Journal of Blood Disorders & Transfusion

Nasreldin et al., J Blood Disord Transfus 2017, 8:1
DOI: 10.4172/2155-9864.1000374

Research Article OMICS International

The Effect of Crystalloid *vs.* Crystalloid plus Colloid Infusion on the Coagulation System in Patients Undergoing Cancer Breast Surgery

Eman Nasreldin[1*], Nagwa Gamal[2] and Abeer M Darwish[3]

[1]*Department of Clinical Pathology, Faculty of Medicine, Assiut University, Egypt*

[2]*Department of Anesthesiology, Faculty of Medicine, Aswan University, Egypt*

[3]*Department of Clinical Pathology, South Egypt Cancer Institute, Assiut University, Egypt*

[*]**Corresponding author:** Eman Nasreldin, Department of Clinical Pathology, Faculty of Medicine, Assiut University, Egypt, Tel: +20 127 811 5568; E-mail: emannasr2000@yahoo.com

Received: November 1, 2016; **Accepted:** January 25, 2017; **Published:** January 31, 2017

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Abstract

Background: To explore whether administration of routinely used intravenous solutions differently affects the coagulation system in breast cancer patients undergoing surgery receiving crystalloid alone or plus colloid fluid regimen.

Patients and Methods: The study included 60 female cancer breast patients scheduled for surgery; patients were randomized to undergo acute normovolemic hemodilution with either crystalloid or crystalloid plus colloid. Six samples were collected from each patient at different period of the study.

Results: IV administration of crystalloid plus colloid as well as crystalloid fluid cause significant effect in coagulation factors variables which is more obvious in administration of both crystalloid and colloid fluid together; where most investigated coagulation variables were significantly increased or decreased. This recorded variation reverts to normal value after 24 hour of infusion samples

Conclusion: Generally the least effect was observed in the group receiving crystalloid; special consideration should be given to the use of colloid rather than crystalloid solutions for rapid fluid loading.

Keywords: Coagulation system; Fluid infusion

Introduction

The colloids are highly effective volume expander but there has been a recurring question about their effects on coagulation. Many of studies that comment on the effects of colloids on coagulation have used a crystalloid control [1-3] or have not made allowance for any crystalloid to be used for patients in addition to colloids. Acute normovolemic hemodilution (ANH) is a useful and cost-effective blood conservation strategy in procedures with an expected blood loss of more than one litre [4,5]. The red blood cell (RBC) loss is decreased in the hemodiluted patient because blood that is lost during surgery has a reduced hematocrit [5]. This technique effectively reduces the need for allogenic blood transfusion and the accompanying risk of transfusion related infection and transfusion reactions [6]. In addition evidence that the transfusion of allogenic blood may induce immunosuppression in patients undergoing surgery for malignancies [7]. The administration of intravenous fluid is a routine therapy either crystalloid or colloid solutions are used for volume replacement to maintain hemodynamic stability and prevent hypotension and hypoperfusion. Colloid administration reduces clot strength and platelets function [8,9]. Conversely, hypercoagulability occasionally occurs during and after surgery [8,10]. The aim of this study was to analyze the effect of progressive hemodilution on the coagulation system, comparing a crystalloid versus colloid infusion.

Subjects and Methods

The current study was performed on 60 female cancer breast patients admitted through the clinics of South Egypt Cancer Institute and scheduled for surgery; patients age ranged from 39 - 55 years, ASA physical status I-III. The local ethics committee of Assiut University Hospital approved the study, and written informed consent was obtained from all patients or their legal representatives. Patients were classified randomly into two groups: Group I including 30 female patients who infused 1.5 litre Ringer lactate solution, and Group II included the remaining 30 patients who infused 0.5 litre of 6% hesteril and one litre Ringer lactate solution.

Exclusion criteria

Patients were excluded from participation if they had a history of a known coagulation disorder, platelet count less than 100, 000/mm3, preoperative hemoglobin (Hb) less than 9 g/dl, history anticoagulant therapy within 10 days before surgery, aspirin, herbal medications or non-steroidal anti-inflammatory drug use less than 10 days before surgery, morbid obese patients or if they had a documented allergy to any of the IV fluids used in the protocol.

All patients were premeditated with midazolam in the preoperative holding area and received a standardized general anesthetic induction consisting of propofol (2-3 mg/kg), cisatriacurium (0.15 mg/kg), and fentanyl (2.5 μg/kg). After tracheal intubation, anesthesia was maintained with isoflurane, nitrous oxide (67% in oxygen), and a

continuous fentanyl infusion (1–3 μg/kg/h). Six samples were withdrawn from each patient, Before anesthesia "base line" (B.L), directly after induction of anesthesia, after infusion of either crystalloid or crystalloid plus colloid solution, after 6 hours of infusion, after 12 hours of infusion and lastly after 24 hours of infusion. Prothrombin time (PT), Prothrombin concentration (PC), and activated partial thromboplastin time (aPTT) were measured using an automated coagulation analyzer(Diagnostic Stago, France). Plasma fibrinogen concentration, anti-thrombin III, thrombin-antithrombin complexes (TAT) and factor VIII (F VIII) were determined also using Enzyme Linked Immunosorbent Assay (ELISA) technique.

All patients were continuously monitored with electrocardiogram, pulse oximeter, end tidal CO2, capnography, central venous pressure, urine output, esophageal thermometer. Body temperature was kept within normal range using an active air warming blanket and warm fluids.

Statistical analysis

Statistical package for social sciences (SPSS), version 16 was used for data analysis. Data were presented as mean ± SE and were analyzed by calculating the variation between the groups and tested using student t-test. P-value is significant when less than 0.05.

Results

Patients in both groups, group I (Crystalloid infusion) and group II (crystalloid plus colloid infusion) were the same as regarding demographic data. No one of our patients received red cells or fresh frozen plasma during the surgery. Base line measurement of investigated variables did not show any difference among groups and they all were within normal ranges. Some mean values of measured coagulation analysis variables significantly affected in group II than group I (Table 1).

There were significant changes between the two groups at all-time intervals of reading as regard PT ($p<0.01$) except after 24 hours of infusion where PT were progressively increased in group I from 12.7 ± 0. 0.2 to 14.1± 0. 0.5 after 24 hours and from 13.6 ± 0. 0.3 to 16.0 ± 0. 0.2 after 12 hour and decreased again to 14.3 ± 0. 0.3 after 24 hours in group II. The same results were observed as regard PC (Table 1), (Figures 1 and 2).

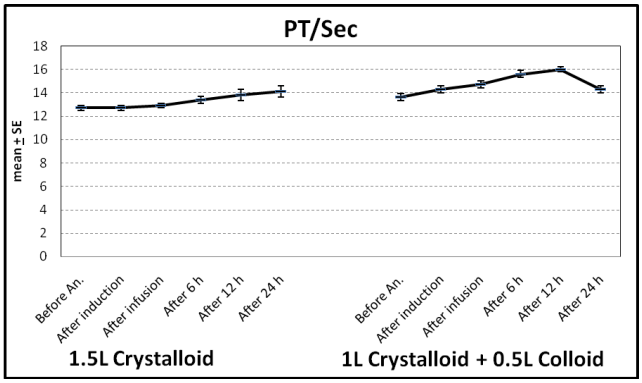

Figure 1: Changes in PT after IV fluid infusion.

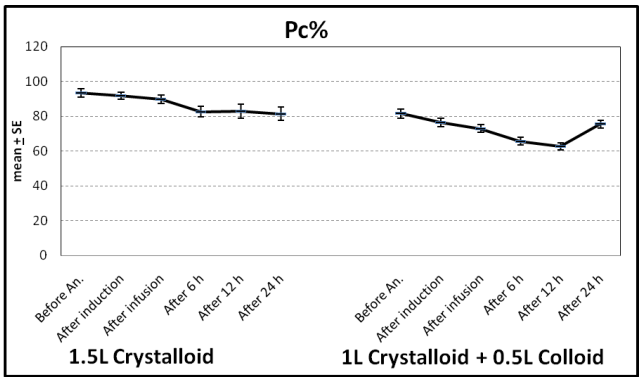

Figure 2: Changes in PC after IV fluid infusion.

There were significant difference between both groups over time as regard aPTT and fibrinogen level ($p<0.01$). The mean value of aPTT were increased and fibrinogen levels were decreased over times in both group until 24 hours of infusion in group I and until 12 hours of infusion in group II (Table 1), (Figures 3 and 4).

		Before Anesthesia	After induction	After infusion	After 6 hours	After 12 hours	After 24 hours
		Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Group I	PT	12.7 ± 0.2	12.7 ± 0.2	12.9 ± 0.2	13.4 ± 0.3	13.8 ± 0.5	14.1 ± 0.5
	PC	93.4 ± 2.4	91.8 ± 2.2	89.8 ± 2.3	82.7 ± 2.9	83.0 ± 4.1	81.5 ± 4.0
	aPTT	28.4 ± 0.5	28.4 ± 0.5	28.7 ± 0.5	28.9 ± 0.5	29.2 ± 0.5	29.5 ± 0.5
	Fibrinogen	3.6 ± 0.1	3.4 ± 0.1	3.4±0.1	3.3 ± 0.1	3.3 ± 0.1	3.2 ± 0.1
	AT	110.0 ± 3.7	107.0 ± 3.6	105.1 ± 3.6	103.1 ± 3.5	100.8 ± 3.5	98.4 ± 3.5
	TAT	6.4 ± 0.3	6.7 ± 0.2	7.1 ± 0.2	7.1 ± 0.2	6.6 ± 0.2	6.0 ± 0.2
	FVIII	138.2 ± 4.9	135.0 ± 4.9	132.5 ± 4.9	129.8 ± 4.8	127.5 ± 4.5	124.3 ± 4.4
Group II	PT	13.6 ± 0.3	14.3 ± 0.3*	14.7 ± 0.3*	15.6 ± 0.3*	16.0 ± 0.2*	14.3 ± 0.3

	PC	81.6 ± 2.6	76.4 ± 2.5*	73.0±2.3 *	65.8 ± 2.2*	62.8 ± 2.0*	75.6±2.2
	aPTT	31.2 ± 1.0	33.5 ± 1.3*	34.4 ± 1.3*	36.2 ± 1.2*	38.3 ± 1.4*	33.2 ± 0.8*
	Fibrinogen	3.1 ± 0.2	2.5 ± 0.2*	2.2 ± 0.2*	2.0 ± 0.2*	1.7 ± 0.1*	2.6 ± 0.1 *
	AT	133.7 ± 5.9	119.8 ± 6.3	112.6 ± 6.3	102.5 ± 6.6	110.3 ± 7.1	124.5 ± 7.8*
	TAT	7.4 ± 0.2	7.1 ± 0.2	6.6 ± 0.2	6.2 ± 0.2*	5.8 ± 0.2*	6.0 ± 0.2
	FVIII	134.7 ± 5.9	122.4 ± 5.3	115.5 ± 4.8	110.8 ± 4.3*	101.4 ± 4.8*	119.4 ± 4.7

*Comparison between group I and II : P value< 0.05 = significant

PT: prothrombin time in seconds; PC: prothrombin concentration; aPTT: activated partial thromboplastin time in seconds; F VIII: factor VIII; AT III: anti thrombin III; TAT: thrombin ant thrombin complex.

Table 1: Coagulation parameter changes during the study period in both groups.

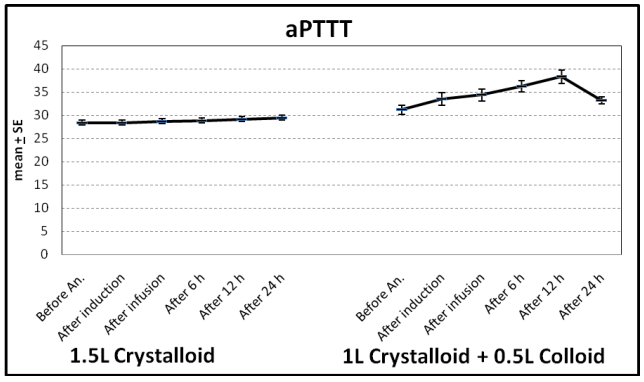

Figure 3: Changes in PTT after IV fluid infusion.

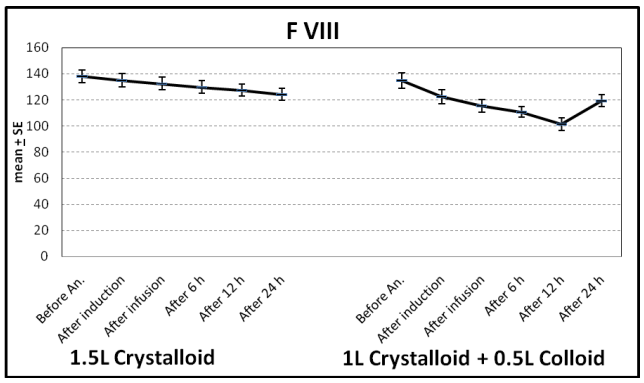

Figure 4: Changes in F VIII after IV fluid infusion.

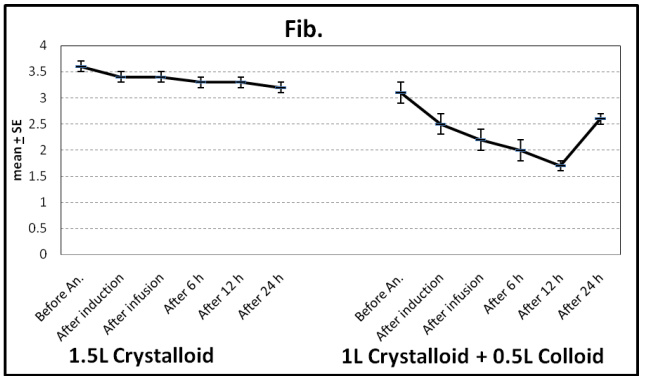

Figure 5: Changes in Fibrinogen after fluid infusion.

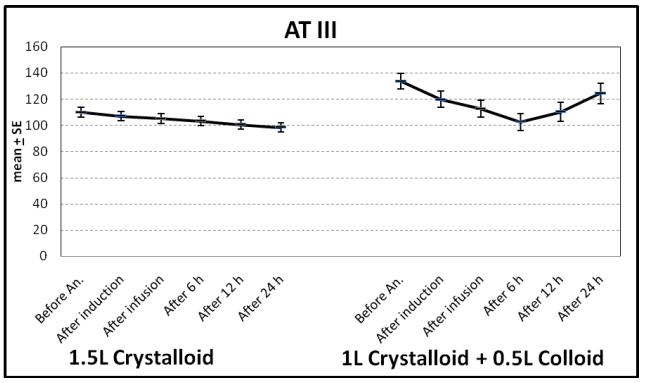

Figure 6: Changes in AT III after IV fluid infusion.

Factor VIII and ATIII were gradually decreased over time in both group until after 24 hours of infusion in group I and after 6 hours for AT III and 12 hours of infusion for F VIII and this recorded reduction reverts to normal value after 24 hours of infusion in group II (Table 1); (Figures 5 and 6).

Those differences between both groups were statistically significant after 6 and 12 hours of infusion for F VIII (p=0.06 and <0.001 respectively) and significant only after 24 hours for ATIII (p=0.004).

TAT was increased after infusion until after 6 hours of infusion and then start to decreased again in group I while TAT were decreased over time in group II until 24 hours of infusion (Table 1), (Figure 7).

Table 2 shows the comparison in percentage of changes in different coagulation parameters between base line value and the rest of samples in both groups.

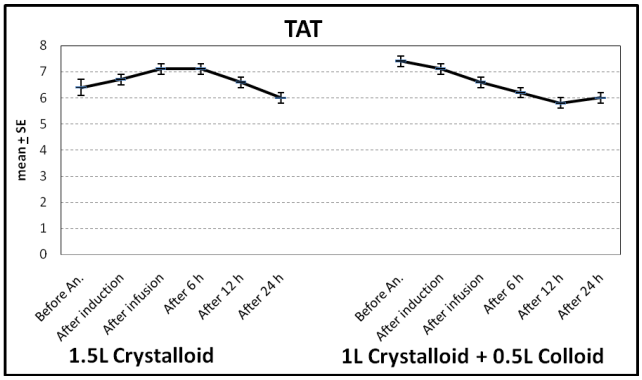

Figure 7: Changes in TAT after IV fluid infusion.

Samples	PT		PC		aPTT		Fibrinogen		Factor VIII		AT III		TAT	
	Group I (n= 30)	**Group II (n= 30)**	**Group I (n=30)**	**Group II (n=30)**	**Group I (n=30)**	**Group II (n=30)**	**Group I (n=30)**	**Group II (n=30)**	**Group I (n=30)**	**Group II (n=30)**	**Group I (n=30)**	**Group II (n=30)**	Group I (n=30)	Group II (n=30)
% Change between before anesthesia and after induction	-0.2 ± 1.0	5.1 ± 0.8*	-1.3 ± 1.9	-6.3 ± 0.9	0.2 ± 0.4	6.7 ± 0.7*	-3.7 ± 0.9	-23.2 ± 4.4*	-2.3 ± 0.4	-8.9 ± 1.0*	-2.7 ± 0.4	-11.3 ± 1.3*	6.4 ± 2.7	-4.7 ± 0.8*
% Change between before anesthesia and after infusion	1.7 ± 1.2	8.0 ± 0.9*	-3.5 ± 2.0	-10.2 ± 1.3*	± 0.5	10.0 ± 0.9*	-5.4 ± 1.1	-33.5 ± 3.5*	-4.2 ± 0.4	-13.7 ± 1.1*	-4.5 ± 0.4	-16.5 ± 1.6*	14.3 ±3.5	-11.5 ± 1.3*
% Change between before anesthesia and after 6 h	5.5 ± 1.4	14.8 ± 1.6*	-11.4 ± 2.4	-18.7 ± 2.0*	1.8 ± 0.6	16.0 ± 1.1*	-6.8 ± 1.1	-38.0 ± 3.5*	-6.2 ± 0.4	-17.0 ± 1.0*	-6.2 ± 0.4	-24.1 ± 2.7*	15 ± 4.6	-16.8 ± 2.3*
% Change between before anesthesia and after 12 hr	8.1 ± 2.7	18.0 ± 1.5*	-11.5 ± 3.8	-22.2 ± 2.1*	3.1 ± 0.8	22.4 ± 1.3*	-8.7 ± 1.3	-47.7 ± 2.7*	-7.8 ± 0.4	-24.8 ± 0.8*	-8.4 ± 0.5	-18.8 ± 2.3*	6.2 ± 4.2	-21.6 ± 2.0*
% Change between before anesthesia and after 24 hr	10.6 ± 2.9	5.2 ± 0.9	-13.2 ± 3.6	-6.9 ± 1.3	4.2 ± 1.0	6.8 ± 1.5	-10.9 ± 1.4	-17.4 ± 2.5*	-10.0 ± 0.6	-10.8 ± 1.1	-10.6 ± 0.7	-8.1 ± 2.2*	-3.2 ± 3.9	-18.3 ± 2.4*

*Comparison between group I and II : P value<0.05=significant

PT: prothrombin time in second; PC: prothrombin concentration; aPTT: activated partial thromboplastin time in second; F VIII: factor VIII; AT III: anti thrombin III; TAT: thrombin ant thrombin complex.

Table 2: Percentage of coagulation parameters changes at different time of analysis from the Base line samples in group I and II.

Discussion

Both crystalloid and colloid replacement fluids have been successfully used to maintain normovolaemia during operation. At present there is various crystalloid and colloid solutions are available for resuscitation of hypovolaemic patients, and their effects on coagulation are clearly of interest. Colloids such as hetastarch decrease hypercoagulability in some studies, whereas crystalloid administration may not [11].

In injured patients, however, these are hard to assess because the stress of trauma or surgery can alter blood coagulation. The effect of stress, tissue trauma, pain, endogenous catecholamine levels and anesthesia per se on global coagulation status are poorly understood. Such factors can be confounding variables in any study of coagulation in relation to blood loss and fluid replacement. In addition, when blood is diluted with an intravenous fluid the hemodilution effect can itself alter hemostatic mechanism [12]. Patients undergoing extensive prolonged surgery are prone to develop coagulopathy, even when there is no preoperative coagulopathy or dysfunction of primary hemostasis [13]. This called dilution coagulopathy which results from blood loss, consumption of coagulation factors and platelets, and intravascular volume replacement. *In vivo* and *in vitro* hemodilution coagulation studies in normal individuals are therefore an important source of information regarding the effect on hemostasis of intravenous fluid resuscitation [12], their results have clearly demonstrated that natural and artificial colloids impair hemostasis more than crystalloids do [13].

Our studies is one of the *in vivo* studies investigate the influence of combined crystalloid plus colloid IV administration on the coagulation system compared with crystalloid infusion alone, and to exclude possible confounding factors; no red cell or fresh frozen plasma were transfused.

We investigated the effects of commonly used intravenous solution (Ringer lactate, and Colloid) on the activated coagulation system in patients undergoing breast cancer surgery. Multiple samples were withdrawn at different periods from all patients, before and after anesthesia, after infusion of IV fluids at standard durations aiming to detect any differences on coagulation profiles in both investigated groups. We decrease the volume of infused colloid solution, aiming to reduce the coagulation disturbances.

The choice of replacement fluid during hemodilution has varying effects on coagulation values [14]. Previous studies have confirmed that hemodilution with isotonic crystalloid solution increases blood coagulation another study have demonstrated that in vitro saline hemodilution at 20% and 30% dilution promotes coagulation [15,16]. Our results agree with these previous studies however this impaired coagulation profiles is temporary after that all investigated coagulation variables revert to normal values.

Most investigated coagulation variables were significantly increased like PT and aPTT or decreased like fibrinogen, factor VIII, AT III and TAT in group II than group I throughout the study and reverting to normal values after 24 hours of IV fluid infusion.

The effect of colloids on platelet function is of clinical relevance because colloids are used mainly to bridge blood loss, especially in trauma patients. There are increasing number of studies that investigate the influence of different types of solutions on platelets function and coagulation. They concluded that colloid administration reduces clot strength and platelets function [17]. Conversely hypercoagulability occasionally occurs during and after surgery [18]. These opposite results may be explained as that the patients may have both reduced clot strength and hypercoagulability at the same time if both the coagulation cascade and fibrinolytic system are damaged.

IV administration of crystalloid plus colloid as well as crystalloid fluids caused a significant decrease in the coagulation factors involved in platelet adhesion, a measurable impairment of platelet function, and changes in the speed and quality of clot formation [10].

Hydroxyethyl starch (HES) solutions are the most frequently used colloids due to the volume efficacy and low risk of adverse effects [19]. Development of HES solutions have centered on designing starch molecules with an increased oncotic pressure and hemodynamic efficacy while minimizing the risk of adverse reaction such as plasma and tissue accumulation and anticoagulant effects [20].

Jamnicki et al. [21] conclude that a higher molecular weight (MW) has generally been considered a significant factor in determining the effect of a given HES solution in blood coagulation in that the higher the MW the more the blood coagulation is expected to be compromised [22].

Most of the previous studies used first generation high MW HES (450,000 Dalton), this slowly degradable solution may induce type I VWF like syndrome with decreased F VIII coagulant activity [23]. High MW hestril also resulted in the overall most pronounced impaired platelets aggregation, whereas medium MW hestril did not show the same negative effect on platelets and coagulation function [24]. Other studies in humans confirmed that low MW Hestril preparations can be used without resulting in major bleeding problems [25].

One previous study by Haisch et al. [26] who compare the effect of gelatin and another colloid preparation HES on coagulation in patients who undergo abdominal surgery, concluded that administration of moderate doses of HES 130/0.4 preparation result in mild negative coagulation ultration as those after using an established gelatin replacement therapy. They commented that the MW and degree of substitution (SD) of HES are mainly responsible for impaired hemostasis with an increased bleeding tendency [27]. Another study recorded contradictory results that the effects of the different HES solution on hemostasis were marked and obvious [28]. The concordance between our results and Haisch et al and discrepancy with Baldassarre et al recorded results can be explained that the used HES preparation and its amount by our and Haisch was the modified HES 130/0.4 with low MW and high degree of SD in moderate dose (500 ml) has mild negative effect on coagulation system [29].

Janverin and Colleges have previously shown an increase in coagulation and incidence of deep venous thrombosis in patients receiving crystalloid fluid during surgery [30]. Hesteril 0.6% had almost no effect on coagulation either at the time of acute hemodilution or during surgery; it appears that the major part of alteration in coagulation seen in the crystalloid group was attributable to fluid administered, rather than the surgical stimulus. In the colloid group the enhancement of coagulation may have been inhibited by the anti-platelet activation effect of hesteril through its prevention of platelet clumping.

An earlier study found statistically significant correlation between deteriorating coagulation functions and administration of more than 3 litres of crystalloids during abdominal surgery and there is also correlation between administration of more than 500 ml colloid administration and elongation of prothrombin time; the negative

correlation between volumes of fluids and coagulation is gradual [31]. On the other hand there are advantages of fluid administration that cannot be overlooked: One should consider all of the different aspects of fluid therapy while using it [32].

Barak et al. [32] also added that the problem with clinical studies investigating the perioperative fluid administration is the complexity of so many variables that may affect volume status. These include variables such as the degree of preoperative dehydration, the amount of blood loss, the extent of surgical dissection, any of these factors could influence coagulation rather than simply the quantity of fluid administrated.

A larger decrease in factor VIII levels might have been expected in HES group based upon previous studies [15,17]. This effect may have been masked by the stress response to surgery, which lead to increase some variables like factor VIII [18]. Our result showed that F VIII were gradually decreased over time in both group until after 24 hours of infusion in group I and 12 hours of infusion and this recorded reduction reverts to normal value after 24 hours of infusion in group II and the % change for F VIII level is significantly differing in all samples.

PT and aPTT tests are usually used to detect coagulation factor deficiencies and the need for FFP transfusion, previous results found that these coagulation tests become pathological soon, although no critical reduction in coagulation factor was present [13]. Our findings that changes in PT were comparable between both groups come in accordance with other studies [10], whereas aPTT and fibrinogen were significantly more impaired with crystalloid plus colloid infusion as compared with crystalloid.

Mittermayr et al. [13] found that colloid influence the speed and quality of clot formation by interfering with fibrinogen concentration and functional measured fibrinogen/fibrin polymerization.

Fibrinogen concentration decreased more in the colloid group during the observation period, and also earlier than in the crystalloid group. The same result was observed by Innerhofer et al. [10] where fibrinogen concentration showed only a weak trend toward a larger decrease with colloids.

Analysis of clotting factors during progressive hemodilution revealed that fibrinogen was the first factor to become critically low. Moreover, all synthetic colloid solutions are believed to impair fibrin polymerization, which can additionally reduce blood clot stability [33].

Values of coagulation times depend on concentration of procoagulant factors and AT levels as only 5% thrombin are needed for initiation of coagulation. Hemodilution decreases the levels of ATIII and possibly other inhibitors of coagulation. This will result in lowering the threshold for initiation of positive feedback into the coagulation cascade and subsequently stimulated coagulation via intrinsic pathway, decrease in concentration of ATIII to below 70% of normal increased the risk of thrombosis [13]. While, hemodilution have a minimal effect on the level of continuously formed active coagulants, this then results in unchecked positive feedback, and accelerated formation of thrombin [34]. We found that hemodilution decreases the levels of ATIII this enhances thrombus formation.

One of the mechanism seems to be responsible for enhanced coagulation after dilution with saline is an imbalance in thrombin and anti-thrombin concentration. Like other studies [35] we were unable to demonstrate a disproportional reduction in ATIII concentration following *in vivo* hemodilution with crystalloids. So although the measurement of ATIII and TAT showed slight defects it cannot excluded that dynamics of thrombin generation are probably disturbed specially in colloid group which may lead to pathological clot formation during surgery.

Conclusion

Fluid resuscitation with colloid solutions may adversely affect outcome by decreasing blood coagulation and impairing surgical hemostasis. Acquired coagulopathy induced by progressive hemodilution has an earlier onset and more severe when induced with crystalloid plus colloid infusion. Consideration should be given to the use of colloid rather than crystalloid solutions for rapid fluid loading.

References

1. London MJ, Franks M, Verrier ED (1992) The safety and efficacy of ten percent pentastarch as a cardiopulmonary priming solution. J Thor Cardiovasc Surgery 104: 284-296.
2. Kuitunen A, Hynynen M, Salmenpera M (1993) Hydroxyethyl starch as a prime for cardiopulmonary bypass: effects of two different solution on hemostasis. Acta Anaethesiol Scand 37: 652-658.
3. Nagy KK, Davis J, Duda J (1993) A comparison of pentastarch and lactated riger solution in the resuscitation of patients with hemorrhagic shock. Circ Shock 40:289-294.
4. Goodnough LT, Despotis GJ, Merkel K (2000) A randomized trial comparing acute normovolemic hemodilution and preoperative autologous blood donation in total hip arthroplasty. Transfusion 40: 1054-1057.
5. Ness PM, Bourke DL, Walsh PC (1992) A randomized trial of perioperative hemodilution versus transfusion of preoperatively deposited autologous blood in elective surgery. Transfusion 32: 226-230.
6. Stehling L, Zauder HL (1994) Controversies in transfusion medicine: perioperative hemodilution-pro. Transfusion 34: 265-267.
7. Schriemer PA, Longnecker DE, Mintz PD (1988) The possible immunosuppressive effects of perioperative blood transfusion in cancer patients. Anesthesiology 68: 422-428.
8. MacCammon AT, Wright JP, Fegueroa M (2002) Hemodilusion with albumin, but not Hextend, results in hypercoagulability as assessed by thromboplastograpgy in rabbits: role of heparin-dependent serpins and factor VIII complex. Anesth Analg 95: 844-850.
9. Rogers MC (1993) Principles and practice of anaethesiology. St.Louis, MO: Mobsbi- 923.
10. Innerhofer P, Freis D, Margriter J (2002) The effect of perioperatively administered colloids and crystalloids on primary platelet-mediated hemostasis and clot formation. Anesth Analg 95: 858-865.
11. Mortelmans YJ, Vermaut G, Verbruggen AM (1995) Effects of 6% hydroxyethyl starch and 3% modified fluid gelatin on intravascular volume and coagulation during intraoperative hemodilution. Anesth Analg 81: 1235-1242.
12. Brazil EV, Coata TJ (2000) Sonoclot coagulation analysis of in-vitro haemodilution with resuscitation solutions. Journal of the royal society of medicine 93: 507-510.
13. Mittermayr M, Streif W, Haas T (2007) Hemostatic changes after crystalloid or colloid fluid adminstration during major orthopedic surgery: the role of fibrinogen adminstration. Aaesth Analg 105: 905.
14. Jones SB, Whitten CW, Depotis GJ (2003) The influence of crystalloid and colloid replacement solutions in acute normovolemic hemodilution: a preliminary survey of hemostatic markers. Anesth & Analg 96: 363-368.
15. Egli GA, Zollinger A, Seifert B (1997) Effect of progressive haemodilution with hydroxyethyl starch, gelatin, and albumin on blood coagulation. Br J Anaesth 78: 684-689.

16. Ng KF, Lam CC, Chan LC (2002) *In vivo* effect of haemodilution with NaCl 0.9% on coagulation: a randomized controlled trial. Br J Anaesth 88: 475-480.
17. Fries D, Innerhofer P, Klingler A (2002) The effects of combined adminstration of colloids and lactated Ringer solution on the coagulation system: an *in vitro* study using thrombelastograph coagulation analysis (ROTEG). Anesth Analg 94: 1280-1287.
18. Ickx BE, Bepperling F, Melot C (2003) Plasma substitution effects of a new hydroxyethyl starch HES 130/0.4 compared with HES 200/0.5 during and after extended acute normovolaemic haemodiltion. Br J anaesth 91: 196-202.
19. Westphal M, James M, Kozek-Langenecker S (2009) Hydroxyethyl starches: different products--different effects. Anesthesiology 111: 187-202.
20. Jamnicki M, Bombeli T, Seifert B (2000) Low- and medium-molecular-weight hydroxyethyl starches: comparison of their effect on blood coagulation. Anaseth 93: 1231-1237.
21. Deusch E, Thaler U, Kozek-Langenecker SA (2004) The effects of high molecular weight hydroxyethyl starch solutions on platelets. Anaseth Analg 99: 665-668.
22. Kozek-Langenecker SA (2009) Benefits of fluid therapy on the hemostatic system of intensive care patients. J Coag Dis 4: 1-5.
23. Zarychanski R, Abou-Setta AM, Turgeon AF (2013)Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA 309: 678-688.
24. Myburgh JA, Finfer S, Bellomo R (2012) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J med 367: 1901-1911.
25. Haisch G, Boldt J, Krebs C (2001) The influence of intravascular volume therapy with a new hydroxyethyl stach preparation(6% HES 130/0.4) on coagulation in patients undergoing major abdominal surgery. Anesth Analg 92:565-571.
26. Hartog C, Reinhart K (2009) CONTRA: Hydroxyethyl starch solutions are unsafe in critically ill patients. Intensive Care Medicine 35: 1337-1342.
27. Baldassarre S, Vincint J (1997) Coagulopathy induced by hydroxyethyl starch. Anasth Analg 84: 451-453.
28. Perner A, Haase N, Guttormsen AB (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. The New England Journal of Medicine 367: 124-134.
29. Janvrin SB, Davies G, Greenhalgh RM (1980) Postoperative deep venous thrombosis caused by intravenous fluids during surgery. Br J Surgery 67: 690-693.
30. Barak M, Rudin M, Vofsi O (2004) Fluid administration during abdominal surgery influences the coagulation on the postoperative period. J Cur Sur 61: 495-462.
31. Roberts J, Evans P, Bunn F (2001) Is the normalisation of blood pressure in bleeding trauma patients harmful? Lancet 357: 385-387.
32. De Lorenzo C, Calatzis A, Welsch U (2006) Fibrinogen concentrate reverses dilutional coagulopathy induced *in-vitro* by saline but not by hydroxyethyl starch 6%. Anesth analg 102: 1194-1200.
33. Ruttmann TG, James ME, Lombard EH (2001) Haemodilution- Induced enhancement of coagulation is attenuated *in-vitro* by restoring antithrombin III to pre-dilution concentrations. Anaesth Intensive Care 29: 489-493.
34. Fries D, Streif W, Margreiter J (2004) The effects of perioperatively adminstrated crystalloids and colloids on concentrations of molecular marckers of activated coagulation and fibrinolysis. Blood Coagulation and fibrinolysis 15: 213-219.
35. Ruttmann TG, James MF, Finlayson J (2002) Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery. Br J Anaesth 89: 226-230.