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REVIEW ARTICLE

Is perioperative goal-directed therapy able to reduce surgical complications in different surgical settings? A meta-analytic study

Mariateresa Giglio[1]✉, Giandomenico Biancofiore[2], Filomena Puntillo[1], Stefano Romagnoli[3], Luigi Tritapepe[4], Nicola Brienza[1]

[1] *Anesthesia and Intensive Care Unit, Department of Emergency and Organ Transplantation, University of Bari, Italy*

[2] *UO Anestesiae Rianimazione Trapianti, Università Degli Studi, Pisa*

[3] *Dipartimento di Anestesia e Rianimazione, Azienda Ospedaliero-Universitaria Careggi, Firenze*

[4] *Direttore UOC Anestesia e Rianimazione, AO San Camillo Forlanini-Roma*

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Abstract

Introduction: Goal directed therapy (GDT) is a method aiming at optimizing doses and timing of fluids, inotropes and vasopressors, through monitoring of cardiac output and other basic hemodynamic parameters. Several meta-analyses confirm that GDT can reduce postoperative complications in high risk patients, and a recent trial suggests its significant effect also in low-moderate risk patients. The aim of the present meta-analysis is to investigate the effect of GDT on postoperative complications, in both high and low risk patients. Moreover, we stratified the effect of GDT in different kind of surgical procedures.

Methods: Randomized controlled trials (RCTs) on perioperative GDT in adult surgical patients were included. The primary outcome measure was complications, defined as number of patients with a least one postoperative complication. A subgroup-analysis was also performed including RCTs with a mortality rate in control group <10%, and considering the kind of surgery: major abdominal (including also major vascular), only vascular, only orthopedic surgery and so on. Meta-analytic techniques (analysis software RevMan, version 5.3.5, Cochrane Collaboration, Oxford, England, UK) were used to combine studies using odds ratios (ORs) and 95% confidence intervals (CIs).

Results: In 47 RCTs, 2329 patients developed at least one complication: 1030 out of 2781 (37%) were randomized to perioperative GDT, and 1299 out of 2772 (47%) were randomized to control. Pooled OR was 0.58 and 95% CI was 0.47-0.70. The sensitivity analysis confirmed main result. The subgroup analysis including only studies in which the mortality rate in the control group was higher than 10% showed significant results (OR 0.51, 95% CI 0.35-0.74, p=0.004, 10 RCTs), as well as a statistical significant effect was observed in those RCTs with a mortality rate in control group <10% (OR 0.59, 95% CI 0.47-0.74, p<0.0001, 37 RCTs). The subgroup analysis enrolling major abdominal patients showed a significant result (OR 0.69, 95% CI 0.57-0.83,p <0.0001, 29 RCTs, 3881 patients) as well as a significant effect was observed in those RCTs enrolling exclusively orthopedic (OR 0.48, 95% CI 0.30-0.79,p=0.004, 6 RCTs, 501 patients) and neurosurgical procedures (OR 0.40, 95% CI 0.21-0.78, p=0.008, 2 RCTs, 208 patients).

Conclusions: The present meta-analysis suggests that GDT can reduce postoperative complication rate in high risk as well as in low risk patients. Moreover, the beneficial effect of GDT on postoperative morbidity is significant on major abdominal, orthopedic and neurosurgical procedures. However, heterogeneity was found in some subgroups, reducing the strength of the results. Several well-designed RCTs are needed to further explore the effect of GDT in low risk patient and in different kind of surgeries.

Key words: Cardiac output, Fluid therapy, Meta-analysis, Postoperative complications

Tel: +985632381203
Fax: +985632440488
Po Bax 97175-379
Email: jsurgery@bums.ac.ir

✉**Correspondence to:**
Mariateresa Giglio, Anesthesia and Critical Care Division, Department of Emergency and Organ Transplantation, Policlinico, Piazza G. Cesare University of Bari, Italy;
Telephone Number: 00390805595153
Email Address: mariateresagiglio@gmail.com

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Introduction

Approximately 240 million anesthesia procedures are performed annually worldwide (1). 10% of these procedures are related to high-risk patients, and this group accounts for > 80% of perioperative deaths (2). Moderate-risk surgery is much more common and constitutes about 40% of total surgical procedures (3). Nonetheless, even moderate and low-risk patients could experience minor postoperative complications, including postoperative ileus, nausea, vomiting, and wound complications (4) which can prolong hospital stay, increase health-care costs, and reduce long term survival (5-7).

Many postoperative complications are thought to be related to tissue hypoperfusion and imbalance between oxygen delivery and consumption. Goal-directed therapy (GDT) is a method which monitors the cardiac output and other basic hemodynamic parameters to optimize doses and timing of fluids, inotropes, and vasopressors. Several meta-analyses (8, 9) have suggested that GDT can reduce postoperative complications in high- risk patients, and a recent trial has also pointed to the significant effect of GDT on low or moderate-risk patients (10). Although hemodynamic monitoring is recommended by national guidelines (11, 12), a worldwide variability still exists in the adaptation of this strategy.

The present meta-analysis aimed to investigate the effect of GDT on postoperative complications in both high and low-risk patients. Moreover, we stratified the effect of GDT on different kinds of surgical procedures.

Methods

Eligibility criteria

Randomized controlled trials (RCTs) were selected according to the following inclusion criteria (13):

1) Types of participants: Adult patients aged ≥18 years who had undergone major non-cardiac surgeries were taken into account. On the other hand, studies involving mixed populations of critically ill, nonsurgical patients, or postoperative patients with sepsis or organ failure were excluded.
2) Types of interventions: GDT was defined as monitoring and manipulation of hemodynamic parameters to reach normal or supranormal values by fluid infusion alone or in combination with inotropic therapy in the perioperative period within 8 h after the surgery. On the other hand, studies including late hemodynamic optimization treatment were ruled out.
3) Types of comparisons: The trials which compared the beneficial and harmful effects of GDT to standard hemodynamic therapy were considered. On the contrary, RCTs with no description or no difference in optimization strategies between groups, as well as RCTs in which therapy was titrated to the same goal in both groups or was not titrated to predefined end-points, were excluded.
4) Types of outcome measures: Complications which are defined as the number of patients with a least one postoperative complication were regarded as the primary outcome measure. Sensitivity analysis was planned including only trials with low risk of bias (see below). A subgroup analysis was also performed which included RCTs with a mortality rate of >10% in the control group (defined as high risk of mortality/morbidity). This cut-off was selected based on the results of a previous meta-analysis (14). Another sub-group analysis was carried out considering the type of surgery. Moreover, for the overall group, as well as for every specific type of surgery, studies were divided on the basis of the target used in the GDT protocol and the adopted strategy (i.e., only fluids or fluids and inotropes). The targets which were used in the GDT protocol included indices of preload responsiveness, cardiac output or oxygen delivery, or other indirect indices of oxygen delivery, such as lactate and central or mixed venous oxygen saturation. It is worthy to note that the volume of crystalloids and colloids, as well as the total volume of fluid received during the GDT period, were also analyzed in those studies that used fluids alone.
5) Types of studies: RCTs on perioperative GDT in surgical patients were included. No language, publication date, or publication status restrictions were imposed.

Information sources

Different search strategies (last update September 2019) were performed to retrieve relevant RCTs using MEDLINE, The Cochrane Library and EMBASE databases. No date restriction was applied for MEDLINE and Cochrane Library databases, while the search was limited to 2008-2018 for the EMBASE database (15). Additional RCTs were searched in Cochrane Library, the Database of Abstracts of Reviews of Effects (DARE), and in the reference lists of previously published reviews and retrieved articles. Other data sources were manually

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searched in the annual proceedings (2008-2018) of the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the Society of Cardiovascular Anesthesiologists, the Royal College of Anesthetists, and the American Society of Anesthesiologists. In order to reduce publication bias, abstracts were also searched (16). Publication language was not a search criterion.

Search terms

Trials selection was performed using the following search terms: randomized controlled trial, controlled clinical trial, surgery, goal-directed, goal-oriented, goal target, cardiac output, cardiac index, DO2, oxygen consumption, cardiac volume, stroke volume, fluid therapy, fluid, fluid loading, fluid administration, optimization, optimization, and supranormal. The search strategies used for the MEDLINE, The Cochrane Library, and EMBASE databases are reported in supplementary material 1.

Study selection

Firstly, two investigators (F. P, L. D) examined each title and abstract to exclude irrelevant studies and identify the potentially relevant ones. The other two investigators (M. G, N. B) independently determined the eligibility of retrieved full-text articles. During this time, the two investigators were blind to the names of the author, institution, journal of publication, and the results.

Data abstraction and study characteristics

Data were independently collected by two investigators (G. B, S. R), and any discrepancy was resolved by re-inspection of the original article. To avoid transcription errors, the data were input into statistical software and rechecked by different investigators (M. G, N. B).

Gathered randomized controlled trial data

Data abstraction included surgical risk (defined by the authors on the basis of Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) score (17), American Society of Anesthesiologists (ASA) physical status classification, age >60 years, pre-operative morbidity, and type of surgery), mortality of control group, type of surgery (i.e., elective or emergent, abdominal, thoracic, or vascular), anesthesiological management, hemodynamic goal-directed therapy (end-points, therapeutic intervention, and monitoring tools). The volume of crystalloids and colloids, as well as the total volume of fluid which was received during the GDT period, were also analyzed.

Risk of bias in individual studies

A domain-based evaluation, as proposed by the Cochrane Collaboration, was used to evaluate the methodological quality of RCTs (18). This is a two-part tool which addresses seven specific domains that are strongly associated with bias reduction (19, 20). Each domain in the tool includes one or more specific entries in a 'Risk of bias' table. Within each entry, the first part of the tool fully describes the procedure of the study to confirm the earlier judgment about the risk of bias. The second part of the tool makes a judgment on the risk of bias for that entry. Each risk of bias was rated as Low risk/High risk/Unclear risk. Upon the completion of each domain, a 'Risk of bias summary' figure was generated which presented all of the judgments in a cross-tabulation of study by entry. The green plus indicates a low risk of bias, the red minus denotes a high risk of bias, and the white color implies an unclear risk of bias. For each study, the number of green pluses obtained for every domain was calculated: RCTs with five or six green plus were regarded as having an overall low risk of bias.

Summary measures and planned method of analysis

Meta-analytic techniques (RevMan software, version 5.3.5, Cochrane Collaboration, Oxford, England, UK) were used to combine studies using odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables. On the other hand, Weighted Mean Difference (WMD) and 95% CI were used for continuous variables. A statistical difference between groups was considered to occur if the pooled 95% CI did not include 1 for the OR. An OR less than 1 favored GDT, as compared to the control group. Two-sided p-values were also calculated. A random-effects model was selected for all analyses. Statistical heterogeneity and inconsistency were assessed using Q and I^2 tests, respectively (21, 22). When the p-value of the Q-test was < 0.10 and/or the I^2 was >40%, heterogeneity and inconsistency were considered significant (23).

Results

Study selection

The search strategies identified 3553 (MEDLINE), 10299 (Cochrane Library) and 3108 (EMBASE) articles. In addition, 13 more articles were found in other sources (e.g., congress abstracts, reference lists). After the initial screening and subsequent selection, a pool of 133

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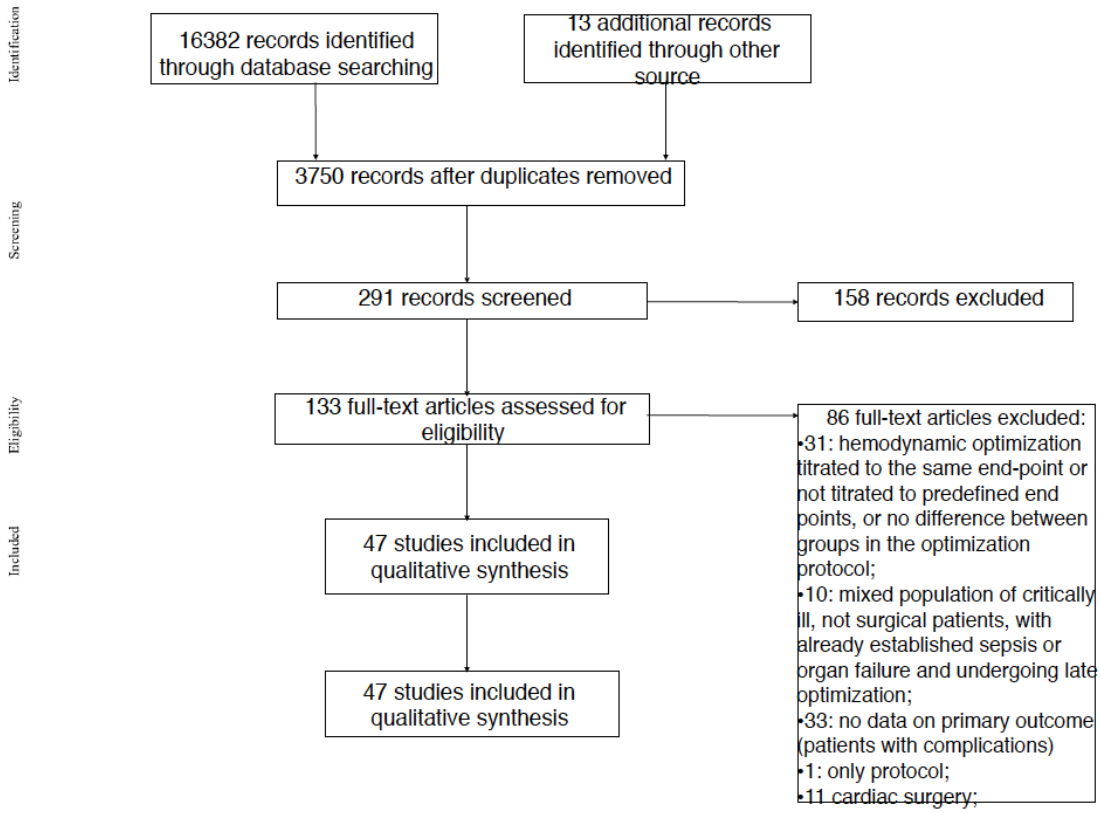

Figure 1: Flow chart summarizing study selection procedure for the meta-analysis. RCT: randomized controlled trial

potentially relevant RCTs was identified. The subsequent eligibility process (Figure 1) excluded 86 articles. Consequently, 47 articles (10, 24-69) with a total sample of 5553 patients were considered for the analysis.

Study characteristics

All included articles evaluated the effects of hemodynamic optimization on mortality as the primary or secondary outcome and included adult surgical patients who had undergone both elective and emergent procedures (Table 1). The studies were performed in Australia, the United States, Europe, Canada, Brazil, China, and India within 1991-2019 (Table 1) and were all published in English.

Data concerning population and type of surgery are presented in Table 1. The risk of bias assessment for each trial is illustrated in Table 2. Out of 47 studies, 10 cases reported a mortality rate of >10% in the control group.

Quantitative data synthesis

In 47 RCTs, 2329 patients developed at least one complication: 1030 out of 2781 (37%) were assigned to the perioperative GDT group, and 1299 out of 2772 (47%) were randomized to the control group. Pooled OR was reported as 0.58 and 95% CI was measured at 0.47-0.70 (Figure 2). The sensitivity analysis revealed that the significant effect of GDT on postoperative complications was confirmed by a low risk of bias RCTs, with high statistical heterogeneity and inconsistency (OR 0.60, 95% CI 0.49-0.75, P<0.00001, Q-statistic P= 0.0003; I2 =54 %, 30 RCTs) (Figure 2).

The subgroup analysis which only included studies in which the mortality rate in the control group was higher than 10% demonstrated significant results (OR 0.51, 95% CI 0.35-0.74, P=0.0004, Q-statistic P = 0.21, I2 =25 %, 10 RCTs). Moreover, a statistical significant effect was observed in those RCTs with a mortality rate of <10% in the control group (OR 0.59, 95% CI 0.47-0.74, P<0.00001, Q-statistic P< 0.00001; I2 =60%, 37 RCTs) (Figure 3).

In the overall population, GDTs which used indices of preload resulted in a significant reduction of perioperative complications (OR 0.65, 95% CI 0.45-0.96, P=0.003, 6 RCTs; Table 3). Moreover, the GDTs which used indices of CO yielded significant results with high statistical heterogeneity and inconsistency (OR 0.55, 95% CI 0.44-0.70, P=0.00001, 38 RCTs; Table 3). Both adopted strategies (fluids only or fluids and

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Table 1: Characteristics of included studies

Author, Year, Country	Surgery	Goal-Directed Therapy (Tools and goals)	Modality of optimization
Ackland et al. (24) 2015, Europe	Major elective abdominal surgery	Lidco plus; SV< 10%, DO_2 > 600 L·min^{-1}·m^{-2}	Fluids and inotropes
Bender et al. (25), 1997, USA	Elective aortic and vascular	PAC; CI ≥ 2.8 L min^{-1}·m^{-2}, 8 ≤ Pcwp ≤ 14 mmHg, SVR ≤ 1100 dyne·sec·cm^{-5}	Fluids and inotropes
Benes et al. (26), 2010, Europe	Elective abdominal	FloTrac/Vigileo; CI ≥ 2.5 L·min-1·m-2	Fluids and inotropes
Bisgaard et al. (27), 2013, Europe	Elective peripheral vascular	Lidco; SV < 10%, DO_2 > 600L·min^{-1}·m^{-2}	Fluids and inotropes
Brandstrup et al. (28), 2012, Europe	Elective abdominal	Esophageal Doppler SV increase > 10%	Fluids
Broch et al. (29), 2016, Europe	Major abdominal	Nexfin system; PPV >10% CI ≥ 2.5 L·min-1·m-2	Fluids and inotropes
Calvo Vecino et al.(10), 2018, Spain	Major abdominal, urological, gynecological, or orthopedic surgery	(CardioQ, EDM; SV increase > 10% CI ≥ 2.5 L·min-1·m-2	Fluids and inotropes
Cecconi et al. (30), 2011, Europe	Orthopaedic	FloTrac/Vigileo; SV < 10%, DO_2 > 600 L·min^{-1}·m^{-2}	Fluids and inotropes
Challand et al. (31), 2013, Europe	Major abdominal	Oesophageal Doppler SV increase of 10%	Fluids
Colantonio et al. (32), 2015, Europe	Cytoreductive surgery	FloTrac/Vigileo; CI ≥ 2.5 L·min-1·m-2 SVI>35 ml·min^{-1}·m^{-2}	Fluids and inotropes
Correa-Gallego et al (33), 2015, Europe	Elective liver resection	FloTrac/Vigileo; SVV ≤ 2 DS of pre-induction	Fluids
Elgendy et al. (34), 2017, Africa	Major abdominal	FloTrac/Vigileo; SVV <12%, CI ≥ 2.5 L·min-1·m-2	Fluids and inotropes
Forget et al. (35), 2011, Europe	Major abdominal	Masimo set pulse oxymeter; PVI < 13%	Fluids
Gomez-Izquierdo et al. (36), 2017, Canada	Colorectal surgery	Cardio Q rise of SV >10%	Fluids
Jammer et al. (37), 2010, Europe	Colo-rectal surgery	CVC $ScVO_2$ >75%	Fluids
Jhanii et al. (38), 2010, Europe	Elective gastro-intestinal	Not stated rise of SV >10%	Fluids and inotropes

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Table 1 Continued.

Kaufmann et al. (39), 2018, Europe	Orthopaedic	Oesophageal Doppler rise of SV >10% CI ≥ 2.5 L·min-1·m-2	Fluids and inotropes
Kumar et al. (40), 2016, India	Elective abdominal	FloTrac/Vigileo; SVV <10%,	Fluids and inotropes
Lobo et al. (41), 2000, Brazil	Elective major abdominal or vascular	PAC; DO_2 >600 mL·min^{-1}·m^{-2}	Fluids and inotropes
Lopes et al. (42), 2007, Brazil	Elective abdominal	Radial artery line; ΔPP ≤ 10%	Fluids
Luo et al. (43), 2017, China	Neurosurgery	FloTrac/Vigileo; SVV <15%, CI ≥ 2.5 L·min-1·m-2	Fluids and inotropes
Mayer et al. (44), 2010, Europe	Major abdominal	FloTrac/Vigileo; CI ≥ 2.5 L·min-1·m-2	Fluids and inotropes
Mikor et al. (45), 2015, Europe	Major abdominal	Cevox ScVO2 >75% or reduction of 3%	Fluids and inotropes
Moppett et al. (46), 2014, Europe	Emergent orthopaedic	LiDCO; SV increase <10%	Fluids
Noblett et al. (47), 2005, Europe	Major abdominal	Oesophageal Doppler; SV optimization	Fluids
Pearse et al. (48), 2005, Europe	Elective or emergent major general	LiDCO; DO_2 >600 mL·min^{-1}·m^{-2}, SV >10%	Fluids and inotropes
Pearse et al. (49), 2014, Europe	Major general	LiDCO; SV increase <10%	Fluids and inotropes
Pestana et al. (50), 2014, multicentric	Major abdominal	NICOM; CI ≥ 2.5 L·min-1·m-2	Fluids and inotropes
Pillai et al. (51), 2011 USA	Radical cystectomy	Cardio Q increase of SV >10%	Fluids
Salzwedel et al. (52), 2013, Europe	Major abdominal	ProAQT PPV >10% CI ≥ 2.5 L/min/m^2	Fluids and inotropes
Schereen et al. (53) 2013, Europe	Major abdominal and urologic	FloTrac/Vigileo; SVV< 10%	Fluids
Schmid et al. (54), 2019, Europe	Orthopedic	PulsioFlex SVI increase <10% CI ≥ 2.5 L/min/m^2	Fluids and inotropes
Shoemaker et al. (55), 1998, USA	Emergent or elective major abdominal (general or vascular)	PAC; CI >4.5 L·min^{-1}·m^{-2}, DO_2 >600 mL·min^{-1}·m^2, VO_2 >170 mL·min^{-1}·m^{-2}	Fluids and inotropes

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Table 1 Continued.

Sinclair et al. (56), 1997, Europe	Orthopedic	Oesophageal Doppler SV optimization with FTc between 0.35 sec-0.4 sec	Fluids
Srinvasa et al. (57), 2012, Australia	Elective colectomy	Oesophageal Doppler SV optimization with FTc between 0.35 sec-0.4 sec	Fluids
Stens et al. (58), 2017, Europe	Major abdominal	Nexfin device PPV <12% CI > 2.5 L $min^{-1}·m^{-2}$	Fluids and inotropes
Szturz et al. (59), 2019, Europe	Major abdominal	Oesophageal Doppler FTc < 330 msec CI > 2.5 L $min^{-1}·m^{-2}$	Fluids and inotropes
Ueno et al. (60), 1998, China	Hepatic resection	PAC; CI >4.5 L$·min^{-1}·m^{-2}$, DO_2 >600 mL$·min^{-1}·m^2$, VO_2 >170 mL$·min^{-1}·m^{-2}$	Fluids and inotropes
Van Beest (61), 2014, Europe	Elective major	In spectra system StO2>80%	Fluids and inotropes
Venn et al. (62), 2002, Europe	Orthopedic	Oesophageal Doppler SV optimization with FTc>0. 4 sec	Fluids
Wakeling et al. (63), 2005, Europe	Elective major bowel	Oesophageal Doppler; SV optimization and rise in CVP < 3 mmHg	Fluids
Weineberg et al. (64), 2017, Australia	Pancreaticoduodenectomy	FloTrac/Vigileo; SVV<20% baseline CI ≥ 2.L $min^{-1}·m^{-2}$	Fluids and inotropes
Weineberg et al. (65), 2019, Australia	Liver resection	FloTrac/Vigileo; SVV<20% baseline CI ≥ 2.2.L $min^{-1}·m^{-2}$	Fluids and inotropes
Wilson et al. (66), 1999, Europe	Elective major (abdominal, vascular, urologic)	PAC; DO_2 >600 mL$·min^{-1}·m^{-2}$	Fluids and inotropes
Wu et al. (67), 2017, China	Neurosurgery	FloTrac/Vigileo; SVV< 12%, CI > 2.5 L $min^{-1}·m^{-2}$	Fluids and inotropes
Zhang el al. (68) 2013, China	Thorascopic lobectomy	FloTrac/Vigileo; SVV< 10%, CI > 2.5 L $min^{-1}·m^{-2}$	Fluids and inotropes
Zheng et al. (69), 2013, China	Elective abdominal	FloTrac/Vigileo; SVI > 35 mL/m^2, CI ≥ 2.5 L $min^{-1}·m^{-2}$	Fluids and inotropes

Abbreviations: PPV :Pulse Pressure Variation, PVI : Pleth Variability Index, SVV : Stroke Volume Variation, SV: stroke volume, CI: Cardiac Index, CVP: Central Venous Pressure, SVI: Stroke Volume Index, SVR: Systemic Vascular Resistance, $ScvO_2$: Central Venous Oxygen Saturation, DO_2: Oxygen Delivery, PCWP: pulmonary capillary wedge pressure, PAC: pulmonary artery catheter, FTC: flow-time-corrected, VO_2: oxygen consumption, LiDCO: lithium diluition cardiac output monitoring, NICOM: non invasive cardiac output monitoring obtained via bioreactance, CVC: central venois catheter, StO2: tissue oxygenation, DS: standard deviation, ΔPP: variation of arterial pressure.

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Table 2: The risk of bias assessment for each trial, according to the Cochrane domain-based evaluation. This is a two-part tool which addresses seven specific domains (namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues') that are strongly associated with bias reduction. The green plus indicates low risk of bias, the red minus denotes high risk of bias, and the white color implies unclear risk of bias.(see text for details).

Author, Year, Country	Blinding of participants and personnel (performance bias)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Ackland et al. (24), 2015, Europe	+	+		+	+	+
Bender et al. (25), 1997, USA	-	-	-		-	
Benes et al. (26), 2010, Europe		+	+	+	+	+
Bisgaard et al. (27), 2013, Europe	+	+		+	+	+
Brandstrup et al (28), 2012, Europe	+	+	+	+	+	+
Broch et al. (29), 2016, Europe		+			+	+
Calvo Vecino et al. (10), 2018, Spain	+	+	+	+	+	+
Cecconi et al. (30), 2011, Europe			+	+	+	+
Challand et al. (31), 2013, Europe	+	+	+	+		+
Colantonio et al. (32), 2015, Europe	+	+		+	+	+
Correa-Gallego et al. (33), 2015, Europe	+	+	+	+	+	
Elgendy et al. (34), 2017, Africa	+	-		+		+
Forget et al. (35), 2011, Europe		+	+	+	+	+
Gomez-Izquierdo et al. (36), 2017, Canada	+	+	+	+	+	+
Jammer et al. (37), 2010, Europe		+	+	+	+	+

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Table 2 Continued.

Jhanii et al. (38), 2010, Europe		+	+	+	+	+
Kaufmann et al. (39), 2018, Europe	+	+	+	+	+	
Kumar et al. (40), 2016, India		-	+	+	+	+
Lobo et al. (41), 2000, Brazil		+			+	+
Lopes et al. (42), 2007, Brazil	-	-	+	+	+	
Luo et al. (43), 2017, China	-	-	+	-		
Mayer et al. (44), 2010, Europe			+	+	+	+
Mikor et al. (45), 2015, Europe	+	+		+	+	+
Moppett et al. (46), 2014, Europe	+	+	+	+	+	+
Noblett et al. (47), 2005, Europe	+	-	+	+	+	+
Pearse et al. (48), 2005, Europe		+	+	+	+	+
Pearse et al. (49), 2014, Europe	+	+	+	+	+	+
Pestana et al. (50), 2014, Multicentric	+	+	+	+	+	
Pillai et al. (51), 2011 USA	-	-	-	-		
Salzwedel et al. (52), 2013, Europe	+	+	+	+	+	+
Schereen et al. (53), ,2013, Europe			+	+	+	+
Schmid et al.(54), 2019, Europe	+	+	+	+	+	
Shoemaker et al. (55), 1998, USA	-	-	-	-	-	+

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Table 2 Continued.						
Sinclair et al. (56), 1997, Europe	+		+	+	+	+
Srinvasa et al. (57), 2012, Australia	+	+	+	+	+	
Stens et al. (58), 2017, Europe		+	+			+
Szturz et al. (59), 2019, Europe	+	+	+	+	+	
Ueno et al. (60), 1998, China	-	+	-			
Van Beest. (61), 2014, Europe	-	-	-	+	+	+
Venn et al. (62), 2002, Europe		+	+	+	+	+
Wakeling et al. (63), 2005, Europe		+	+	+	+	+
Weineberg et al. (64), 2017, Australia	+	+	+	+	+	+
Weineberg et al. (65), 2019, Australia	+	+	+	+	+	+
Wilson et al. (66), 1999, Europe	+	+	+	+	+	
Wu et al. (67), 2017, China	-	-	-			
Zhang el al. (68), 2013, China		+	+		+	+
Zheng et al. (69), 2013, China	+	+	+	+	+	+

inotropes) demonstrated significant results (OR 0.61, 95% CI 0.43-0.88, P=0.009, 15 RCTs: for fluids only, and OR 0.55, 95% CI 0.44-0.70, P<0.00001, 32 RCTs: for fluids and inotropes) (Table 3).

Furthermore, the subgroup analysis which enrolled major abdominal patients showed a significant result (OR 0.69, 95% CI 0.57-0.83, P=0.0001, Q-statistic P= 0.04, I2 =33 %, 29 RCTs, 3881 patients; Figure 4). In this specific kind of surgery, GDTs which used indices of preload as target resulted in a significant reduction in perioperative complications (OR 0.65, 95% CI 0.45-0.96, P<0.03, 6 RCTs). On the other hand, the use of indices of CO yielded significant results with high statistical heterogeneity and inconsistency (OR 0.70, 95% CI 0.56-0.86, P<0.008, 23 RCTs). The strategy of adopting only fluids only showed non-significant results (OR 0.81, 95% CI 0.61-1.08, P=0.16,), while the use of both fluids and inotropes significantly reduced postoperative complications (OR 0.63, 95% CI 0.49-0.79, P<0.0001, 18 RCTs: for fluids and inotropes; Table 3). In those RCTs which only adopted fluids as optimization strategy, patients in the GDT group received more colloid (Table 4) and less crystalloid (Table 4), as compared to the patients in the control group. The total volume of fluid was not significantly different between the GDT and the control group.

A significant effect was observed in those RCTs which exclusively included orthopedic procedures (OR 0.482, 95% CI 0.230-0.790, P=0.004, Q-statistic p P= 0.24; I2 =26 %, 6 RCTs, 501 patients;

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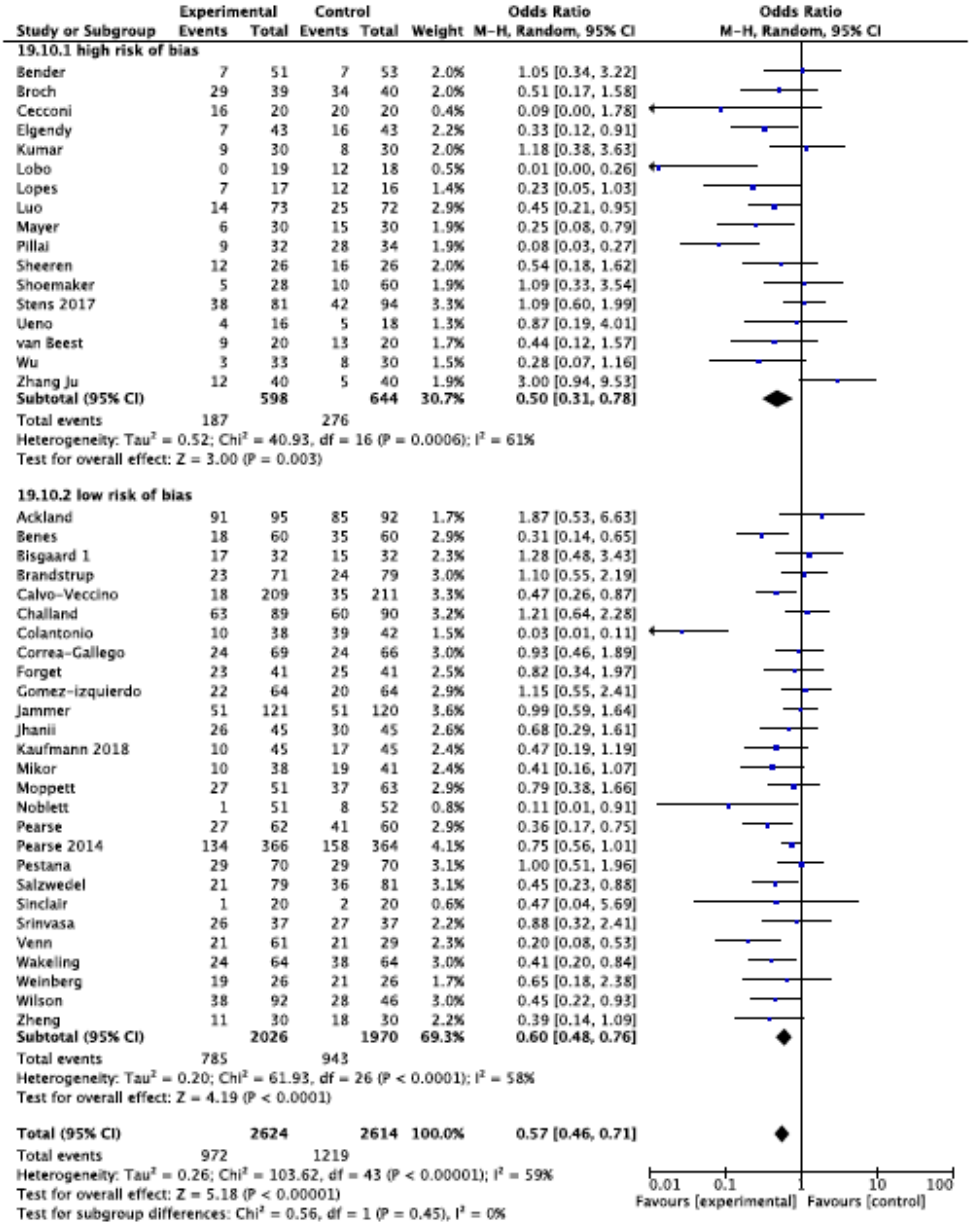

Figure 2: Rates of postoperative complications in subgroups are defined according to risk of bias (see text for details) with Odds Ratios (ORs) and 95% Confidence intervals (CI). The pooled OR and 95% CI are depicted as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamonds represent the point estimate of the pooled ORs and the length of the diamonds is proportional to the CI.

Figure 5), as well as in those RCTs enrolling neurosurgical procedures (OR 0.40, 95% CI 0.21-0.78, P=0.008, Q-statistic P=0.56; I2= 0%, 2 RCTs, 208 patients). Only two RCTs exclusively considered vascular surgery, and the pooled OR pointed to the non-significant effect of GDT on postoperative complications (OR 1.18, 95% CI 0.56-2.46, P=0.67, Q-statistic p P= 0.79; I2 =0 %, 2 RCTs, 168 patients) (supplementary material). For these other surgeries, no other subgroup analyses were performed due to the very low number of RCTs included.

Discussion

The present meta-analysis suggested that GDT can significantly reduce postoperative complications. This effect was confirmed when only low risks of bias for RCTs were included in the analysis. Both targets which were used in

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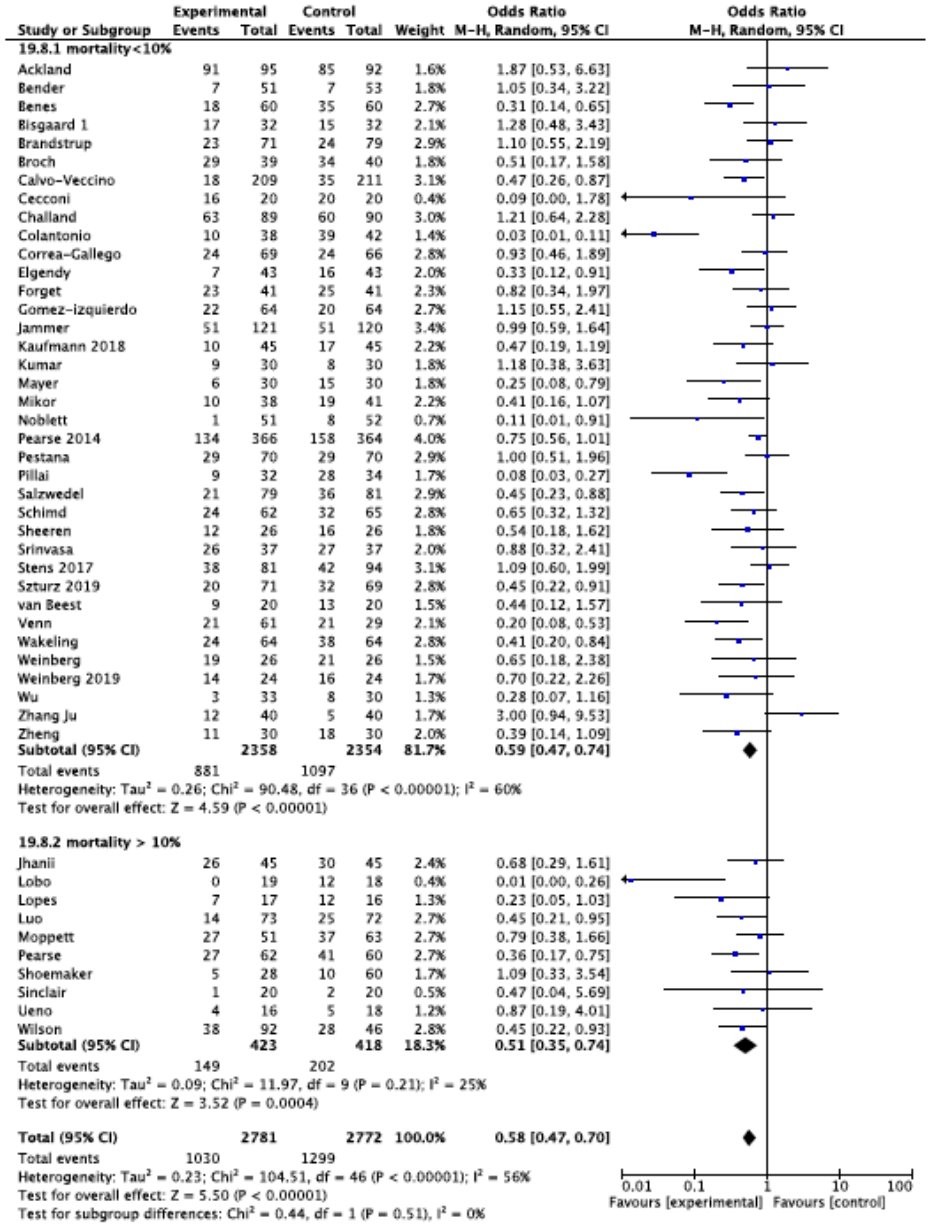

Figure 3: Rates of postoperative complications in subgroups are defined according to the mortality/morbidity risk (see text for details) with Odds Ratios (ORs) and 95% Confidence intervals (CI). The pooled OR and 95% CI are illustrated as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamonds represent the point estimate of the pooled ORs and the length of the diamonds is proportional to the CI.

hemodynamic management (i.e. indices of preload responsiveness or indices of CO) and both strategies (i.e. fluids only or fluids and inotropes) yielded significant results, even with heterogeneity. The observed significant reduction was confirmed in both high and low- risk patients who underwent abdominal, orthopedic, and neurosurgical procedures.

Hemodynamic monitoring and guided fluid administration can allow early detection and prompt rectification of inadequate oxygen supply, thereby preventing cellular hypoxia-mediated tissue injury. Adjustments in the administration of fluid and drugs must be performed in a timely manner to avoid both hypoperfusion and fluid overload. As evidenced by several RCTs and meta-analyses, GDT reduces postoperative complications in high- risk surgical patients, regardless of the monitoring or the achieved target (7-9, 14). Nonetheless, the evidence concerning the effect of

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Table 3: OR:odds ratio, CI: confidence interval, RCT: randomized controlled trial, CI: cardiac output

Patients with complications	Number of RCTs (references)	Treatment n/N	Control n/N	OR (95%CI)	P-value	I^2	Q-statistic P-value
Indices of preload	6 (33,35,40,42,52,53)	96/262	121/260	0.65 (0.45-0.96)	0.03	8%	0.37
Indices of CI	38 (10,24-32,34,36-39, 41,43-51,54-60,62-69)	864/2340	1095/2331	0.55 (0.44-0.70)	<0.00001	61%	<0.00001
Fluids	15 (28,31,33,35-37,42, 46,47,51,53,56 57,62,63)	334/814	393/801	0.61 (0.43-0.88)	0.09	61%	0.01
Fluids and inotropes	32 (10,24-27,29,30,32, 34,38-41,43-45,48-50,52,54,55,58-61,64-69)	696/1967	906/1971	0.55 (0.44-0.70)	<0.00001	54%	0.0002
Abdominal surgery only							
Indices of preload	6 (33,35,40,42,52,53)	96/262	121.260	0.65 (0.45-0.96)	0,03	8%	0.37
Indices of CI	23 (10,28,29,31,34,36-38,44,47-50,57-61,63-65,67-69)	613/1669	738.1690	0.70 (0.56-0.86)	0.008	39%	0.03
Fluids	11 (28,31,33,35-37,42, 47,53,57,63)	276/650	305/655	0.81 (0.61-1.08)	0.16	29%	0.17
Fluids and inotropes	18 (10,29,34,38,40,44, 48-50,52,58-61, 64,65,68,69)	399/1186	506/1202	0.63 (0.49-0.79)	0.0001	32%	0.09

GDT on postoperative complications in low- risk patients is much more unclear. The present meta-analysis demonstrated that GDT is able to reduce postoperative complications in both high and low-risk patients.

Postoperative complications are related to ischemia that triggers a vicious cycle of inflammation, fibrosis, oxidative stress, apoptosis, and necrosis. Like in a "U-shape" manner, excessive fluid loading can result in fluid overload which eventually leads to endothelial injury and shedding of the glycocalyx, promotes endothelial leak, further oedema that worsens oxygen convection, and postoperative complications. Therefore, it can be argued that GDT allows the judicious use of fluid when it is needed. Moreover, it prevents unnecessary fluid loading when hemodynamic targets are already met (70). This personalized and prompt strategy can explain the reduction of postoperative complications in low- risk patients. It was traditionally believed that these patients are able to adapt to perioperative stress therefore, they do not need any hemodynamic monitoring and strategy. A recent RCT (10), which was included in the present meta-analysis, supported this hypothesis. It is noteworthy that the most robust result of the present meta-analysis was observed in the subgroup analysis enrolling trials that adopted indices of preload as a hemodynamic target. All these trials also enrolled low- risk patients suggesting that a less invasive approach could be sufficient in order to preserve tissue perfusion at least in this category. Nevertheless, the high heterogeneity of the subgroup analysis which included low- risk patients reduced the strength of the evidence.

Another finding of our meta-analysis was that the total volume of fluid did not increase with the use of GDT. Patients received more colloids but fewer crystalloids; accordingly, the total volume of fluid was not significantly different between the control and GDT group. This finding goes against the perception or the fear that using hemodynamic optimization protocols may be associated with

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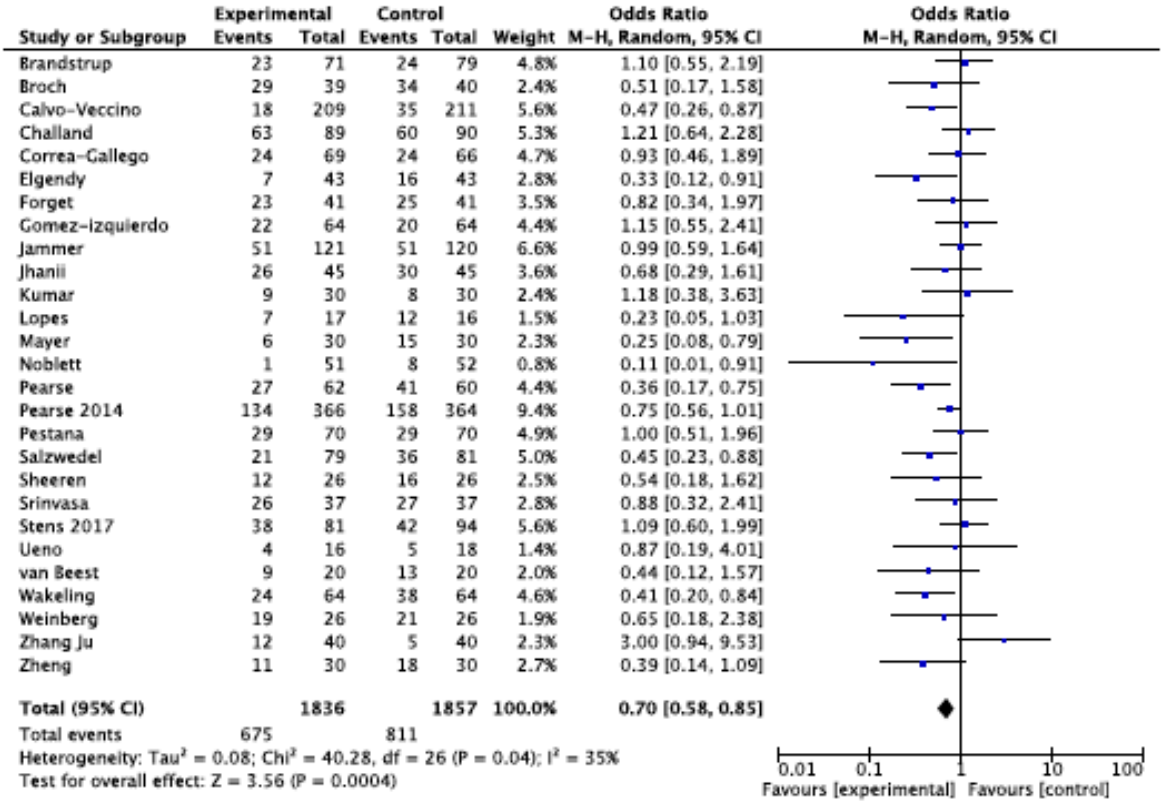

Figure 4: Rates of postoperative complications in patients undergoing abdominal surgery, with Odds Ratios (ORs) and 95% Confidence intervals (CI). The pooled OR and 95% CI are displayed as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamonds represent the point estimate of the pooled ORs and the length of the diamonds is proportional to the CI.

Table 4: OR: odds ratio, RCT: randomized controlled trial

Patients with complications All studies	Number of studies (references)	Treatment	Control	Standard Mean Difference (95%CI)	P-value	I^2	Q-statistic P-value
Total fluids	6 (33,35,36,42,46,43)	268	276	-1.38 (-3.83,107)	0.06	99%	P<0.00001
Colloids	8 (28,31,35,36,46,47, 53,56)	439	461	0.76 (0.19,1.33)	0.009	94%	P<0.00001
Crystalloids	7 (28,31,35,36,46,47, 56)	388	408	-1.63 (-2.84,-0.43)	0.008	98%	P<0.00001
Only abdominal							
Total fluids	5 (33,35,36,42,53)	217	213	-1.95 (-5.60,1.71)	0.30	99%	P<0.00001
Colloids	6 (28,31,35,36,47,53)	368	378	0.45 (-0.11,1.01)	0.11	93%	P<0.00001
Crystalloids	5 (28,31,35,36,47)	317	325	-1.24 (-2.49,0.00)	0.05	98%	P<0.00001

excessive fluid administration. On the contrary, it supports the idea that GDT helps clinicians to give the right amount of fluid to the right patients at the right time without necessarily modifying the average amount of fluid given to a patient.

The beneficial effect of GDT on abdominal surgery is widely known and supported by other meta-analyses (71, 72), and the results of the present study also confirmed this effect. Real-life implementation of an intraoperative GDT protocol

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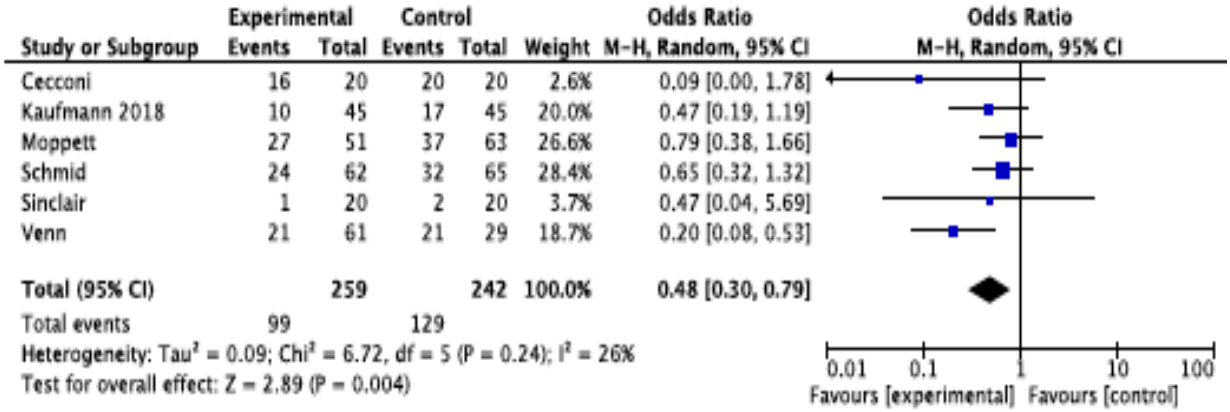

Figure 5: Rates of postoperative complications in patients undergoing orthopedic surgery with odds ratios (ORs) and 95% confidence intervals (CI). The pooled OR and 95% CI are shown as the total. The size of the box at the point estimate of the OR gives a visual representation of the "weighting" of the study. The diamonds represent the point estimate of the pooled ORs and the length of the diamonds is proportional to the CI.

was associated with a significant reduction in the incidence of complications following gastrointestinal surgery. Moreover, the observed improvement in the quality of surgical care was not associated with a significant increase in hospital costs (73).

Different from other studies; however, the present meta-analysis also demonstrated significant results in other kinds of surgeries suggesting that GDT application could be extended to other surgical settings. The incidence of postoperative complications is well- known in abdominal surgery ranging from 12% after hepatectomy to 44% following esophagectomy (74). However, similar incidences are reported in other types of surgical procedures. For orthopedic surgery (i.e. hip fracture surgery), postoperative complications range from 7% for pulmonary adverse events to 42% for cardiac complications (75). In addition, vascular surgery shows similar trends varying from 21 to 33% (74). Moreover, all these surgical patients usually belong to the "high-risk" category, due to age, comorbidity, and reduced cardiovascular reserve. Therefore, a strategy which is aimed to maintain cardiac output in these frail patients undergoing specific surgical procedure could result in reduced postoperative complications. Nevertheless, we did not manage to study the effect of GDT on vascular surgery since most studies involved a mixed population of abdominal and vascular patients, and no individual data were available.

A major limitation of our analysis is the presence of heterogeneity in defining postoperative complications, and a random-effects model was used even when the estimated amount of heterogeneity was low. High heterogeneity was found in almost all subgroups which reduced the strength of the results. Moreover, even if we try to control clinical heterogeneity with subgroup analysis by splitting studies on the basis of monitoring tools and targets, statistical heterogeneity will remain high; therefore, the obtained results should be interpreted with caution.

Conclusions

Despite the clinical and statistical heterogeneity and paucity of data, Tthe present meta-analysis made new suggestions concerning the beneficial effect of GDT on the reduction of postoperative morbidity rates in low- risk patients, as well as in other types of surgeries, different from major abdominal operations. These results require other RCTs with the aim of exploring the real impact of hemodynamic GDT and its specific issues (i.e. monitoring tools and targets, means adopted, patients to enroll) on low- risk patients, as well as other surgical settings.

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Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of the current article.

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