More than half of the postoperative complications were of a surgical nature **(Table 2).** These complications had a high impact on the costs of the four categories considered: pharmaceuticals, procedures, hospital stay and diagnostic testing. In patents with surgical complications, the increase of cost due to such complications was statistically significant **(Table 6).**

Our results suggest that an appropriate fluid therapy could be more effective on high- risk patients with evident fluid balance alterations, rather than on relatively healthy patients; moreover, from an economic point of view, the advantages of a proper fluid therapy seem to be offset by surgical complications which are the main determinants of costs.

In our study, dobutamine has been mainly administered in GDFT group. Increase the supply of oxygen in surgical patients at high risk during the peri-operative period showed considerable advantages [26]. To obtain adequate tissue oxygenation, boluses of fluids may not be sufficient. The use of vasopressors and inotropes has proved important in integrating GDT protocols [7]. In particular dobutamine, a positive inotropic agent and peripheral vasodilator, it can play a crucial role in achieving effective tissue oxygenation.

The main limit of the study is that it is a prospective observational study in which the allocation of patients in the groups depended on the availability of the “Vigileo” device in the hepatobiliopancreatic operating room. A randomized controlled trial is needed to confirm our results and it should only consider a high-risk patient population (e.g., ASA ≥ 3) to clarify whether the lack of economic and clinical benefits of a GDFT based on a mini-invasive hemodynamic monitoring system found in our trial is due to the relatively health state of patients (ASA I-III).

Furthermore, the fact that the length of hospital stays, which we used as a clinical outcome parameter, is conditioned by different clinical factors besides the GDFT might have influenced our results.

Acknowledgments

Authors would like to acknowledge departmental funding only.

Conflict of Interest

The authors declare that there is no conflict of interest.

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