The role of antifibrinolytic agents in gynecologic cancer surgery

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ABSTRACT

Objective: To compare the effects of crystalloid and colloid solutions, tranexamic acid and epsilon-aminocaproic acid on the need for allogenic blood transfusion and on coagulation and fibrinolysis parameters.

Methods: We conducted the study in the Anesthesiology and Reanimation Department of Hacettepe University Medical Faculty, Ankara, Turkey between March 2004 and April 2005. The study included 105 patients, classified by the American Society of Anesthesiology as physical status groups I-II, undergoing gynecologic cancer treatment. We divided them into 5 groups: group I (crystalloid) received crystalloid solutions, group II (colloid) received colloid solutions, group III (tranexamic acid) received 10 $mg.kg^{-1}$ tranexamic acid, and group 5 (epsilon-aminocaproic acid) received 100 $mg.kg^{-1}$ epsilon-aminocaproic acid. All patients' bleeding amount was measured and recorded perioperatively, and at the 12th and 24th hours postoperatively. We then evaluated the patients' hemoglobin, hematocrit, activated thromboplastin time, international normalized ration, fibrinogen, and thrombocyte count and symptoms of pulmonary embolism.

Results: In comparing the amount of bleeding, the bleeding in the tranexamic acid group was 30.8% less than the crystalloid group ($p<0.05$), 33.3% less than the colloid group ($p<0.05$), and 23.9% less than the epsilon-aminocaproic acid group ($p<0.05$).

Conclusion: When the negative effects of blood transfusions were considered, tranexamic acid administration can be recommended for decreasing the need for blood transfusion in gynecologic cancer surgery.

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In radical surgical procedures for gynecologic malignancy, a large amount of blood loss can be seen and this blood loss can make allogenic blood transfusion necessary. Blood transfusions are known to increase complications and morbidity.[1]

The purpose of this study was to compare the effects of crystalloid and colloid solutions, tranexamic acid and epsilon-aminocaproic acid on the need for allogenic blood transfusion and on coagulation and fibrinolysis parameters.

Hypovolemia is frequently encountered in surgery, trauma and intensive care unit patients. During surgery, there is often an absolute or relative decrease in blood volume. In radical surgical procedures for gynecologic malignancies, there is a significant amount of blood loss. Although it is widely accepted that it is important to replace fluids sufficiently, discussions continue regarding the optimal strategy.[2] The strategies can be considered to be between crystalloid and colloid use and blood product transfusions. In procedures in which more than a liter of blood loss is anticipated, we are prepared with the use of acute normovolemic hemodilution and cheap blood conservation strategies.[2,3] In a patient

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which has been hemodiluted the red blood cell loss decreases as during the surgical procedure the blood that is lost decreases the hematocrit.[3] Use of crystalloid and colloid solutions can sometimes result with coagulation system changes, deposition, itching, anaphylactic reactions and decrease in renal function.[4,5] Acute normovolemic hemodilution and decrease in the hematocrit does not cause problems in high risk patients like coronary heart disease, severe valvular disease and chronic renal disease as compensatory mechanisms guarantee tissue oxygenation and systemic oxygen transport.[6,7] However, in patients with severe anemia or coagulation disorders a need for blood and blood products may occur.

Methods. After obtaining permission from the local ethics committee and informed patient consents, 105 patients between the ages of 20-60 years old in American Society of Anesthesiology (ASA) physical status groups I-II, cervix cancer stage I or II, scheduled for type III hysterectomy (total abdominal hysterectomy and bilateral salpingo oophorectomy and bilateral para aortic and pelvic lymphadenectomy) were included in the study. A double blind, randomized and prospective study was carried out and the patients were randomly divided into 4 groups. Patients with cardiac, endocrine or renal diseases and those with coagulopathy and medication allergies, and patients who needed blood transfusion during surgery were excluded from the study. The patients' demographic characteristics are shown in **Table 1**. For fluid replacement, crystalloid solutions (0.9% NaCl, Ringers Lactate, Isolyte-S) were given to group I (n=26), colloid solutions (Isohes, Hemaccel, HAES) to group II (n=26), crystalloid solutions and 10 $mg.kg^{-1}$ tranexamic acid to group III (n=27), and crystalloid solutions and 100 $mg.kg^{-1}$ epsilon-aminocaproic acid to group IV (n=26). Considering the patients' weight perioperative fluid therapy was managed in order to replace maintenance requirements, preexisting fluid deficits caused by preoperative fasting, surgical wound losses including blood loss.[8] After patients were taken to the operating room they were placed on ECG monitoring, SpO_2 saturation, and non-invasive blood pressure monitoring before induction. For induction of anesthesia 1-3 $mg.kg^{-1}$ propofol and 0.08 $mg.kg^{-1}$ vecuronium bromide were used in all groups. Following 20 $\mu g\ kg^{-1}$ alfentanil endotracheal intubation was performed. After induction and before the surgical incision, group III patients were given tranexamic acid and group IV patients were given epsilon-aminocaproic acid. Anesthesia was maintained with 70% N_2O, 30% O_2, 2% sevoflurane and vecuronium bromide when necessary. Before beginning the surgical procedure a central venous catheter was placed, and central venous pressure, invasive blood pressure and urine output were monitored.

Blood loss was recorded intraoperatively and at the 12th and 24th hours postoperatively in all groups. The lost blood was estimated by calculating the blood in suction plus sponge counting plus the blood drained in postoperative 24 hours. All patients' preoperative and 12th and 24th hour postoperative hemoglobin, hematocrit, activated thromboplastin time (aPTT), international normalized ration (INR), fibrinogen, thrombocyte count and symptoms of pulmonary embolism were evaluated preoperatively and 12th and 24th hour postoperatively in all groups. It was planned that any patient with clinical symptoms of pulmonary embolism (with symptoms such as, dyspnea, hemoptysis, pleuritic chest pain, apprehension, cough in addition to tachypnea, rales, elevated *p* in electrocardiography, tachycardia, fever) would be evaluated with pulmonary scintigraphy.

One-way analysis of variance, Duncan test and Krusskal-Wallis variance analysis were used to compare the variables in the 4 groups. Time related variables were analyzed using paired t-test and Wilcoxon test. The differences in variables related to time and coagulation values were analyzed with Chi-square and Kappa tests. A $p<0.05$ was accepted as statistically significant.

Results. There were no significant differences in demographic data between groups (**Table 1**). The Hct, total blood loss, mean arterial pressure (MAP), central venous pressure (CVP), peripheral oxygen saturation ($Sa0_2$) are shown in **Table 2**. No significant changes were found between or within groups with respect to MAP, CVP, SaO_2, and ascites. Thrombocytes (Plt), fibrinogen, aPTT and INR values are shown on **Table 3.**

Table 1 - Demographic data (mean ± SD).

Variants	Group I (N=26)	Group II (N=26)	Group III (N=27)	Group IV (N=26)
Age (year)	39.2 ± 8.8	40 ± 7.2	42 ± 6.8	43 ± 7.2
Weight (kg)	65 ± 3	66 ± 4	67 ± 4	64 ± 2
Height (cm)	158 ± 7	160 ± 9	157 ± 9	162 ± 5
Duration of surgery (minutes)	57 ± 9	51 ± 13	60 ± 11	51 ± 9

Table 2 - Research groups' Hgb, Hct, Blood loss, mean arterial pressure, peripheral oxygen saturation and central venous pressure values (mean ± SD).

Parameters	Group I (N=26)		Group II (N=26)		Group III (N=27)		Group IV (N=26)	
Hb_0 (g/dl)	12.7 ± 0.3		11.6 ± 1.1		12.11 ± 0.7		12.08 ± 0.4	
Hb_1 (g/dl)	11.2 ± 0.5	(p=0.023)	9.9 ± 1.7	(*p*=0.003)	10.29 ± 1.6	(*p*=0.023)	9.8 ± 0.6	(*p*=0.007)
Hb_2 (g/dl)	11 ± 0.3	(*p*=0.023)	7.8 ± 1.2	(*p*=0.003)	10.32 ± 0.4	(*p*=0.025)	9.6 ± 0.2	(*p*=0.003)
Hct_0 (%)	36.21 ± 1.3		31.28 ± 2.1		35.28 ± 1.8		36.02 ± 2.1	
Hct_1 (%)	32.32 ± 1.8	(*p*=0.007)	29.38 ± 1.8	(*p*=0.025)	30.01 ± 2.1	(*p*=0.003)	30.92 ± 2.2	(*p*=0.001)
Hct_2 (%)	32.28 ± 1.1	(*p*=0.002)	29.55 ± 1.2	(*p*=0.025)	30.14 ± 2.2	(*p*=0.007)	29.30 ± 2.2	(*p*=0.000)
Total blood loss (cc)	405 ± 40		390 ± 35		270 ± 40	(*p*=0.005)	355 ± 40	
CVP (mm Hg)	4 ± 1		5 ± 0.8		5 ± 1.1		4 ± 1.2	
MAP (mm Hg)	91 ± 15		92 ± 15		95 ± 15		96 ± 15	
SaO_2 (%)	98 ± 2		98 ± 1		98 ± 2		98 ± 2	

Group 1 - crystalloid group, group II - colloid group, group III - tranexamic acid group, group IV - epsilon-aminocaproic acid group, Hb_o - beginning hemoglobin, Hb_1 - 12th hour hemoglobin, Hb_2 - 24th hour hemoglobin Hct_o - beginning hematocrit, Hct_1 - 12th hour hematocrit, Htc_2 - 24th hour hematocrit, CVP - central venous pressure, MAP - mean arterial pressure, SaO_2 - peripheral oxygen saturation

Table 3 - Research groups' thrombocyte, fibrinogen, aPTT and international normalized ration (INR) values (mean ± SD).

Parameters	Group I (N=26)		Group II (N=26)		Group III (N=27)		Group IV (N=26)	
Plt_0 ($\times 10^3$/uL)	319.36 ± 42		284.72 ± 44		284.3 ± 38		278.4 ± 48	
Plt_1 ($\times 10^3$/uL)	284.25 ± 38		250.60 ± 37		273.42 ± 35		260.72 ± 35	
Plt_2 ($\times 10^3$/uL)	264.46 ± 34		245.60 ± 30		257.63 ± 34		249.3 ± 38	
$Fibrinogen_0$ (mg/dl)	393.29 ± 42		345.92 ± 65		360.89 ± 44		380.04 ± 54	
$Fibrinogen_1$ (mg/dl)	478.74 ± 37	(*p*=0.023)	437.08 ± 42	(*p*=0.007)	463.15 ± 52	(*p*=0.001)	492.01 ± 58	(*p*=0.000)
$Fibrinogen_2$ (mg/dl)	475.83 ± 34	(*p*=0.025)	454.52 ± 65	(*p*=0.000)	459.37 ± 38	(*p*=0.003)	440.42 ± 48	(*p*=0.015)
$aPTT_0$ (sec)	45.65 ± 8.4		47.19 ± 7		45.57 ± 5		44.38 ± 4.5	
$aPTT_1$ (sec)	73.67 ± 6.8	(*p*=0.001)	61.82 ± 4.5	(*p*=0.007)	47.41 ± 4.6		43.24 ± 5.2	(*p*=0.045)
$aPTT_2$ (sec)	38.39 ± 9.8		40.19 ± 4.6		52.51 ± 4.2		48.72 ± 3.9	
INR_0	1.93 ± 0.04		1.39 ± 0.03		1.19 ± 0.03		1.24 ± 0.03	
INR_1	3.33 ± 0.02	(*p*=0.023)	2.16 ± 0.04	(*p*=0.025)	1.35 ± 0.02		1.44 ± 0.02	(*p*=0.037)
INR_2	1.88 ± 0.04		1.35 ± 0.03		1.31 ± 0.04		1.38 ± 0.04	

*$p<0.05$ (according to beginning values)
#$p<0.05$ (according to beginning and 24th hour values)
Plt_o - beginning thrombocyte count, Plt_1 - 12th hour thrombocyte count; Plt_2 - 24th hour thrombocyte count, $fibrinogen_0$ - beginning value, $fibrinogen_1$ - 12th hour value, $fibrinogen_2$ - 24th hour value, $aPTT_o$ - beginning active partial thromboplastic time value, $aPTT_1$ - 12th hour value, $aPTT_2$ - 24th hour value, INR_o - beginning value, INR_1 - 12th hour value, INR_2 - 24th hour value.

No significant difference was found between groups in Hct, Hb, thrombocyte count and mean fibrinogen t_0 (starting time), t_1 (value at 12th hour) and t_2 (24th hour value) values. No significant difference was found between crystalloid group, colloid group and epsilon-aminocaproic acid group with respect to total blood loss ($p>0.05$); however, the total blood loss in tranexamic acid group was significantly less than the other groups ($p<0.05$). An examination of the t_0, t_1 and t_2 mean aPTT and INR values showed that there was a significant difference in t_1 value between crystalloid group and the other groups ($p<0.05$).

Discussion. The percentage of blood transfusions given in gynecologic procedures has been reported between 1.3% and 2.6%.[9,10] There are some risks associated with blood transfusion such as hemolytic reactions, allergy, anaphylaxis, transfusion related acute pulmonary damage and infection transmission. In addition to discussion on the effect of intraoperative blood transfusion in oncologic surgery on the recurrence of cancer, work continues to decrease the need for intraoperative blood transfusion.[11]

In dealing with problems of prolonged intravascular homeostasis, an alternative method for decreasing blood loss is the use of some medications. Tranexamic acid shows antifibrinolytic effect by blocking the lysine-binding sites of plasminogen and plasmin molecules and in that way prevents attachment of plasminogen and plasmin to the fibrin substrata. In addition, tranexamic acid inhibits the conversion of plasminogen to plasmin by plasminogen activators.[12] Aprotinin and epsilon-aminocaproic acid has been shown to decrease blood loss in major surgical procedures.[13-15] However, aprotinin is an expensive medication and can cause anaphylaxis. In vitro epsilon-aminocaproic acid attaches to the lysine-binding sites of the plasminogen molecule causing a change in the conformation of plasminogen. Its major in vivo effects are antifibrinolytic and in high concentrations, it inhibits plasmin and plasminogen activation.[16] On the other hand, tranexamic acid in vitro is 10 times more potent than aminocaproic acid. In addition, epsilon-aminocaproic acid has been reported to cause obstructive uropathy, thrombosis in glomerular capillaries, rhabdomyolysis and myoglobulinuria.[15]

The pre incisional use of tranexamic acid has been reported to decrease bleeding in cardiopulmonary bypass surgery, total hip arthroplasty, total knee arthroplasty and cesarean operations.[13,17-19] However, when it is given intraoperatively it does not decrease bleeding.[20] In our study, in comparing the tranexamic acid group with the crystalloid group the percentage of bleeding was 33.3% less, and in comparison with the colloid group it was 30.8% less. In comparison with the epsilon-aminocaproic acid group, however, a 23.9% decrease was seen. This decrease in blood loss obtained in tranexamic acid group was statistically significant in comparison with the other 3 groups.

Harley et al[21] reported that epsilon-aminocaproic acid clearly decreased total bleeding amount in total hip arthroplasty compared to placebo.[21] Kluger et al[22] reported a decrease in chest tube drainage in coronary artery bypass surgery with the use of both pre incisional epsilon-aminocaproic acid and after heparinization.[22] Florentino-Pineda et al[23] also reported that epsilon-aminocaproic acid clearly decreased perioperative bleeding in patients with idiopathic scoliosis undergoing posterior surgery.[23] There are, however, contrary findings in the literature. Amar et al[24] reported that while there was a decrease in perioperative blood loss with the use of aprotinin and epsilon-aminocaproic acid in major orthopedic procedures in cancer patients, no clinical benefit was seen.

In comparing of epsilon-aminocaproic acid group with the crystalloid and colloid groups in our study, although there was a decrease of 14% and 9% in total bleeding amount, there was no significant difference between the groups. Chauhan et al,[25] however, reported that epsilon-aminocaproic acid and tranexamic acid clearly and equally effectively decreased bleeding in pediatric cardiac surgery.[25] This situation may be due to the relatively small number of patients in the groups and the minimal amount of bleeding seen in the groups. If the number of patients in the groups had been greater, a clearer decrease in blood loss may have been seen.

As cerebral, mesenteric, pulmonary and retinal thromboses have been reported, the hypercoagulability of tranexamic acid and epsilon-aminocaproic acid arouses concerns.[26] We did not observe any decrease in oxygen saturation during surgery for any of the groups. We also did not find any clinical findings that would make one suspect thrombosis in any of our patients.

There was a clear decrease in blood loss with the pre incisional use of tranexamic acid in gynecological cancer surgery in our study compared to acute normovolemic hemodilution method and epsilon-aminocaproic acid. This situation that tranexamic acid decreases bleeding in gynecological cancer surgery supports the fact that it is more potent than epsilon-aminocaproic acid. No clinical finding of thromboembolism occurred in our study for either medication.

As a result, considering the negative effects of blood transfusions, we recommend that tranexamic

acid can be used in gynecological cancer surgery to decrease the need for transfusion.

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