Effect of perioperative colloid and crystalloid fluid therapy on coagulation competence, haemorrhage and outcome

Kirsten Cleemann Rasmussen

Correspondence: Department of Anaesthesiology 2043, Rigshospitalet, University of Copenhagen

E-mail: dockcr@yahoo.com

LISTS OF PAPERS

This PhD thesis is based on the following five original papers:

PAPER I
Rasmussen KC, Johansson PI, Højskov M, Kridina I, Kistorp T, Thind P, Nielsen HB, Ruhnau B, Pedersen T, Secher NH. Hydroxyethyl starch reduces coagulation competence and increase blood loss during major surgery. Results from a randomized controlled trial. Ann Surg. 2014;2:249-54.

PAPER II
Rasmussen KC, Hoejskov M, Johansson PI, Kridina I, Kistorp T, Salling L, Nielsen HB, Ruhnau B, Pedersen T, Secher NH. Coagulation competence for predicting perioperative haemorrhage in patients treated with lactated Ringer's vs. Dextran - a randomized controlled trial. BMC Anesthesiology. 2015, 15:178 DOI: 10.1186/s12871-015-0162-1.

PAPER III
Rasmussen KC, Højskov M, Johansson PI, Kridina I, Kistorp T, Salling L, Nielsen HB, Ruhnau B, Pedersen T, Secher NH. Impact of albumin on coagulation competence and haemorrhage during major surgery. A randomized controlled trial. Medicine. 2016 Mar; 95(9):e2720. doi:10.1097.

PAPER IV
Rasmussen KC, Højskov M, Ruhnau B, Salling L, Pedersen T, Goetze JP, Secher NH. Plasma pro-atrial natriuretic peptide to indicate fluid balance during cystectomy: a prospective observational study. BMJ Open. 2016; 6:e010323.doi:10.1136.

PAPER V
Rasmussen KC, Secher NH, Pedersen T. Effect of Perioperative Crystalloid or Colloid Fluid Therapy on Hemorrhage, Coagulation Competence and Outcome. A Systematic Review and stratified Meta-analysis. Medicine. Submitted.

BACKGROUND

During surgery the circulation is supported by a crystalloid and eventually by a colloid that stays within the circulation while as much as 30% of a crystalloid may be "lost" to the interstitial space.[1] The use of colloids to support the circulation during surgery is considered in order to delay the need for blood transfusion when haemorrhage is significant.[2] On the other hand, the use of colloids is controversial, that is they are costly, may cause anaphylaxis and have possible adverse renal and coagulation effects, and neither their safety nor their efficacy are demonstrated in systematic reviews by meta-analysis.[3-12] Also it is accepted that some synthetic colloids affects coagulation competence, but whether or to what extent that translates to increased blood loss is not settled.

Monitoring perioperative coagulation competence has relied on clinical estimates besides on plasma coagulation tests. Plasma coagulation tests were, however, introduced to evaluate lack of coagulation factors and not to predict risk of bleeding or for guiding haemostatic therapy. In contrast, viscoelastic evaluation of whole blood enables rapid diagnosis of coagulation competence and may be displayed in real time within the operating theatre. Thus, the use of perioperative coagulation monitoring by, e.g. thromboelastography (TEG) for targeted treatment of coagulopathy is recommended by the European Society of Anaesthesiology.[13]

To address perioperative haemorrhage and patient outcome versus coagulation competence, two strategies were followed. Three randomized controlled trials (RCTs) for evaluation of haemorrhage, coagulation competence, and outcome were conducted with the use of HES 130/0.4, Dextran 70, or 5% human albumin as intervention while administration of lactated Ringer's solution (LR) served as control,[14-16] and a prospective observational study evaluated to what extent the circulation was supported during

surgery as indicated by deviations in plasma atrial natriuretic peptide (proANP).[17] Secondly a stratified systematic review was undertaken including a meta-analysis of RCTs for perioperative use of colloids versus crystalloids.[18] Perioperative coagulation competence was monitored by TEG, platelets, and plasma coagulation variables and all evaluations involved cystectomy were carried out under supervision of two surgeons to standardize the trauma. It was considered that cystectomy involves non-cleavage surgery and haemorrhage was therefore expected to depend critically on coagulation competence.

AIM OF THE PH.D.

- To evaluate administration of HES 130/0.4, Dextran 70, or albumin versus the use of LR during cystectomy in regard to perioperative coagulation competence, haemorrhage, blood transfusion, and outcome.
- To evaluate coagulation competence by TEG, platelet counts and plasma-derived coagulation variables, and their association to perioperative haemorrhage.
- To evaluate to what extent the circulation is supported during surgery as indicated by deviations in plasma proANP.
- To perform a meta-analysis evaluating perioperative coagulation competence, haemorrhage and outcome in randomized controlled trials (RCTs) addressing administration of crystalloid versus colloids.

HYPOTHESES

We expected HES 130/0.4, Dextran70, and human albumin 5% to affect coagulation competence to the extent that haemorrhage during major surgery increased when compared to the use of LR. In addition, we noted the need for blood transfusion and patient outcome. Finally, we tested the hypothesis that TEG analysis predicts the blood loss more accurately than plasma coagulation variables.
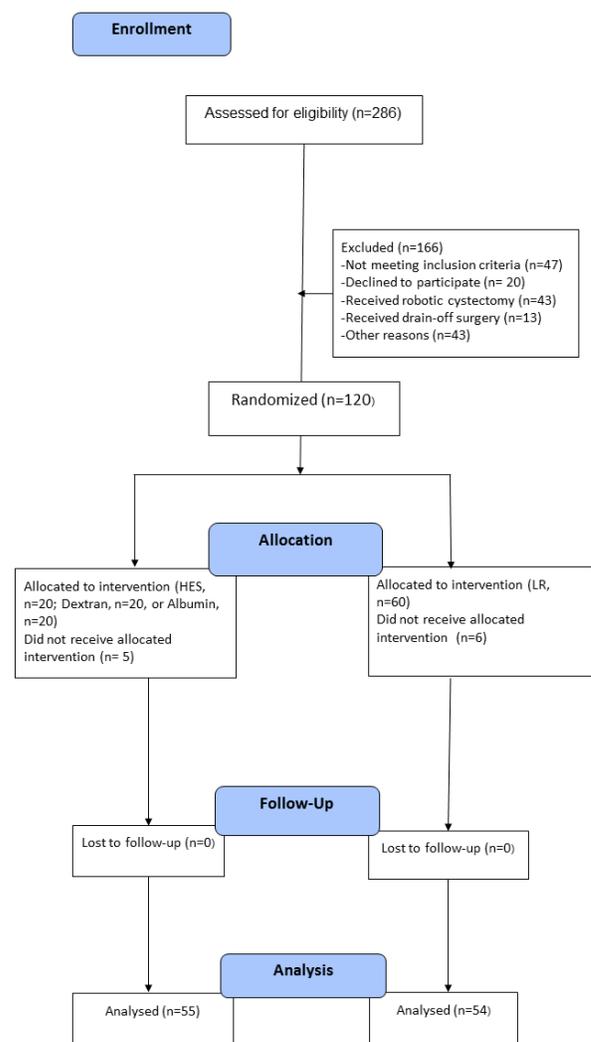
DESIGN, METHODS AND POPULATION

One hundred and twenty patients scheduled for open cystectomy were enrolled in randomized, prospective, controlled studies after providing their written and oral content. The trials were approved by ClinicalTrials.gov (NCT01444508, NCT02270723), the Danish Health and Medicine Authority (EudraCT 2011-003270-80, 2012-005040-20 and 2013-005350-29), the local Ethics Committee (H-2-2011-063, H-1-2012-135 and H-1-2013-142) and were registered by the Danish Data Protection Agency. The trials were monitored by the Agency for Good Clinical Practice at the University of Copenhagen and the Declaration of Helsinki criteria was followed.

Conduct of the trials and the safety of the participants were overseen by the authors who gathered the data that remained confidential throughout the process. The authors were involved in all stages of manuscript generation and vouched for completeness and accuracy. No third party influenced the study design, data analysis, or reporting.

Screening, randomization and inclusion of patients took place between August 30th 2011 and July 21th 2015. Written and oral informed consent was obtained at least 24 h before surgery. If consent was withdrawn, the patient was excluded. We included patients older than 18 yrs. scheduled for elective cystectomy with no history of cardiac or hepatic insufficiency, no disability of

coagulation disorders, cerebral haemorrhage, or haemodialysis. If a patient used medication that was considered to affect coagulation competence, that medication was paused five days prior to surgery according to international guidelines.[19] Seventeen of 20 patients scheduled for elective cystectomy were randomized to receive HES 130/0.4, 19 of 20 patients received either Dextran 70 or human albumin, while 16, 18 and 20 patients respectively were randomized to receive LR by a computer-generated allocation sequence produced without blocks by the biostatistic department (Figure 1). The patients received an empirically defined fixed volume of the allocated fluid - that is 35 mL/kg HES 130/0.4, 25 mL/kg Dextran70, human albumin 5%, or LR. In an observational study, we analysed plasma for the hydrate hormone proANP in 20 patients in the dextran trial and in 20 patients during robotic cystectomy.

Figure 1.

Randomization of the study population

Interventions
The patients were allowed to eat solid foods up to 6 h before surgery and 2 h before that time the patients were asked to drink 300 mL clear fluid. An IV line was established and flushed with the randomized fluid placed in an opaque bag to blind the outcome assessor (the surgical nurse), who recorded the volume of lost blood by suction and weight of swabs. After induction of anaesthesia a catheter was placed in the radial artery of the non-dominant arm and connected to a transducer (Baxter) and a modified Nexfin monitor (Bmeye B.V, Amsterdam, The Netherlands). From the blood pressure curve, Nexfin estimates a beat-to-beat stroke volume (SV) and thereby cardiac output (CO) by use of a non-linear, three-component model of arterial impedance (Modelflow).[20]

For induction of anaesthesia remifentanil infusion (0.5 μg kg^{-1} min^{-1}) was initiated and when the patient reported sedation, propofol (2.0 mg kg^{-1}) was administered. Propofol (5-10 mg kg^{-1} h^1) and remifentanil (1.75-2.25 mg h^{-1}) were used to maintain anaesthesia. With the patient supine normovolaemia was established, i.e. it was secured that after eventual repeated administration of 200 mL of the randomized fluid, SV increased by less than 10% according to goal directed fluid therapy (GDT) criteria.[21] Heart rate (HR), mean arterial pressure (MAP), SV, and CO were determined after induction of anaesthesia and insertion of the arterial catheter (T_0), start of surgery (T_1), after resection of the urinary bladder (T_2), at the end of anaesthesia (T_3), and two hours thereafter in the recovery room (T_4). If systolic pressure was below 80 mmHg, 5 to 10 mg of ephedrine was administered. Arterial blood was analysed by TEG, rate of clot initiation (TEG-R), clot growth (TEG-angle), maximal amplitude reflecting clot strength (TEG-MA), and lysis after 30 min (TEG-Ly30), depicting

coagulation competence (TEG 5000, Hemoscope Corporation, Niles, IL).[22] We also analysed blood for haemoglobin, creatinine, international normalised ratio (INR), and fibrinogen. Furthermore, blood was drawn from the central venous catheter for determination of lactate and blood gas variables (ABL 825, Radiometer, Copenhagen, Denmark). All patients received either LR or genuine blood products if considered in need after infusion of the allocated fluid (non-study fluid). Fluid balance was determined at T_2, T_3, and T_4.

End-points
The end-points were chosen to represent the blood loss during surgery and in the recovery room: coagulation competence was assessed by TEG and plasma coagulation variables besides postoperative complications assessed by surgical incidents, e.g. bleeding and leak requiring re-operation. Also cardiopulmonary and infectious complications were registered. A straight postoperative track was defined as length of hospital stay ≤ 7 days without complications requiring treatment.

Statistical analyses
Patients were analysed in the group to which they were assigned. The statistical analyses were performed before breaking the randomization code and data were analysed from the modified intention-to-treat population, defined as all randomly assigned patients except for those who could be excluded without the risk of bias. We used two-sided or unadjusted chi-square tests with odds ratio (OR), t-test and Fisher's exact test for continuous and dichotomous variables, respectively (SPSS version 20.0). Evaluation of differences were performed using χ2 test for categorical data and analysis of variance or Mann-Whitney U-test and Wilcoxon signed ranks test for continuous data when appropriate. Results are presented as mean (SD) or median with range for skewed variables and two-sided P values < 0.05 was considered to indicate statistical significance. Correlations were evaluated by Spearman's coefficient and group comparisons of continuous data of perioperative fluid administration were performed using analysis of variance (ANOVA). The meta-analysis was conducted by Review Manager 5.3 software package (The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration, 2015).

Preoperative characteristics of patients in the studies
The effects of the three RCTs in relation to preoperative data are shown in Table 1.[14-16] The anamnestic and preoperative data were without significant difference among the studies as were the length of anaesthesia and surgical procedure.

Goal directed therapy
In order to secure GDT, a bolus of 200 mL allocated IV fluid was infused and SV measured after induction of anaesthesia and before start of surgery. At that time 7 patients (41%) in the HES 130/0.4 group, 5 patients (26%) in the Dextran group and 3 patients (16%) in the albumin group were intravascular hypovolaemic according to individualized GDT criteria as compared to 5 (31%), 7 (39%) and 1 patient (5%) in the LR group, respectively. Further boli were not protocolled, but SV did not vary by more than 5% on average during surgery by retrospective examination. Furthermore, the volume load was evaluated by variation in the central blood volume as assessed by deviations in plasma proANP.

Dose of colloids
The patients received on average 33.3 mL kg^{-1} HES 130/0.4, 24 mL kg^{-1} Dextran 70, or 23.5 mL kg^{-1} albumin. Three, three and four

patients, respectively, did not receive the full fixed volume scheduled since they were considered haemodynamic stable before the intended volume was infused.

Table 1:

	Ringer´s (n=54)	HES (n=17)	Dextran (n=19)	Albumin (n=19)
Preoperative				
Age, yrs.	67±8	64±8	68±13	69±10
Weight, kg	80±15	79±15	77±12	77±15
ASA, class III, n (%)	14 (26%)	2 (12%)	8 (42%)	3 (16%)
Cardiopulmorary disease, n (%)	28 (52%)	5 (29%)	11 (58%)	8 (42%)
Intraoperative				
Ephedrine (mg)	35±19*	19±12	17±16	23±11
Anaesthesia time, min	240±48	229±43	237±79	263±55
Operation time, min	180±45	163±43	172±62	194±48

*Preoperative and intraoperative characteristics for 109 patients allocated to either colloid or lactated Ringer's solution during cystectomy. Values are mean with SD. Group comparisons of continuous data calculated by analysis of variance, *P<0.001.*

IMPACT OF FLUID THERAPY ON COAGULATION, HAEMORRHAGE AND OUTCOME

Following trauma, bleeding and exsanguination are responsible for more than fifty percent of deaths in the operating theatre and almost half of these patients are coagulopathic at arrival.[23,24] Haemorrhage and transfusion of allogenic blood products independently increase morbidity, mortality, length of stay in intensive care unit and hospital, and costs.[13]

The causes of haemorrhage during surgery include comorbidity, preoperative medication, surgical technique including damage control and perioperative haemostatic therapy. The complexity of the surgical procedure in itself also influences the blood loss.

To address perioperative haemorrhage and patient outcome versus coagulation competence, a stratified systematic review was undertaken including a meta-analysis of RCTs for perioperative use of colloids vs. crystalloids.[18] Thirty two studies including 2198 participants comparing HES, Dextran, and human albumin vs. crystalloids besides HES vs. albumin were identified.[14-16,25-53]

In the following the class effect of the three included RCTs[15-17] is addressed and related to results from the meta-analysis[18] as well as relevant systematic reviews. Going through the class effect, the IV fluids are divided (classified) into two groups; crystalloid (LR) versus colloids (HES products, dextran and human albumin) of which the latter may be subdivided into non-protein (synthetic) and protein colloids. Meanwhile the choice of the interventional IV fluids is described.

Fluid therapy

In order to assess the impact of colloids compared to crystalloids during major surgery, three colloids used in Denmark - Voluven, Dextran, and the genuine protein colloid human albumin 5% - were evaluated. LR was chosen as comparator as it, apart from the dilution effect, supposedly does not influence coagulation competence and does not provoke the hyperchloraemic metabolic acidosis associated with the use of physiologic saline.[54]

Hydroxyethyl starches are polysaccharides derived from plants and defined by their chemical composition - molecular weight, degree of substitution and C2/C6 ratio. The latest developed low molecular ("third generation") HES product, Voluven 130/0.4, molecular size 130 kD, was developed to reduce renal and coagulation side-effects often provoked by HES products with higher molecular size.[31,55,56] The risk of coagulopathia administering HES 130/0.4 is considered minimal.[57,58]

Dextran70, molecular weight 70 kD, is a polysaccharide synthesized by bacteria. These colloids are used in vascular surgery for their thromboprophylactic qualities, i.e. increased decomposition of the fibrin structure in the clot and reduced aggregation of thrombocyts - thereby reducing viscosity - followed by improved microcirculatory blood flow.[59] The risk of anaphylactic reactions is reduced by pre-treatment with a small sized (1 kD) dextran molecules (Promiten).[60]

Albumin is a protein with molecular weight 69 kD providing 50 g protein per litre. Albumin is a component of human plasma and its effect corresponds to that of physiologic albumin, i.e. it maintains blood oncotic pressure. Yet, all colloids dilute blood, including platelets and coagulation factors, thereby influencing coagulation competence. Although human albumin may reduce coagulation competence, there is no evidence that albumin increases haemorrhage during surgery.[10,48]

Perioperative coagulation competence

Perioperative coagulation competence is of interest because if reduced, the requirement for transfusion of blood increases and that appears to be an independent predictor of complications including death.[61,62] Monitoring of perioperative coagulation competence has been based on clinical judgement besides on plasma coagulation variables. Yet, the use of plasma coagulation variables is limited by their usually delayed presentation. Cotton et al.[63] found that the results were available in the operating room only within 48 min, while TEG results can be displayed online by computer tracing within 15 min, i.e. TEG seems advantageous for identifying coagulopathy in patients with severe haemorrhage.[62]

TEG has been available in laboratory setting since 1944.[13] However, a Cochrane review in 2011 found lack of evidence for point of care monitoring improving mortality compared with "usual care".[64] On the other hand, point of care monitoring of TEG has also been reported to guide haemostatic therapy and

decrease the requirement of allogeneic blood transfusions and is associated with improved outcome.[13]

The class effect of perioperative changes in TEG
The class effect of perioperative changes in TEG MA and angle are presented in Table 2. The lowest perioperative values of TEG-MA and angle compared to start of anaesthesia in the variance analysis were observed in the HES (-19% and -14%) and dextran groups (-25% and -17%), whereas the changes were almost similar in the LR (-2% and 2%) and albumin groups (-5% and -2%) at the end of surgery and in the recovery room. In conclusion human albumin reduced the development and strength of the clot, but to a smaller degree than both dextran and HES 130/0.4.

Table 2:

	Ringer´s (n=54)	HES (n=17)	Dextran (n=19)	Albumin (n=19)
MA(mm)				
T_2	0.4* (-1.0-1.8)	-7.2 (-10.4- -4.0)	-10.9 (-14.6- -7.2)	-1.5 (-4.2-1.2)
T_3	-1.1* (-2.5- -0.3)	-12.0 (-16.9- -7.2)	-16.3 (-18.7- -13.8)	-2.7 (-5.2- -0.2)
T_4	-1.7* (-3.0- -0.5)	-10.8 (-15.0- -6.6)	-16.1 (-18.7- -13.5)	-2.5 (-5.2- 0.3)
Angle (degrees)				
T_2	2.2* (0.6-3.7)	-6.7 (-10.7- -2.7)	-9.8 (-13.8- -5.9)	-0.4 (-4.0-3.2)
T_3	1.7* (0.1-3.3)	-8.8 (-13.4- -4.2)	-15.8 (-19.8- -11.7)	-1.5 (-5.6-2.7)
T_4	2.3* (0.8-3.8)	-6.6 (-10.6- -2.7)	-11.8 (-15.5- -8.2)	0.0 (-3.1-3.2)

*Perioperative changes in Thromboelastography (TEG) variables from start of anaesthesia (T_1) for 109 patients allocated to a colloid or lactated Ringer's solution during cystectomy. Values are mean with 95% CI. Group comparisons of continuous data were calculated by analysis of variance, *P<0.0001.*

Comparison of the results with reported observations
Most RCTs evaluated the quality of coagulation competence by TEG and concluded that clot firmness is reduced following administration of HES products compared to crystalloid solutions.[14,25,31,32,34,39-40,42,43]

Coagulation competence was evaluated in almost equal number of cardiac, orthopedic and abdominal surgery patients besides in one neurosurgical RCT conducted with the patient in prone position. The loss of blood in these trials varied from 0.2 to 1.0 litre while the number of participants varied from 30 to 202. Also TEG-MA varied between trials, resulting in a heterogeneity of 69%. Only one RCT did not demonstrate reduced firmness of the clot by administering HES 130/0.4.[43] In that investigation coagulation competence was evaluated in 34 patients during on pump cardiac surgery with mean 0.80 and 0.78 litre loss of blood in the two groups. In the HES group, the priming solution was 20 mL/kg HES 130/0.42 with additional LR up to 2 litre and LR was provided only during the cardiopulmonary bypass resulting in maximum clot firmness, i.e. TEG-MA 57 and 55 mm in the HES and LR group, respectively. Thus, the design does not seem to explain the unique result on coagulation competence in that trial. However, synthetic colloids generally induce coagulopathy and subsequent reduce the function of platelets and polymerization of fibrin.[65,66] These effects may occur after administration of about 1000 mL HES[67] and regarding dextrans, a similar effect manifests with administration of a smaller volume.[66,68] Yet, the sensitivity analysis still reveals that coagulation competence is reduced by administering starch products rather than a crystalloid.[18] Accordingly, the reduced clot firmness due to infusion of non-protein colloids in the three RCTs does not differ from reported results.

Table 3:

	Ringer´s (n=54)	HES (n=17)	Dextran (n=19)	Albumin (n=19)
Fibrinogen (µmol l⁻¹)				
T_2	-2.17** (-2.52- -1.83)	-3.78 (-4.83- -2.72)	-4.06 (-5.11- -3.02)	-2.66 (-3.47- -1.85)
T_3	-3.8** (-3.54- -2.62)	-5.33 (-6.38- 4.29)	-5.67 (-6.65- 4.69)	-4.21 (-4.90- -3.51)
T_4	-3.3** (-3.46- 2.60)	-4.98 (-6.08- -3.89)	-5.68 (-6.66- -4.70)	-4.18 (-4.88- -3.48)
Platelets count (n l⁻¹)				
T_2	-24** (-33- -15)	-59 (-74- -45)	-48 (-63- -34)	-38 (-53- -23)
T_3	-28** (-40- -15)	-71 (-86- -57)	-70 (-87- -53)	-53 (-72- -34)
T_4	-38* (-50- -26)	-72 (-91- -54)	-64 (-79- -49)	-52 (-73- -32)
INR				
T_2	0.11* (0.09-0.14)	0.24 (0.13-0.34)	0.23 (0.16-0.29)	0.17 (0.14-0.22)
T_3	0.82 (-0.57-2.23)	0.31 (0.21-0.42)	0.31 (0.26-0.35)	0.28 (0.19-0.37)
T_4	0.79 (-0.51-2.09)	0.30 (0.18-0.41)	0.28 (0.24-0.32)	0.19 (0.16-0.23)
APTT (sec)				
T_2	0.42 (-0.38-1.22)	3.47 (1.90-5.03)	1.71 (-2.88-6.30)	1.53 (0.58-2.47)
T_3	-0.44** (-1.15-0.27)	5.41 (3.32-7.50)	3.57 (1.88-5.27)	1.63 (-1.38-4.64)
T_4	-3.04** (-3.78- -2.30)	1.29 (-0.16-2.75)	2.16 (0.38-3.94)	0.56 (-2.10-3.21)

*Perioperative changes in plasma coagulation variables from start of anaesthesia (T_1) in 109 patients allocated to a colloid or lactated Ringer's solution during cystectomy. Values are mean with 95% CI. Group comparisons of continuous data were calculated by analysis of variance, *P<0.05, and ** P<0.001*

The class effect of coagulation competence analysed by plasma coagulation variables

The class effect of conventional coagulation variables shows that fibrinogen and platelet counts were reduced in all groups and mainly in the dextran and the HES 130/0.4 group followed by albumin and LR group (Table 3). The lowest perioperative values for fibrinogen and platelets compared to start of anaesthesia in the variance analysis were observed in the HES 130/0.4 (-51% and -32%) and in the dextran groups (-49% and -34%), whereas the changes were somewhat smaller in the LR (-28% and -16%) and albumin groups (-40% and -22%). INR increased less in the albumin group (by 26% compared to the LR group by 54%) and even less in the dextran (29%) and HES 130/0.4 groups (27%) as assessed at the end of surgery and in the recovery room. In the retrospective evaluation of the plasma coagulation analyses, fibrinogen and platelets were reduced during resection of the urinary bladder and correlated to TEG-alfa and TEG-MA (r=0.7-0.8).[14-16] In contrast, the correlation between TEG-MA and TEG-R, TEG-Ly30, INR and APTT were low (r< 0.5).

In conclusion, most fibrinogen and platelets were consumed with HES and dextran administration, suggesting that human albumin reduced the development and strength of the clot, but to a smaller extent than both dextran and HES.

Comparison of the results with the literature
The literature concerning the impact of colloids and crystalloids on coagulation competence evaluated by plasma coagulation analyses during major haemorrhage is extensive, although of old date. In regard to emergency situations and high-risk surgical procedures, Holcomb *et al*. concluded that rapid TEG analysis in almost 2000 trauma patients is superior to results from plasma coagulation variables to predict blood component transfusion.[69] Still, transfusion of blood during standard operating procedures remains a subjective decision.

Perioperative haemorrhage and fluid balance

Perioperative coagulation competence is of interest because increased haemorrhage followed by administration of blood seems to predict complications including death.[70] Yet, a reduction in TEG-MA during surgery does not necessarily translate into increased use of blood products.

The class effect of perioperative haemorrhage
Table 4 shows the class effect of perioperative blood loss, need for transfusion and fluid administration after infusion of LR, HES, dextran or albumin. The perioperative blood loss was 2.2-2.3 L in the synthetic colloid groups compared to 1.6-1.7 L in the LR and albumin groups, equating the lowest need for transfusion in the LR group (P<0.03). In a comparison administering either LR / albumin (n=73) or HES/ Dextran (n=36), the perioperative bleeding was low after administration of LR/albumin - 1475 mL (95%CI 1272-1679) vs. 2090 mL (95% CI 1657-2524), P=0.004, respectively.

Comparison of the results with the literature
During cystectomy, the extent of tissue resected besides the urinary bladder differs in regard to the local degree of cancer dispersion and the sex of the patient[14-16] and may contribute to variations in haemorrhage between RCTs. A meta-analysis including 12 RCTs showed increased bleeding following administration of HES products,[14,25,27,29-31,35,37,40-43] that is favored crystalloids and 5 RCTs showed increased hemorrhage following infusion of crystalloids.[28,32,33,38.,39]

Restricting the meta-analysis (subgroup analysis) to studies administering a low molecular weight HES product did not change the association between lesser bleeding and administration of crystalloids.[18]

During the twelve trials favoring administration of crystalloids to HES, the heterogeneity was moderate. For instance, the volume of lost blood varied from 0.1 to only 2.2 litre, the number of participants enrolled in each study varied from 21 to 240, and the investigations were conducted during different types of surgery (abdominal, cardiac, orthopedic and neurosurgery). In contrast, the present RCTs were conducted during the same type of abdominal major surgery - cystectomy.

Table 4.

	Ringer's (n=54)	HES (n=17)	Dextran (n=19)	Albumin (n=19)
Fluid administration				
Lactated Ringer's	3060** (2835-3285)	532 (199-865)	986 (691-1282)	711 (461-961)
Colloids	0 (0-0)	2605 (2342-2868)	1885 1765-2006)	1892 (1720-2037)
Packed red blood cells	152** (50-255)	286 (84-488)	597 (301-892)	235 (56-414)
Blood loss	1559* (1292-1825)	2181 (1569-2793)	2339 (1630-3048)	1658 (1328-1988)
Transfusion	14 (26%)	7 (41%)	12 (63%)	7 (37%)
Blood loss >1.5L	15** (28%)	12 (71%)	11 (58%)	6 (32%)
Fluids balance				
Fluid infusion	3979 (3665-4293)	3755 (3177-4333)	4157 (3300-5015)	3168 (2745-3592)
Fluid loss	1978* (1684-2272)	2762 (2147-3376)	2638 (1919-3356)	2020 (1672-2370)
Fluid overload	2008** (1796-2220)	995 (701-1289)	1520 (1198-1842)	1095 (883-1307)

Perioperative blood loss, fluid administration and balance with infusion of lactated Ringer's solution or colloids to patients undergoing cystectomy.

Fluid balance calculated from the administered IV fluid solutions inclusive transfusion of blood products, urine output, and blood loss (suction and drainage) during anaesthesia and in the recovery room. Blood products included packed red blood cells (PRBC), and colloids including HES, Dextran 70 and human albumin 5%. Values are expressed in mL as mean with 95% CI. Group comparisons of

continuous data were calculated by analysis of variance, *p<0.05, and ** P<0.001.

Among investigations favoring administration of hydroxyethyl starches, three studies were performed during cardiac bypass surgery, however, their designs were different.[28,32,33] One trial administered the allocated fluid as priming fluid and registered haemorrhage in postoperative drainage.[28]Another trial was conducted as off pump surgery and in contrast to most studies concerning haemorrhage, the patients were treated with clopidogrel and aspirin 5 days prior to surgery.[32] In contrast in the present RCTs the same two surgeons supervised every cystectomy and the marked reduction in coagulation competence following administration of non-protein colloids indicates that perioperative haemorrhage does not only depend on the surgical intervention. Furthermore, the administered volume of study solution (mL/kg) varied between studies in the systematic review[18], however the administered volume was often around two thirds of the maximum allowed daily fluid volume, as also used in the present RCTs.

Two studies in the meta-analysis[18] administered albumin versus crystalloids and both studies disclosed increased blood loss following albumin infusion .[16,41] Likewise, only two RCTs administered dextran versus crystalloids, however, in contrast to the present data, they did not demonstrate differences in regard to bloodloss, even though more patients had a severe blood loss (>1.5 L) in the Dextran group compared to the LR group.[15,44]

Advanced Trauma Life Support recommends haemorrhage class I-II to be treated by infusion of crystalloid and class III-IV haemorrhage (> 1500 mL) by administration of both crystalloid and blood transfusion.[71] Perioperative haemorrhage tended to increase when colloids – HES and Dextran - rather than LR were administered and more patients in the colloid groups were exposed to severe blood loss, identified by a larger than 1500 mL blood loss and oxygen transport to the tissue may thereby become affected.[72]

The presented meta-analysis demonstrates that perioperative haemorrhage tends to increase by about 4% with the use of HES 130/0.4 rather than crystalloids, and the use of HES 130/ 0.4 rather than albumin increased the perioperative haemorrhage by almost 8%.[18]

The class effect of fluid balance
Table 4 shows the perioperative fluid balance in the four groups. Number of patients in the LR group compared to the colloid groups having a positive fluid balance exceeding 1500 mL was 78% vs. 21%, OR=13.1 (2.7 to 62.8), *P*=0.001. Likewise, the fluid balance was positive by 1095 mL (883 to 1307) in the albumin group and by 2008 mL (1796 to 2220) in the LR group, P<0.001. More patients in the LR group had a positive fluid balance that we considered significant (exceeding 2000 mL): 9 patients versus 1 patient, OR=14.7 (1.6-132.6), *P*=0.016.

Comparing LR with synthetic solutions, the fluid balance was positive by 2.0 L in the LR group and by 1.2 L in the colloid group also with more patients in the LR group having a positive fluid balance exceeding 2000 ml: 27/54 (50%) compared to 1/17 (6%) in the HES group, 4/19 (21%) in the dextran group, and 1/19 (5%) in the albumin group (*P*<0.001).

Comparison with the literature
Normovolaemia is defined as the central volume that does not limit cardiac output,[73] and efforts to identify that volume has

been intense. As a reduced central blood volume may develop into a hypovolemic shock, while abundant administration of IV fluids may cause oedema, a normal central blood volume must exist.

LR expands the blood volume by as much as 60% of the continuous infused fluid during TURP performed under general anaesthesia.[74] A multicentre trial revealed that a "restrictive" perioperative fluid regimen reduced complications after elective colorectal resections,[75] although liberal versus restrictive perioperative fluid therapy is not well defined.[72] Similary, there is only weak evidence to support a fluid-induced release of peptides of sufficient size to alter the kinetics of colloid fluids by shedding the endothelial glycocalyx layer.[76] Nevertheless, within the last 10 years only, more than 100 medical journals have published systematic reviews on "perioperative transfusion strategies".[3] indicating that individualized perioperative fluid strategies is the key to decrease the human and economic burden of postoperative complications.[77]

Plasma pro-atrial natriuretic peptide to indicate fluid balance
Plasma proANP is a polypeptide isolated from human atrial tissue released in response to atrial distension independently of central venous pressure [78,79] and we considered an increase in plasma proANP to reflect intravascular volume expansion and, conversely, a reduction to indicate a reduced central blood volume.

The presented data suggest that plasma proANP was associated both with the perioperative blood loss, *r* = -0.475 (0.632 to -0.101), p = 0.002 and with fluid balance *r*=0.561 (0.302 to0.740), p = 0.001, indicating that a stable plasma proANP required a fluid surplus of about 2.5 litre in patients undergoing radical cystectomy.[17]

Table 5:

Coagulation	Perioperative bleeding	
	R	P
TEG angle	-0.30	0.002
TEG MA	-0.55	<0.0001
TEG R-time	-0.01	0.90
TEG Ly30	-0.03	0.80
Platelet counts	-0.27	0.004
APTT	0.32	0.002
INR	0.05	0.60

Spearman's correlation test demonstrates changes in TEG values and plasma coagulation analyses related to perioperative bleeding in three RCT`s (n=109 patients). TEG R-time (Rate of clot initiation, minutes); TEG angle (clot growth, degrees); TEG MA (Maximal Amplitude, mm); Ly30 (Lysis after 30 min); APTT (active Partial Thromboplastin Time, seconds) and INR.

Correlations between coagulation variables and perioperative haemorrhage

Correlations between perioperative bleeding and coagulation variables are shown in Table 5. Perioperative bleeding was correlated to TEG-MA ($P<0.0001$) followed by TEG-angle, platelet counts, and aPTT while the correlation to TEG-R time, Ly 30, and INR was non- significant. Figure 2 shows the class effect of administrated HES, dextran, albumin and lactated Ringer's solution on blood loss and coagulation competence expected by changes in TEG-MA during anaesthesia. The synthetic fluids result in more pronounced reduction in TEG-MA equating a greater loss of blood than the non-synthetic fluids.

Figure 2:
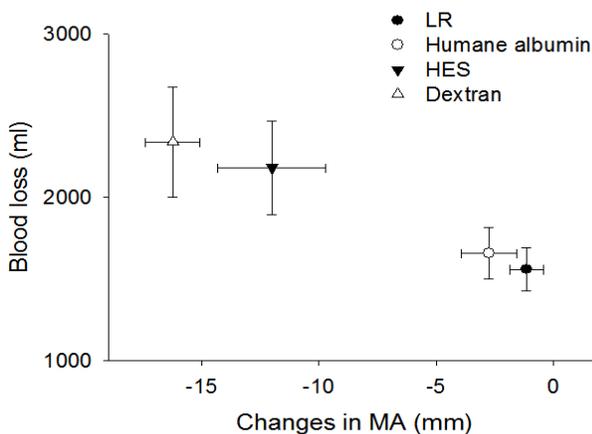
Changes in coagulation competence at the end of surgery expressed as TEG-MA compared to haemorrhage in patients receiving either HES, Dextran, albumin, or lactated Ringer's solution (LR). Data are mean and SE, and group comparisons were calculated by analysis of variance, P<0.02.

Postoperative outcomes

The class effect of postoperative outcomes is presented in Table 6. In the LR/albumin groups more than 41/47% of patients had a postoperative straight track compared to only 12/26% in the HES/Dextran group ($P=0.08$). In a comparison of patients receiving non- synthetic (n=73) versus synthetic fluids (n=36), a postoperative straight track was more frequently seen after the former versus the latter fluid strategy, 43% (31/73) vs. 19% (7/36), $P=0.02$, OR=0.33 (CI 95% 0.13-0.84). Creatinine was elevated one day after surgery in the HES 130/0.4 group compared with the LR group, $P< 0.01$. Apart from this, there was no difference between the two groups in the postoperative period.[5]

Seventy percent of patients re-operated due to leak were allocated to crystalloid. In patients with surplus ≤ 2.0 L, the incidence of leak requiring surgical intervention was 3.9% (3/77) compared to 21.9% (7/32) in patients with a surplus > 2.0 L, OR=6.5 (CI 95% 1.5-27.2), $P<0.004$. Nevertheless, the length of hospital stay was similar among groups ($P=0.88$). In conclusion, postoperative surplus more than 2.0 L seems associated with complications (leak).

Comparison with the literature
For the outcome variable "reoperation", only few RCTs report events describing postoperative bleeding or leaks, and the number of trials that inform about the frequency of reoperations is

small. Five RCTs compared HES products with crystalloids,[14,37,40-42] two compared Dextran [15,44] and other two human albumin with crystalloids[16,41], while four studies compared human albumin to HES preparations.[41,45,47,50] During the last mentioned four trials, reoperations seemed to occur more often after HES infusion compared to use of albumin as 19 patients in the HES group needed reoperation compared to only 6 patients in the albumin group.[18] The remaining nine RCTs did not disclose differences in number of reoperations, among which the studies by Yates et al.[42] and Bueno et al.[44] were weighted high in the forest analysis – 48% and 78%, respectively. Five other studies declare no difference in their number of reoperations when administration of a colloid was compared to a crystalloid. In a meta-analysis, Raiman et al. concluded that data to identify differences in outcomes including mortality, length of hospital stay, major infectious complications, acute kidney injury and renal replacement therapy associated with crystalloids and HES in scheduled non-cardiac surgery are insufficient.[9]

Table 6:

	Ringer´s (n=54)	HES (n=17)	Dextran (n=19)	Albumin (n=19)
Straight track*	22 (41%)	2 (12%)	5 (26%)	9 (47%)
Cardiopulmonary complications**	9 (18%)	3 (17%)	2 (11%)	3 (16%)
Wound infection**	4 (7%)	1 (6%)	2 (11%)	1 (5%)
Re-operations *Leak**** *Bleeding*	7 (13%) 7 1	1 (6%) 1 0	5 (26%) 2 3	3 (16%) 0 1
Hospital stay (days)	8.0 (3-30)	9.0 (6-21)	9.0 (5-24)	8.0 (5-90)

*Postoperative outcomes in the 109 patients. Values are numbers (n), percentages (%), medians with range, *length of stay ≤ 7days without complications requiring treatment, ** cardiovascular insufficiency or pulmonary oedema/wound infection requiring treatment, *** anastomotic leak requiring surgical intervention.*

STRENGTHS AND LIMITATIONS

The strength of the presented meta-analysis[18] concerning fluid therapy for 2198 patients during major elective surgery comprises a strict selection process and more than half of the included RCTs were scored in the top of Jadad´s quality scale. However, the RCTs were often small and single-centre studies and publication bias may exist, even though it seems not to be substantial as visualized by the funnel plot.[18]

The levels of heterogeneity comprising the trials in the meta-analysis were high and there are obviously flaws in the analysis. However, the main purpose was to borrow strength from multiple trials without statistical significance and therefore it is not solely a limitation of the analysis.

The present RCTs were strengthened by the triple-blinded design regarding the first and third endpoint (laboratory results and outcome), and the double-blinded design regarding the second endpoint (volume of lost blood), as the patient and the outcome assessor (the surgical nurse) were ignorant of the intervention.[80] The sample size was calculated to reduce risk of a type 2 error and the procedures were standardized as the team accomplishing the trials was limited to few persons to reduce confounding and bias.

During surgery, haemorrhage seemed to be related to injury on the common iliac vein in two patients. Likewise, a few mL of plasma was erroneously infused in two patients. Yet, it is a strength that blood specimens were analysed immediately after withdrawal by personal handover to the laboratory, thereby reducing number of missing and mistaken coagulation variable results.

The study has a short observation period as the randomized fluid strategy supposedly not influence 90 days mortality directly. During the studies, the hospitalization time was reduced slightly, and furthermore the perioperative setting concerning cystectomies is since then changed and the hospitalization time thereby decreased further.

CONCLUSIONS

The RCTs comparing administration of LR with synthetic colloids during cystectomy were in favour of crystalloid treatment with regard to coagulation competence and volume of lost blood. The impact of albumin and LR on coagulation and haemorrhage is small and almost identical. Based on these results, we suggest that administration of crystalloids should be preferred during major surgery. However, if surplus approaches 2 litre, albumin may be added.

SUGGESTIONS FOR FUTURE RESEARCH

According to plasma proANP, the established intravascular volume deficit - despite a positive calculated volume balance - reflects distribution of LR to the extravascular space. It remains to be established whether the clinical outcome would be improved by administration of some colloid rather than base fluid support on LR only.

Other means of evaluating cardiac filling during surgery including, e.g. echocardiography or a determination of blood volume may be required to generalize the present findings and the evaluation could be extended to include frequent evaluation of plasma proANP during surgery.

Finally, assuming that ANP causes shedding of the endothelial glycocalyx layer, the plasma level for executing this event should be investigated – perhaps shedding occurs when hypervolaemia develops.

SUMMARY

Background. Haemorrhage follows surgical intervention, but also fluid substitution may affect the blood loss. Here influence of colloids and lactated Ringer's solution (LR) on coagulation competence and haemorrhage is evaluated during cystectomy.

Methods. A meta-analysis, a prospective observational study and three randomized controlled trials were conducted - 17 patients received HES 130/0.4, 19 patients Dextran 70, 19 patients human albumin, and 54 patients LR - with blinded evaluation of blood loss and outcome while coagulation competence was evaluated by thromboelastography (TEG) and plasma coagulation analyses.

Results. Administration of HES reduced TEG determined "maximal amplitude" (TEG-MA) from 64±6 to 52±7 mm associated with a 2181±1190 mL blood loss. For Dextran values were 65±7 to 49±9 mm and 2339±1471 mL, respectively, for albumin 62±6 to 59±6 mm and 1658±684 mL compared to 65±6 to 64±6 mm and 1559±976 mL with the use of LR. Furthermore, reduced TEG-MA was independently associated with the perioperative blood loss. A straight postoperative course was seen less often after infusion of synthetic colloids versus albumin/LR (7/36 vs. 31/73), P=0.02.

Conclusions. Perioperative bleeding is related to administration of Dextran 70 followed by HES 130/0.4 whereas albumin and LR result in a similar low level of haemorrhage. Furthermore, evaluation of coagulation competence by TEG-MA appears superior to plasma coagulation analyses for predicting the perioperative blood loss and supports that haemorrhage depends not only on the surgical intervention but also on the perioperative fluid therapy of apparent consequence for outcome.

ACKNOWLEDGEMENTS

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