



REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br



REVIEW ARTICLE

Colloids versus crystalloids in objective-guided fluid therapy, systematic review and meta-analysis. Too early or too late to draw conclusions



Javier Ripollés^{a,*}, Ángel Espinosa^b, Rubén Casans^c, Ana Tirado^a, Alfredo Abad^d,
Cristina Fernández^e, José Calvo^f

^a Anestesia y Reanimación, Hospital Universitario Infanta Leonor, Madrid, Spain

^b Thorax Anesthesiology and Intensive Care Consultant, Thorax Centrum, Karlskrona, Sweden

^c Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

^d Anestesia y Reanimación, Hospital Universitario La Paz, Madrid, Spain

^e Universidad Complutense de Madrid, Unidad de Metodología de la Investigación y Epidemiología clínica, Servicio de Medicina Preventiva, Hospital Clínico San Carlos, Madrid, Spain

^f Universidad Complutense de Madrid, Hospital Universitario Infanta Leonor, Madrid, Spain

Received 29 May 2014; accepted 3 July 2014

Available online 3 May 2015

KEYWORDS

Fluid therapy;
Objective-guided
fluid therapy;
Colloids;
Hydroxyethyl starch;
Crystalloids;
Systematic review;
Meta-analysis

Abstract

Introduction: Several clinical trials on Goal directed fluid therapy (GDFT) were carried out, many of those using colloids in order to optimize the preload. After the decision of European Medicines Agency, there is such controversy regarding its use, benefits, and possible contribution to renal failure. The objective of this systematic review and meta-analysis is to compare the use of last-generation colloids, derived from corn, with crystalloids in GDFT to determine associated complications and mortality.

Methods: A bibliographic research was carried out in MEDLINE PubMed, EMBASE and Cochrane Library, corroborating randomized clinical trials where crystalloids are compared to colloids in GDFT for major non-cardiac surgery in adults.

Results: One hundred thirty references were found and among those 38 were selected and 29 analyzed; of these, six were included for systematic review and meta-analysis, including 390 patients. It was observed that the use of colloids is not associated with the increase of complications, but rather with a tendency to a higher mortality (RR [95% CI] 3.87 [1.121–13.38]; $I^2 = 0.0\%$; $p = 0.635$).

* Corresponding author.

E-mails: ripo542@gmail.com, ripo542@hotmail.com (J. Ripollés).

PALAVRAS-CHAVE

Hidratação;
 Hidratação guiada
 por objetivos;
 Coloides;
 Derivados de
 Hidroxietyl Amido;
 Soluções Isotônicas;
 Revisão sistemática;
 Metanálise

Conclusions: Because of the limitations of this meta-analysis due to the small number of randomized clinical trials and patients included, the results should be taken cautiously, and the performance of new randomized clinical trials is proposed, with enough statistical power, comparing balanced and unbalanced colloids to balanced and unbalanced crystalloids, following the protocols of GDFT, considering current guidelines and suggestions made by groups of experts.
 © 2014 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. All rights reserved.

Coloides versus cristaloides em fluidoterapia guiada por objetivos, revisão sistemática e metanálise. Demasiadamente cedo ou demasiadamente tarde para obter conclusões

Resumo

Introdução: Foram realizados múltiplos ensaios clínicos em fluidoterapia guiada por objetivos (FGO), sendo muitos deles com o uso de coloides para otimização da pré-carga. Após a decisão da Agencia Europea de Medicamento, existe ainda controvérsia sobre sua utilização, benefícios e possível contribuição para a falência renal. O objetivo desta revisão sistemática e metanálise é comparar o uso de coloides de última geração, derivados de milho, com cristaloides em FGO para determinar as complicações e a mortalidade associadas.

Métodos: Realização de uma busca bibliográfica em MEDLINE Pubmed, EMBASE e Biblioteca Cochrane comprovando ensaios clínicos aleatórios nos quais se comparam cristaloides com coloides dentro de FGO para cirurgia não cardíaca de grande porte em adultos.

Resultados: Foram obtidas 130 referências das quais se selecionaram 38 e 29 foram analisadas; destas, seis foram incluídas para revisão sistemática e metanálise, incluindo 390 pacientes. Observou-se que o uso de coloides não está associado a um aumento de complicações mas sim com uma tendência a maior mortalidade (RR [IC 95%] 3,87 [1,121-13,38]; $I^2 = 0,0\%$; $p = 0,635$).

Conclusões: Devido às limitações desta metanálise em decorrência do número escasso de ensaios clínicos aleatórios e pacientes incluídos, os resultados devem ser usados com cautela, e propõe-se a realização de novos ensaios clínicos aleatórios, com potência estatística suficiente naqueles em que se comparam coloides balanceados e não balanceados com cristaloides balanceados e não balanceados, dentro de protocolos de FGO, respeitando as indicações atuais e as sugestões emitidas pelos grupos de especialistas.

© 2014 Sociedade Brasileira de Anestesiologia. Publicado por Elsevier Editora Ltda. Todos os direitos reservados.

Introduction

Recently, several clinical trials have been published, as well as meta-analysis¹⁻¹¹ in which it was demonstrated that the use of perioperative goal-directed fluid therapy (GDFT) decreases post-surgical^{2-9,11} complications, hospital stay^{2,3} and mortality.^{1,7,8} The GDFT is based on preload optimization with the use of fluids, inotropes and/or vasoconstrictors through algorithms designed for this purpose, to achieve a particular target of stroke volume (SV), cardiac index or oxygen delivery. The ultimate goal of this optimization is to avoid fluid overload, as well as hypoperfusion and hypoxia.¹²

From a pathophysiological point of view, hemodynamic stabilization with colloids should result in a smaller amount of liquid administered,¹³ and a shorter time in which the patient would find him/herself in a relative position of hypovolemia and possible tissue hypoperfusion.¹⁴

After examining the available evidence, and based mainly on 3 studies,¹⁵⁻¹⁷ in June 2013 the Pharmacovigilance Risk

Assessment Committee of the European Medicines Agency concluded that the benefits of the use of colloids (hydroxethylstarches [HES]) were smaller than their risks,¹⁸ in the same way as the Food and Drug Administration recommended to avoid its use in patients with sepsis and in patients with renal insufficiency (RI).¹⁹ These conclusions were based on studies of patients with sepsis, not in the context of intraoperative hemodynamic stabilization from bleeding or relative hypovolemia, and the possibility of extrapolating the findings is debatable. Recently Gillies et al.,²⁰ after performing a systematic review and meta-analysis in which colloids were compared with different kinds of liquids, concluded that the use of HES did not increase mortality, hospital stay, RI or the need for extrarenal clearance²⁰; however, in this meta-analysis colloids are not compared with crystalloids in studies which used a GDFT algorithm and included only three randomized controlled trials (RCTs), in which colloids were compared to crystalloids in noncardiac surgery.²¹⁻²³ The objective of

this systematic review and meta-analysis is to determine whether the use of the latest generation of colloids derived from corn (HE 6%: 130/0.4) for hemodynamic optimization in GDFT reduces postoperative complications and mortality.

Material and methods

Selection criteria

The studies were searched according to the following selection criteria and according to the PRISMA/CONSORT²⁴ methodology.

1. Participants: adult patients were included (>18 years) undergoing scheduled noncardiac surgery. The studies were not limited according to surgical risk.
2. Types of intervention: intraoperative GDFT which compares the use of crystalloids with colloids derived from last generation corn (6% HE: 130/0.4), defining that as the hemodynamic monitoring that enables the implementation of a hemodynamic optimization algorithm based on the use of liquids, inotropes and/or vasopressors to achieve normal or supernormal hemodynamic values. Pulmonary artery catheter-guided GDFT is excluded, as well as GDFT guided by transesophageal echocardiography or obsolete technology. Those studies comparing HES with colloid in stroke volume (SV) optimization without contributing with outcomes defined for this meta-analysis were excluded. It is limited to colloids derived from low molecular weight corn (HE 6%: 130/0.4).
3. Types of comparison: those studies comparing GDFT with colloids to GDFT with crystalloids were selected for analysis. We excluded those studies comparing balanced versus unbalanced solutions. Those RCTs comparing a monitoring technology with another, and those RCTs comparing different types of hemodynamic algorithms.
4. Outcomes: The primary outcome is the postoperative complications and mortality.
5. Types of studies: RCTs in which intraoperative GDFT is performed in major scheduled noncardiac surgery.

Information sources

Different strategies of search were used (last updated in March 2014) to identify relevant studies that met the inclusion criteria in EMBASE, MEDLINE and Cochrane Library. There was no restriction regarding publication date. The search was limited to articles published in English. An additional manual search was performed with the aim that every study published was analyzed.

Search items

The search was performed using the following keywords "Fluid Therapy" (Mesh) AND "Hydroxyethyl Starch Derivatives" (Mesh) AND "Isotonic Solutions" (Mesh).

Study selection and data extraction

Two independent researchers assessed each title and abstract in order to rule out the irrelevant RCTs and identify those potentially relevant; these were thoroughly analyzed selecting those that met the inclusion criteria set out above. The extraction of data from the included RCTs was carried out by two researchers and any discrepancy required a new analysis, as well as confirmation by a third investigator.

Data extraction included characteristics of included patients (ASA, age), type of surgery, type of hemodynamic monitoring, algorithm used, use of fluids, inotropes and/or vasopressors, and general, respiratory, infectious and surgical complications, transfusion and mortality. Data extraction was revised by the authors in order to avoid errors in data transcription.

Outcomes

The primary outcome of the study was overall complications and mortality.

Abstract measures and analysis method

Statistical analysis

We used Stata 12.0 statistical software to perform statistical analysis. The meta-analysis was performed by inverse variation method for dichotomous outcomes and continuous data, results are presented as relative risk (RR) with 95% confidence interval (CI 95%) The method of mean difference was used with a model of random effects. Forest plots were constructed considering $p < 0.05$ as statistically significant. The heterogeneity of the studies was evaluated by statistical I^2 ; I^2 values are defined as little heterogeneous, 25–50% moderately heterogeneous; and above 50% little homogeneous. χ^2 test for heterogeneity was performed, considering statistical significance $p < 0.01$.

Those studies where complications or mortality are equal to zero cannot be included in the creation of forest plots for statistical purposes. To evaluate the agreement in bias assessment of the author's kappa statistics was used.

Results

Study selection

We found 130 references in electronic databases, of which 38 were reviewed; of these, 29 RCTs were analyzed and those which did not meet the inclusion criteria were excluded. Finally six RCTs^{21,25–29} were included. RCTs were not found in manual search. A total of 390 patients were included in this meta-analysis. In Fig. 1 the flowchart for selecting articles is shown.

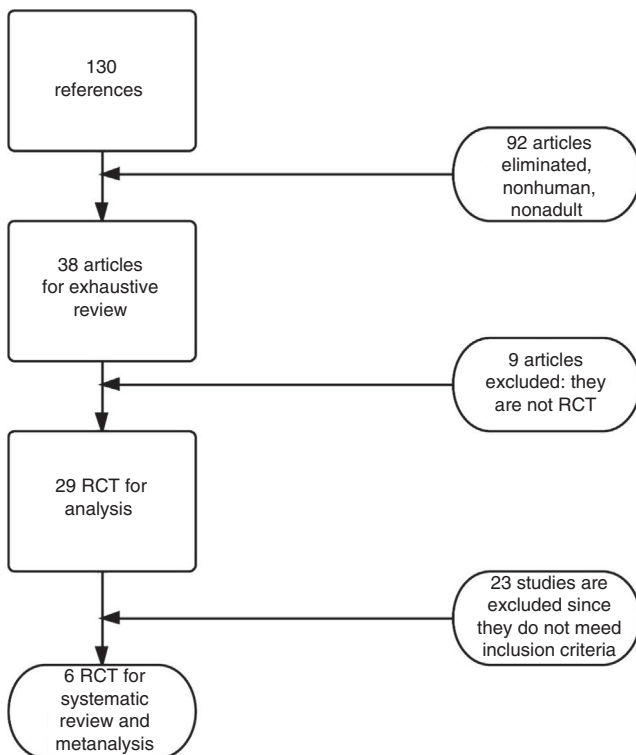
Biases risk evaluation in individual studies

Two independent researchers carried out the quality assessment of RCTs included by Jadad³⁰ score; this scale was used

Table 1 Evaluation of biases risk in isolated studies.

Study	Year	Randomization	Randomization sequence description	Double-blind	Blindness description	Missing description	Total	Comments
Senagore et al. ²⁵	2009	1	1	1	0	0	3	Study not designed to detect complications nor effect of liquid administration
Zhang et al. ²⁶	2012	1	1	0	0	1	3	
Feldheiser et al. ²¹	2013	1	1	1	1	1	5	Not designed to analyze complications
Yates et al. ²⁷	2014	1	1	1	1	1	5	
Lindroos et al. ²⁸	2014	1	1	0	0	1	3	Not designed to analyze complications
Lindroos et al. ²⁹	2013	1	1	0	0	1	3	Not designed to analyze complications

to describe the quality of the studies by assessing five elements of randomization, blindness and application of the protocol, with a score of 1–5; a high-quality trial is the one which has a score of 5. This assessment is shown in [Table 1](#).

**Figure 1** Flowchart of articles included.

Characteristics of studies included

The selected articles describe the results of those RCTs that assess the use of colloids (6% HE: 130/0.4, balanced or unbalanced) versus crystalloid (balanced or unbalanced) in intraoperative GDFT in programmed noncardiac surgery, those which include the postoperative complications and/or mortality as the primary outcome. The characteristics of the RCTs included are shown in [Table 2](#).

Of six RCTs analyzed, three RCTs^{25–27} were carried out in gastrointestinal surgery; two in neurosurgery^{28,29} and one in gynecological surgery.²¹ In five of the six RCTs included^{21,25–27,29} mortality and complications^{21,25–27,29} were described. Twenty-eight were included in a systematic review and meta-analysis as they describe decrease in transfusion, which may be interpreted as a complication. Only two RCTs describe postoperative renal failure as complication.^{21,27}

The GDFT was performed with two CardioQ® in two RCT,^{21,25} in two cases with Flotrac®^{28,29} with LiDCO Rapid® in one case²⁷ and through calculation of pulse pressure variation in another case.²⁶ The characteristics of the patients included are shown in [Table 3](#).

The quality of the RCTs valued by Jadad score is shown in [Table 2](#), as well as RCTs funding included in the meta-analysis. [Table 1](#) presents the description of the possible biases. One kappa agreement of 90% was found in the risk assessment between the two researchers.

[Table 4](#) shows the studies analyzed but not included in the meta-analysis because they did not meet the inclusion criteria previously described.^{23,31–36} Senagore et al.²⁵ compared the standard fluid therapy with GDFT with colloids (Voluven®, Fresenius Kabi, Germany) versus crystalloids

Table 2 Characteristics of RCT included.

Study	Year	Population	Intervention	Comparator	Outcomes
Senagore et al. ²⁵	2009	Adult patients Undergoing colorectal surgery	GDFT through CardioQ® based on algorithm of maximization of SV with HES (Voluven®); n = 21	GDFT through CardioQ® based on algorithm of maximization of SV with Ringer lactate; n = 21	Hospital stay. Parameters of recuperation of bowel function. Complications
Zhang et al. ²⁶	2012	Adult patients undergoing gastrointestinal surgery	GDFT based on optimization PPV < 10% with HE; n = 20	GDFT based on optimization of PPV < 10% with Ringer lactate; n = 20	Hospital stay. Parameters of recuperation of bowel function. Complications
Feldheiser et al. ²¹	2013	Adult patients undergoing ovary surgery	GDFT through CardioQ® based on maximization algorithm of SV with balanced HES (Volulyte®), vasoconstrictors and inotropes for IC > 2.5; n = 24	GDFT through CardioQ® based on maximization algorithm of SV with balanced crystalloids (Jonosteril®), vasoconstrictors and inotropes for CI > 2.5; n = 24	Total fluids administered intraoperatively. Catecholamines administered. Hospital stay. Complications
Yates et al. ²⁷	2014	Adult patients undergoing colorectal surgery	GDFT through LiDCO Rapid® based on algorithm of optimization of SVV (SVV < 10%) with HES and dopexamine; n = 104	GDFT through LiDCO Rapid® based on algorithm of optimization of SVV (SVV < 10%) with Ringer lactate and dopexamine; n = 98	Gastrointestinal complications on day 5. Postoperative complications. Hospital stay. Analytical parameters of coagulation
Lindroos et al. ²⁸	2014	Adult patients undergoing prone neurosurgery	GDFT through Flotrac® based on algorithm of maximization of SV with HES; n = 15	GDFT through Flotrac® based on algorithm of maximization of SV with Ringer acetate; n = 15	Fluids necessary for hemodynamic stabilization. Coagulation changes
Lindroos et al. ²⁹	2013	Adult patients undergoing neurosurgery	GDFT through Flotrac® based on algorithm of maximization of SV with HES and vasopressors; n = 14	GDFT through Flotrac® based on algorithm of maximization of SV with Ringer acetate and vasopressors; n = 14	Fluids necessary for hemodynamic stabilization. Coagulation changes
Study	Design	Jadad score	Conclusions	Funds	Country
Senagore et al. ²⁵	Monocentric Double-blind RCT	3	The use of GDFT with CardioQ® does is not beneficial and is more expensive than conventional. GDFT with colloids is not beneficial	Deltex medical	USA
Zhang et al. ²⁶	Monocentric RCT	3	The use of GDFT with colloids improves the parameters of bowel function and decreases hospital stay	Not declared	China

Table 2 (Continued)

Study	Design	Jadadscore	Conclusions	Funds	Country
Feldheiser et al. ²¹	Monocentric Double-blind RCT	5	The use of GDFT with colloids provides higher hemodynamic stability, with no increase of risk of ARF, and decreases FFP transfusions	Fresenius Kabi	Germany
Yates et al. ²⁷	Monocentric Double-blind RCT	5	The use of HE in GDFT does not provide crystalloid-related benefits, except for a lower balance of fluids in the first 24 h	Fresenius Kabi	United Kingdom
Lindroos et al. ²⁸	Monocentric RCT	3	The use of GDFT with HES decreases the fluids administered. The administration of 400 cc of HES leads to changes in thromboelastogram	Not declared	Finland
Lindroos et al. ²⁹	Monocentric RCT	3	The use of GDFT with colloids allows decreasing the perioperative administration of fluids and water balance	Helsinki University	Finland

RCT, randomized clinical trial; GDFT, Goal-directed fluid therapy; HES, hydroxyethylstarches; CI, cardiac index; ARF, acute renal failure; FFP, fresh frozen plasma; PPV, pulse pressure variation; SV, stroke volume; SVV, stroke volume variation.

(Ringer lactate) in GDFT based on a SV optimization algorithm by CardioQ® in low-risk patients undergoing laparoscopic segmental colectomy within an enhanced recovery program (fast track).³⁷ In those cases where no SV opti-

mization was achieved with 20 mL kg⁻¹ HE 6%, Ringer lactate was used, not exceeding the recommended doses and indications. They found a significant decrease in the amount of liquid needed to get the optimal SV (863 ± 850 mL vs.

Table 3 Characteristics of patients included.

Study	Year	Surgery	Monitoring	ASA	Age	SI duration	Risk	Describes mortality	Describes ARL	Describes complications
Senagore et al. ²⁵	2009	Colorectal	CardioQ®	ND	ND	143 vs. 150	High	Yes	No	Yes
Zhang et al. ²⁶	2012	Gastrointestinal	Arterial	I/II vs. I	52.8 vs. 53.3	183 vs. 190	Low	Yes	No	Yes
Feldheiser ²¹	2013	Gynecological	CardioQ®	II/III vs. III	58 vs. 52	272 vs. 242	Moderate-High	Yes	Yes	Yes
Yates et al. ²⁷	2014	Colorectal	LiDCO Rapid®	II vs. II	72 vs. 70	ND	Moderate-High	Yes	Yes	Yes
Lindroos et al. ²⁸	2014	Neurosurgery	Flotrac®	II vs. II	55 vs. 52	169 vs. 132	High	No	No	No
Lindroos et al. ²⁹	2013	Neurosurgery	Flotrac®	III vs. III	40 vs. 43	145 vs. 146	High	Yes	No	Yes

ARL, Acute Renal Lesion; SI, surgical intervention; ND, no data.

Table 4 Studies analyzed but not included in the meta-analysis.

Study	N	Reason for exclusion
Krebbel et al. ³¹	40	Balanced and unbalanced solutions are compared
Kotake et al. ³²	35	A colloid different from HE 6%: 130/0.4 is used
L'Hermite et al. ³³	56	Does not include complications or mortality as primary result
Dehne et al. ³⁴	60	A colloid different from HE 6%: 130/0.4 is used. GDFT is not performed
Godet et al. ³⁵	65	GDFT is not performed
Guo et al. ³⁶	42	A colloid different from HE 6%: 130/0.4 is used. GDFT is not performed
Hung et al. ²³	84	GDFT is not performed

GDFT, goal-directed fluid therapy; HE, hydroxyethylstarch.

389 ± 289 mL; $p < 0.05$). In the HES group more complications were presented though not significantly, and there was only a deceased patient in the study, corresponding to HES group. The primary outcome of the study was to hospital stay; it is not designed for analysis of major complications and does not describe cases of postoperative renal failure or how it is defined.

Zhang et al.²⁶ compared restrictive fluid therapy protocols with GDFT with colloids (HE 6%: 130/0.4) or crystalloids (Ringer lactate) in GDFT based on pulse pressure variation optimization algorithm, in low-risk patients (ASA I-II and estimated blood loss <500 mL) undergoing gastrointestinal surgery, including gastrectomy and segmental colectomy. There were no reports that the maximum permissible doses of colloid were exceeded, and in any case it was used in patients with RI. They found a significant decrease in the use of intra-operative vasoconstrictors, and a decrease in recovery time of bowel function for the HES group (86.2 ± 7.2 h vs. 95.4 ± 9.1 h; $p < 0.001$); likewise, a decrease in hospital stay in the HES group was detected (9.1 ± 1.4 vs. 11.9 ± 1.2 days; $p < 0.001$). There were no differences in complications between both groups, and no patient died during the study.

Yates et al.²⁷ compared the use of colloids (HE 6%: 130/0.4 balanced) versus crystalloids in GDFT through SV optimization and maintenance of stroke volume variation <10% using LiDCO Rapid in patients at moderate-high risk undergoing colorectal surgery. The maximum dose used was HE 50 mL kg⁻¹ using a balanced gelatin (Geloplasma®, Fresenius Kabi, Germany) in cases where that dose was exceeded. A HES group patient and a patient from the crystalloid group had RI. Patients included in the HES group received less intraoperative fluid, while patients in the crystalloid group received more fluids and demanded higher dose of gelatin to be optimized. During surgery, there was no difference in the use of vasopressors. The primary outcome of this study was the intestinal function recovery time, with no differences found within the groups. There were no significant differences in post-operative complications, nor in hospital stay. It should be noted that four patients in the HES group developed acute RI postoperatively, while only two of the crystalloid group had it. Five patients of HE group, and two in the crystalloid group died. We analyzed the systemic inflammatory response by IL-6 analysis, with no differences between groups.

Feldheiser et al.²¹ compared balanced colloids (HE 6%: Volulyte, Fresenius Kabi, Germany) versus balanced crystalloids (Jonosteril, Fresenius Kabi, Germany) in GDFT based on the optimization of SV and maintenance of the cardiac index >2.5 mL kg min⁻¹, monitored with CardioQ® in low to moderate risk patients requiring cytoreductive resection ovary surgery. The use of HES was limited to the maximum recommended dose, using fresh frozen plasma, when it was exceeded. The use of HES enabled better hemodynamic stabilization, in less time and with less liquid, and a significant decrease of fresh frozen plasma units; however, there were no significant differences in postoperative complications, hospital stay or mortality, although the study is not designed for this purpose, with the primary result of the total fluids administered during the intraoperative period.

Lindroos et al.²⁸ compared the use of colloids (HE 6%: 130/0.4 unbalanced) with balanced crystalloid (Ringer

acetate) in GDFT based on SV optimization with fluids and vasopressors, which is monitored with Flotrac® in low-risk patients undergoing neurosurgery in the prone position. It has been shown that the need for administration of fluids was 25% higher than with crystalloid than with colloid to achieve hemodynamic stabilization. There were no significant differences in hospital stay or in complications. A patient of the HES group received transfusion of red cells concentrate. No deaths were reported in the study. There were no reports that the maximum permissible doses of colloids were exceeded nor of postoperative RI.

In another RCT in neurosurgery, Lindroos et al.²⁹ compared the use of colloids (HE 6%: 130/0.4 unbalanced) with balanced crystalloid (Ringer acetate) with the same GDFT algorithm in patients undergoing craniotomy in the sitting position; similarly, they found a smaller decrease of liquids used for hemodynamic stabilization (<34%) with the use of colloids, although there were no significant differences found in postoperative complications or hospital stay; they did not report postoperative RI nor mortality data, thus assuming that there were no deaths. There is no report that maximum permissible doses of colloids were exceeded.

Primary outcomes

Total complications

Of the six RCTs analyzed, only two describe the total associated complications. No differences were found, nor were there any evidence that the use of colloids was associated with complications (RR: 1.17; 95% CI: 0.86–1.61) (Fig. 2).

Mortality

Mortality was assessed on three of six RCTs analyzed. We found a trend toward increased mortality in favor of GDFT with colloids (RR: 3.87–1.121; 95% CI: 13–38; $I^2 = 0.0\%$; $p = 0.635$), and in the three studies included a higher mortality in the colloid group compared to crystalloid group is estimated. There is no heterogeneity, although it may seem to exist a tendency to publish positive results (Fig. 3).

Discussion

The comparison of colloids and crystalloids in GDFT was performed in multiple surgical procedures with different types of hemodynamic monitoring, with different algorithms, and achieving goals through different methods; as well as in patients with different surgical risk.

The main results of this meta-analysis are: (1) There are no differences in postoperative complications with the use of GDFT with colloids or crystalloids; (2) There is a tendency to higher mortality associated with GDFT with colloids; (3) In the studies analyzed the RI is not determined as a primary outcome or in accordance with internationally accepted criteria, so it is not possible to draw conclusions regarding the RI associated with the use of colloids. It is worth noting that the high number of complications that are indicated in the study by Senagore et al.²⁵ largely correspond to minor complications (particularly those in the HES group [4 vs. 20])

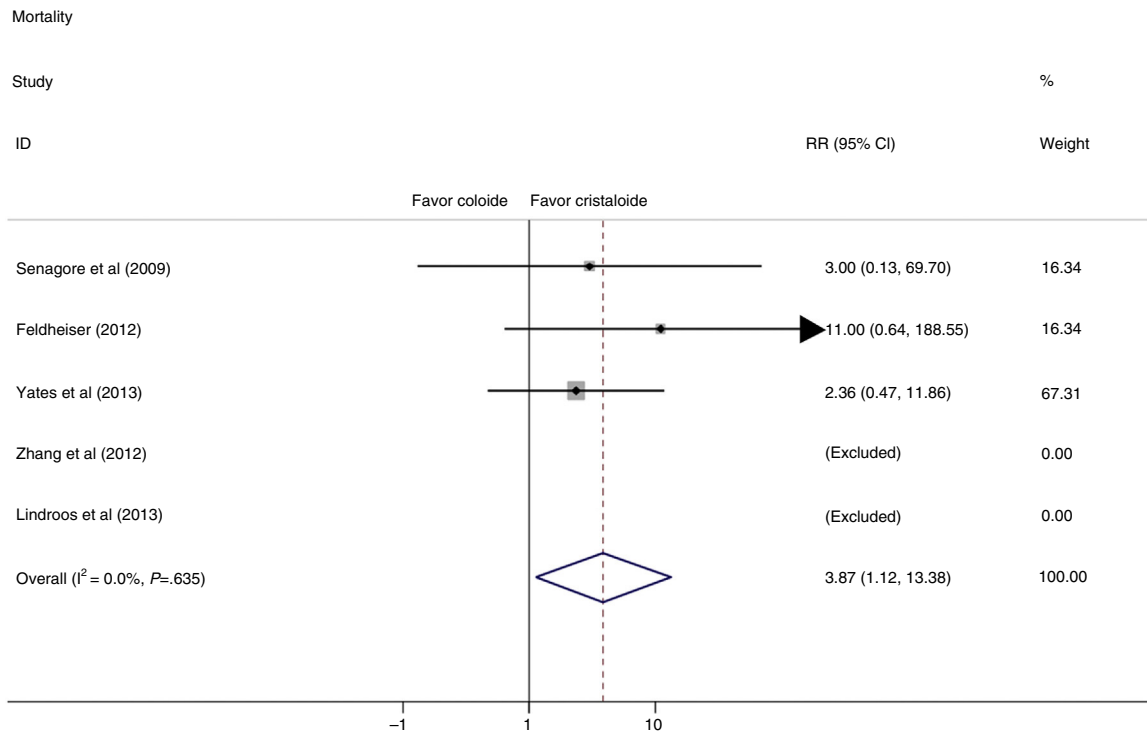


Figure 2 Colloids versus crystalloids. Mortality.

and that this study has as primary outcome hospital stay. It is not designed for analysis of major complications. The cause of death in the HES group is not described. The same occurs in the study by Yates et al.²⁷ where the causes of death are not indicated, and the RCT is not designed for the

analysis of complications; and, on the other hand, patients in the crystalloid group showed a higher baseline oxygen transportation (554 vs. 496; $p = 0.01$), while four patients had a postoperative acute RI in the HES group and only two in the crystalloid group.

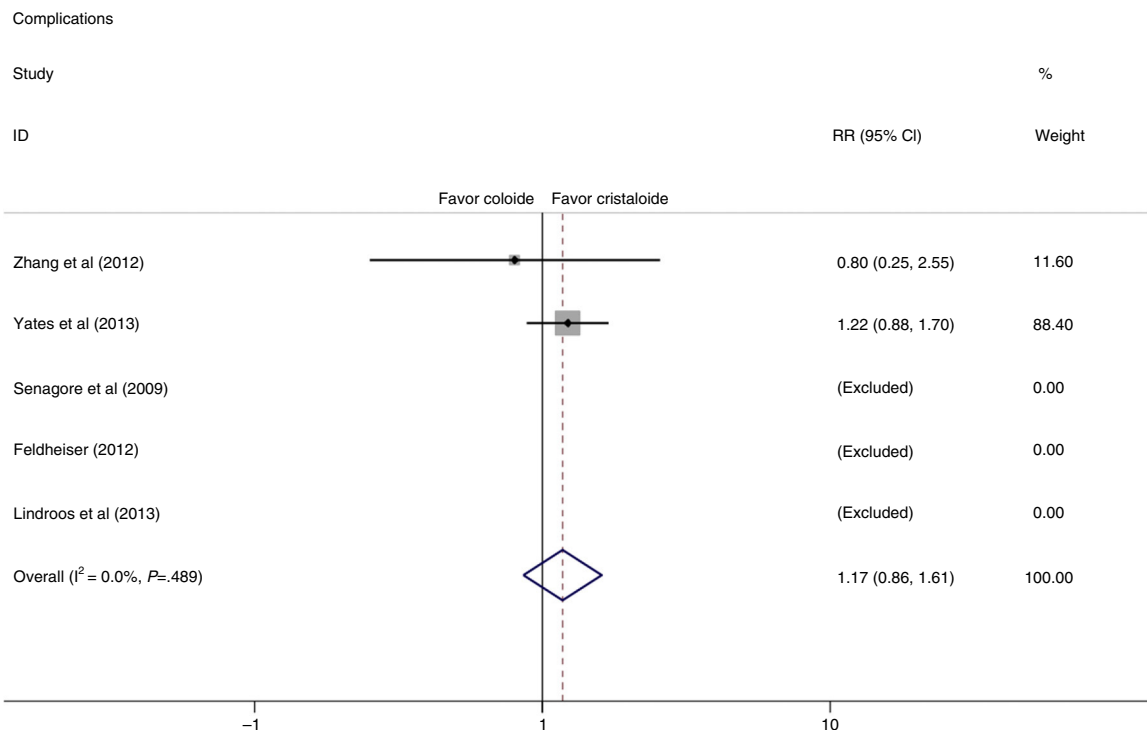


Figure 3 Forest plot. Colloids versus crystalloids. Total complications.

Feldheiser et al.²¹ reported a trend toward increased mortality (5 vs. 0; $p=0.051$), although these deaths correspond to tumor progression, and are not directly related to the hemodynamic algorithm. RI is not indicated as a postoperative complication. Studies by Lindroos et al.^{28,29} are not designed for the analysis of complications and it is assumed that there is no publication bias, that is, no deaths during the study or its follow-up. The results of this meta-analysis show that there is a trend toward increased mortality with the use of GDFT with colloids, although, as described above, this is not directly related to the intervention, since a significant reduction in complications is obtained. The maintenance of an adequate cardiac output could lead to maintenance of immune function and protect the organs that are at risk of intraoperative hypoperfusion,³⁸ particularly in gastrointestinal surgery; it was demonstrated that the use of GDFT with colloids improves the flow of the superior mesenteric artery by 20%, and the microcirculation in the gastrointestinal mucosa³⁹ by up to 40%; thus, a decrease of complications associated with the use of colloids would be expected; however, this is not confirmed with the existing evidence.

Moreover, studies in healthy subjects have shown that blood flow of the perianastomotic colonic mucosa is similar to the fluid therapy with colloids or crystalloids.⁴⁰

The basic premise of the GDFT consists of ensuring an optimal blood volume; the association of restrictive fluid therapy⁴¹ with the identification of optimal preload or of those patients who increased their SV through a volume load (respondent to fluids) implies relative hypovolemia; the quick correction of this problem is essential to ensure correct tissue perfusion. This a priori should be faster with colloids, since, as demonstrated in healthy patients and animal models, the proportion of liquid required to achieve a goal of hemodynamic stabilization is 1:4⁴²; however, this cannot be confirmed by the data obtained in this meta-analysis nor can be demonstrated with recent studies specifically designed to determine it.³³ The association of RI with the use of colloids in the surgical field could not be demonstrated,^{20,43} and in particular in GDFT it can be demonstrated, since no RCT analyzed this as a primary outcome; thus, it is not possible to draw conclusions with regard to colloids association with renal failure in surgical patients who underwent GDFT.

Implications for investigation

Currently, there are two RCTs in which GDFT with colloids is compared with that with crystalloids in large abdominal surgery, one in the USA "Effect of Goal-Directed Crystalloid Versus Colloid Administration on Major Postoperative Morbidity" (NCT01195883) in which they expect to analyze 1112 patients, and with planned completion date on November 2014; and another in Austria, Europe, "Crystalloids Versus Colloids During Surgery (CC)" (NCT00517127), with completion expected to 2016, and that aims to recruit 400 patients.

Both were approved before the resolution of the Pharmacovigilance Risk Assessment Committee and the Food and Drug Administration. The completion and publication of RCT, and the performance of future clinical trials in this area are essential.

In future RCTs, it would be advisable to follow the suggestions provided by Meybohm et al.⁴⁴ adapted to the operating

environment: limit the use of colloids for initial hemodynamic stabilization in cases where there is hypovolemia through GDFT algorithms in order to avoid situations of hypovolemia and hypervolemia, considering in all cases the maximum permissible doses; and avoid the administration of these in patients with RI, and performing adequate patient monitoring.

Moreover, due to the controversy generated by the Pharmacovigilance Risk Assessment Committee, in future clinical trials the determination of renal function will be necessary with the use of internationally validated scales (IRA and RIFLE), because they allow to homogenize criteria and measure this dysfunction clinical behavior,^{45,46} and also the performance of this procedures with balanced and unbalanced colloids, as this could be a determining factor.

Thus, more well-designed multicenter studies are necessary with sufficient statistical power to compare crystalloid versus colloid as fluid therapy in GDFT, according to the recommendations provided by Meybohm et al.⁴⁴ adapted for the surgical environment and in different surgical procedures that enable the clarification of the current controversy surrounding the use of colloids.

Limitations

As the literature search was limited to PubMed and EMBASE; there could be studies that were not analyzed in this meta-analysis.

The statistical power of this meta-analysis to detect an effect on complications and mortality is very limited by the low rate of complications and mortality, as well as due to the limited number of included studies and patients.

As in the RCT that were included the RI is not a primary outcome, conclusions in this field cannot be obtained.

Due to the heterogeneity of surgeries in which the RCTs were performed, the data obtained in this meta-analysis should be evaluated together with the individual analysis of each RCT included.

Thus, the results of this meta-analysis, and especially those which refer to mortality, should therefore be taken with caution.

Conclusions

Despite the major limitations found, this meta-analysis shows that the use of the latest generation of colloids derived from corn (6% HE: 130/0.4) in the GDFT with algorithms which optimizes the preload to avoid situations of relative hypovolemia that could lead to tissue hypoperfusion does not increase postoperative complications; however, there is a tendency to higher mortality with the use of these regarding the use of crystalloids. Although there is a trend to increased mortality, the authors consider that, given the low number of RCTs and patients included, this conclusion should be taken with caution, and it is essential to carry out new RCTs to confirm it, with sufficient statistical power in those comparing balanced to unbalanced colloids with balanced and unbalanced crystalloids within GDFT protocols, in those in which restrictive fluid therapy is held, and that include the use of vasoconstrictors and inotropes in the active algorithm, since they showed better results,⁴⁷⁻⁵¹ considering

current indications and suggestions provided by the groups of specialists.⁴⁴ Clearly, survival is the most important goal, and is a primary result in RCT that is extremely difficult to analyze, given the low incidence of it in the surgical field; therefore, future RCTs should have sufficient sample size in order to determine the influence of administered liquid in it.

Authorship

JR planned this meta-analysis with JC, made the literature search, analyzed the results, wrote the meta-analysis and sent the manuscript.

AE and AT participated in the literature search and selection of articles.

RC participated in the assessment of articles included and in the manuscript writing.

JC planned the meta-analysis with JR, supervised the work in all its phases, and corrected the text up to the final conclusion.

SC worked on statistics.

All the authors read and approved the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

The authors wish to express their gratitude to the professionals at Biblioteca Profesional del Hospital Universitario Infanta Leonor (Madrid).

References

- Poeze M, Greve JWM, Ramsay G. Meta-analysis of hemodynamic optimization: relationship to methodological quality. *Crit Care*. 2005;9:R771–9.
- Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. *Anaesthesia*. 2008;63:44–51.
- Walsh SR, Tang T, Bass S, et al. Doppler-guided intra-operative fluid management during major abdominal surgery: systematic review and meta-analysis. *Int J Clin Pract*. 2008;62:466–70.
- Brienza N, Giglio MT, Marucci M, et al. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med*. 2009;37:2079–90.
- Rahbari NN, Zimmermann JB, Schmidt T, et al. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. *Br J Surg*. 2009;96:331–41.
- Dalfino L, Giglio M, Puntillo F, et al. Haemodynamic goal-directed therapy and postoperative infections: earlier is better. A systematic review and meta-analysis. *Crit Care*. 2011;15:R154.
- Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high risk surgical patients. *Anesth Analg*. 2011;112:1392–402.
- Gurgel ST, do Nascimento PJ. Maintaining tissue perfusion in high-risk surgical patients: a systematic review of randomized clinical trials. *Anesth Analg*. 2011;112:1384–91.
- Corcoran T, Rhodes JEJ, Clarke S, et al. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg*. 2012;114:640–51.
- Srinivasa S, Taylor MHG, Sammour T, et al. Oesophageal Doppler-guided fluid administration in colorectal surgery: critical appraisal of published clinical trials. *Acta Anaesthesiol Scand*. 2011;55:4–13.
- Arulkumaran N, Corredor C, Hamilton MA, et al. Cardiac complications associated with goal-directed therapy in high-risk surgical patients: a meta-analysis. *Br J Anaesth*. 2014;112:648–59.
- Lobo SM, Salgado PF, Castillo VG, et al. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. *Crit Care Med*. 2000;28:3396–404.
- Jacob M, Chappell D, Hofmann-Kiefer K, et al. The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans. *Crit Care*. 2012;16:R86.
- Dubin A, Pozo MO, Casabella CA, et al. Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. *J Crit Care*. 2010;25:659e1–8.
- Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358:125–39.
- Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367:124–34.
- Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–11.
- Pharmacovigilance Risk Assessment Committee of the European Medicines Agency. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144446.pdf [accessed 25.04.14].
- Food and Drug Administration. FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. November 25, 2013 (Revised); 2013.
- Gillies MA, Habicher M, Jhanji S, et al. Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. *Br J Anaesth*. 2014;112:25–34.
- Feldheiser A, Pavlova V, Bonomo T, et al. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. *Br J Anaesth*. 2013;110:231–40.
- Gondos T, Marjanek Z, Ulakcsai Z, et al. Short-term effectiveness of different volume replacement therapies in postoperative hypovolaemic patients. *Eur J Anaesthesiol*. 2010;27:794–800.
- Hung M, Zou C, Lin F, et al. New 6% hydroxyethyl starch 130/0.4 does not increase blood loss during major abdominal surgery. A randomized, controlled trial. *J Formos Med Assoc*. 2014;113:429–35.
- Moher D, Liberati A, Tetzlaff J, et al., PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
- Senagore A, Emery T, Luchtefeld M, et al. Fluid management for laparoscopic colectomy: a prospective randomized assessment of goal directed administration of balanced salt solution or hetastarch coupled with an enhanced recovery program. *Dis Colon Rectum*. 2009;52:1935–40.
- Zhang J, Qiao H, He Z, et al. Intraoperative fluid management in open gastrointestinal surgery: goal-directed versus restrictive. *Clinics (Sao Paulo)*. 2012;67:1149–55.
- Yates DR, Davies SJ, Milner HE, et al. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. *Br J Anaesth*. 2014;112:281–9.

28. Lindroos AC, Niiya T, Randell T, et al. Stroke volume-directed administration of hydroxyethyl starch (HES 130/0.4) and Ringer's acetate in prone position during neurosurgery: a randomized controlled trial. *J Anesth.* 2014;28:189–97.
29. Lindroos ACB, Niiya T, Silvasti-Lundell M, et al. Stroke volume directed administration of hydroxyethyl starch or Ringer's acetate in sitting position during craniotomy. *Acta Anaesthesiol Scand.* 2013;57:729–36.
30. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1–12.
31. Krebbel H, Feldheiser A, Muller O, et al. Influence of goal directed therapy with balanced crystalloid-colloid or unbalanced crystalloid solution on base excess. *J Int Med Res.* 2014;42:468–86.
32. Kotake Y, Fukuda M, Yamagata A, et al. Low molecular weight pentastarch is more effective than crystalloid solution in goal-directed fluid management in patients undergoing major gastrointestinal surgery. *J Anesth.* 2013;28:180–8.
33. L'Hermite J, Muller L, Cuviron P, et al. Stroke volume optimization after anaesthetic induction: an open randomized controlled trial comparing 0.9% NaCl versus 6% hydroxyethyl starch 130/0.4. *Ann Fr Anesth Reanim.* 2013;32:e121–7.
34. Dehne MG, Muhling J, Sablotzki A, et al. Hydroxyethyl starch (HES) does not directly affect renal function in patients with no prior renal impairment. *J Clin Anesth.* 2001;13:103–11.
35. Godet G, Lehot JJ, Janvier G, et al. Safety of HES 130/0.4 (Voluven®) in patients with preoperative renal dysfunction undergoing abdominal aortic surgery: a prospective, randomized, controlled, parallel-group multicentre trial. *Eur J Anaesthesiol.* 2008;25:986–94.
36. Guo X, Xu Z, Ren H, et al. Effect of volume replacement with hydroxyethyl starch solution on splanchnic oxygenation in patients undergoing cytoreductive surgery for ovarian cancer. *Chin Med J.* 2003;116:996–1000.
37. Ljungqvist O. ERAS-Enhanced Recovery After Surgery: moving evidence-based perioperative care to practice. *JPEN J Parenter Enteral Nutr.* 2014;24:559–66.
38. Giglio MT, Marucci M, Testini M, et al. Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. *Br J Anaesth.* 2009;103:637–46.
39. Hildebrand LB, Kimberger O, Arnberger M, et al. Crystalloids versus colloids for goal-directed fluid therapy in major surgery. *Crit Care.* 2009;13:R40.
40. Kimberger O, Arnberger M, Brandt S, et al. Goal-directed colloid administration improves the microcirculation of healthy and perianastomotic colon. *Anesthesiology.* 2009;110:496–504.
41. Lobo SM, Ronchi Is, Oliveira NE, et al. Restrictive strategy of intraoperative fluid maintenance during optimization of oxygen delivery decreases major complications after high-risk surgery. *Crit Care.* 2011;15:R226.
42. Peng Z-Y, Kellum JA. Perioperative fluids: a clear road ahead? *Curr Opin Crit Care.* 2013;19:353–8.
43. Martin C, Jacob M, Vicaut E, et al. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. *Anesthesiology.* 2013;118:387–94.
44. Meybohm P, Aken HV, Gasperi AD, et al. Re-evaluating currently available data and suggestions for planning randomised controlled studies regarding the use of hydroxyethyl starch in critically ill patients—a multidisciplinary statement. *Crit Care.* 2013;17:R166.
45. López JA, Jorge S, Resina C. Prognostic utility of RIFLE for acute renal failure in patients with sepsis. *Crit Care.* 2007;11:408.
46. Mehta RL, Kellum JA, Shah SV. Acute kidney injury network (AKIN): report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* 2007;11:R31.
47. Mayer J, Boldt J, Mengistu AM, et al. Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. *Crit Care.* 2010;14:R18.
48. Benes J, Chytra I, Altmann P, et al. Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: results of prospective randomized study. *Crit Care.* 2010;14:R118.
49. Cecconi M, Fasano N, Langiano N, et al. Goal-directed haemodynamic therapy during elective total hip arthroplasty under regional anaesthesia. *Crit Care.* 2011;15:R132.
50. Pillai P, McElevay I, Gaughan M, et al. A double-blind randomized controlled clinical trial to assess the effect of Doppler optimized intraoperative fluid management on outcome following radical cystectomy. *J Urol.* 2011;186:2201–6.
51. Bisgaard J, Gilsaa T, Rønholm E, et al. Haemodynamic optimization in lower limb arterial surgery: room for improvement? *Acta Anaesthesiol Scand.* 2013;57:189–98.