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Autologous transfusion in radical prostatectomy: Assessment of coagulability by rotational thromboelastometry

Nozomi Yashima*, Tomofumi Watanabe*, Misato Kurota*, Airi Kumasaka*
Futaba Kurihara, Kei Otaki*, Shinya Oda***, Kaneyuki Kawamae***

**Department of Anesthesiology Yamagata University faculty of Medicine*
***Kahoku Hospital*
****Sanyudo Hospital*
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Abstract

Background: Radical prostatectomy can lead to severe bleeding. Therefore, patients undergoing this procedure often donate autologous whole blood prior to surgery. In this study, we aimed to evaluate the clinical efficacy of transfusing preserved autologous whole blood on coagulation activity as assessed by rotational thromboelastometry (ROTEM®).

Methods: This study included patients who underwent radical prostatectomy and donated 1200 mL of whole blood prior to surgery. Blood samples for ROTEM analyses were drawn at four points; after induction, prior to transfusion of autologous whole blood, at the end of surgery and the morning after surgery. Clotting time (CT), clot formation time (CFT) and maximal clot firmness (MCF) were measured using EXTEM tests; MCF was measured using FIBTEM tests.

Results: The average blood loss in 11 patients was 1635 ± 954 g. In EXTEM, CFT was significantly prolonged and MCF was significantly reduced prior to transfusion. These parameters were significantly improved by the next morning. In FIBTEM, there were no significant differences among samples obtained after induction, prior to transfusion and at the end of surgery. In contrast, MCF was significantly improved the morning after surgery.

Conclusion: ROTEM parameters were impaired during the procedure. Transfusion of autologous whole blood did not alter these parameters during the intraoperative period.

Key words : Autologous blood transfusion, Radical prostatectomy, coagulopathy, rotational thromboelastometry

Background

In massive hemorrhage, coagulation dysfunction can occur because of consumption of the coagulation factors due to the bleeding and hemodilution of blood components by a large quantity of infusion.[1), 2)] Radical prostatectomy can lead to severe bleeding, and therefore patients undergoing this procedure often donate autologous whole blood prior to surgery. The main effect of preoperative autologous blood donation (PABD) is increasing red blood cells (RBC) to maintain circulating oxygen-carrying capacity. In fact, PABD has been evaluated as reducing the need for homologous blood transfusion.[3)–7)] Another benefit is including the components of coagulation system. Minatoguchi et al. have investigated coagulation factors in whole blood stored at 4°C for five weeks.[8)] In this study, especially fibrinogen was maintained above the critical level through the stored period. However, there have been few studies of effects on patients' coagulability of PABD.

Recently, rotational thromboelastometry (ROTEM®) has been used as a point-of-care device to monitor coagulation activity in situations, which leads to severe bleeding such as cardiac surgery[9], liver transplantation[10] and trauma[11]. Conventional coagulation tests including platelet counts, fibrinogen concentration, prothrombin time (PT), and activated partial thromboplastin time (aPTT) have some problems. These tests needed a long turn-around time, because the sample was transferred to the laboratory and centrifuged to separate plasma from whole blood. Furthermore, these results were indicated a part of coagulability due to using only the plasma. In contrast, ROTEM can be performed using the whole blood sample at the operation room, therefore, the judgement whether coagulation dysfunction occurs is earlier. Furthermore, these results were visually displayed the graphic date in real-time and represented various parts of hemostasis. Thereby early checkup and appropriate treatment are enabled in the operating room.

In this study, we aimed to evaluate the coagulopathy caused by severe bleeding during surgery assessed by ROTEM®, further, to evaluate the clinical efficacy of transfusing preserved autologous whole blood during surgery on coagulation activity assessed by ROTEM®.

Materials and Methods

This study included patients who underwent elective radical prostatectomy at Yamagata university hospital between September 2012 and January 2014. All patients donated 1200 ml of whole blood within four weeks prior to surgery. Whole blood was collected into a 400-ml blood collection bag containing citrate phosphate dextrose adenine-1 (CPDA-1) liquid as anticoagulant and this procedure was performed three times until surgery. We excluded patients who had already had coagulopathy defined as at least one of follows; PT-INR was more than 1.20, aPTT was more than 35 seconds, or platelet count was less than $10\times10^4/mm^3$. We also excluded patients who had preoperatively dosed anticoagulants.

All patients had general anesthesia and epidural analgesia. Before induction, each patient was inserted epidural catheter first at the level of thoracic or lumber vertebra. Anesthesia protocol was not strictly defined, each anesthesiologist decided to conduct how to manage the general anesthesia by him/herself. Anesthesia was induced with thiopental or propofol and maintained with sevoflurane or propofol and remi-fentanyl. Rocuronium was administrated before intubation and used for muscle relaxation as appropriate. End-tracheal intubation was performed as an airway management.

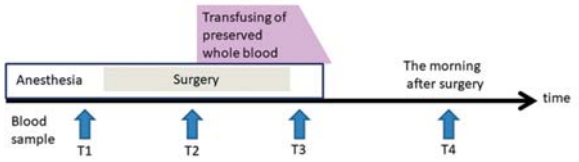

Figure 1. The timing of blood sample for ROTEM® analyses. Blood samples were drawn at four points; after induction as a baseline (T1), prior to transfusion of autologous whole blood (T2), at the end of surgery (T3) and the morning after surgery (T4).

Blood loss during surgery was calculated by the weight change of the absorbent gauzes and by the volume change in the suction reservoirs, although the latter was included urine after urethrectomy.

Blood samples for ROTEM® analyses were collected through arterial cannula into citrated plastic tubes, at a volume ratio of 1:10. Blood samples were drawn at four points; after induction as a baseline (T1), prior to transfusion of autologous whole blood (T2), at the end of surgery (T3) and the morning after surgery (T4) (Figure 1). These were immediately or at least within 2 hours analyzed using ROTEM® delta (Amco Inc, Tokyo, Japan) as follows. The following ROTEM parameters were recorded: clotting time (CT, s), clot formation time (CFT, s) and maximal clot firmness (MCF, mm) using EXTEM test, and MCF using FIBTEM tests at each point in detail in Figure 2, 3.[2), 12)] CT is defined time from start of measurement until initiation of clotting and means initial thrombin and fibrin formation. CFT is defined time from initiation of clotting until a clot firmness of 20 mm and means propagation of clot formation. MCF is the maximum amplitude and means the final clot firmness. The EXTEM test is performed by additional of rabbit brain tissue factor as extrinsic activator and

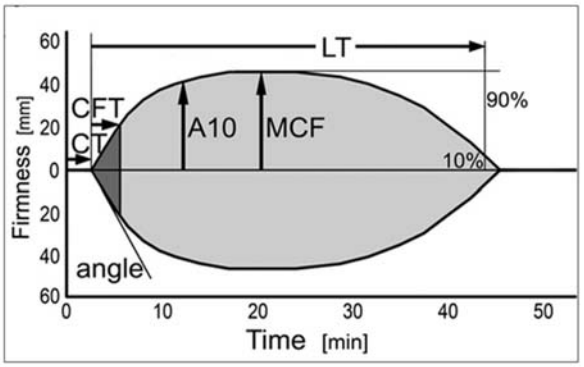

Figure 2. ROTEM parameters. Clotting time (CT) is defined time from start of measurement until initiation of clotting. Clot firmness time (CFT) is defined time from initiation of clotting until a clot firmness of 20 mm. Maximum clot firmness (MCF) is the maximum amplitude. (Daniel B, Klaus G, Kenichi A. T: Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology, 2010; 113: 1205-19)

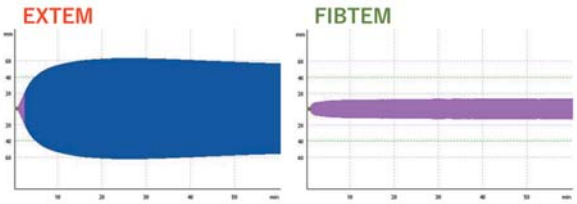

Figure 3. Representative profiles of EXTEM and FIBTEM measured at Yamagata University Hospital.

$CaCl_2$. Therefore, CT and CFT on EXTEM represent extrinsic activators (normal value; CT 42-74 s, CFT 46-148 mm) and MCF on EXTEM represents the complex activity between fibrinogen and platelet (normal value; MCF on EXTEM 49-71 mm). On the other hand, the FIBTEM test is performed by additional of $CaCl_2$ and cytochalasin D as a potent platelet inhibitor, therefore MCF on FIBTEM represents qualitative assessment of fibrinogen levels (normal value; MCF on FIBTEM 9-25 mm).[13)]

Results are expressed as median and observed range or mean ± SD. The general linear model was used to test changes between variables. A two-tailed p value less than 0.05 was taken as a significant difference. Data analysis was performed using SPSS version 19.0.

We received approval by the local ethics committee and written informed consent from each participant.

Table 1. Patients' demographic characteristics

Patients' demographic characteristics	n = 11
Age (yrs)	67 (47 - 74)
BMI (kg/m^2)	23.3 (21.1 – 29.7)
ASA class	1 - 2
Hemoglobin (g/dl)	13.0 ± 0.95
Hematocrit (%)	39.3 ± 3.43
Platelet ($1000/mm^3$)	228.6 ± 83.2
PT (%)	106.4 ± 11.2
PT-INR	0.95 ± 0.06
aPTT (sec)	30.0 ± 1.94
	median (min-max) mean ± SD

Table 2. Patients' perioperative characteristics

Patients' perioperative characteristics		n = 11
Operation time (min)		236 (168 – 537)
Anesthesia time (min)		314 (244 – 606)
Estimated blood loss (g)		1635 ± 954
Intraoperative fluids (ml)		3741 ± 1152
Transfusion (g) (intraoperative) (g) (postoperative) (g)		1018 ± 209 727 ± 237 290 ± 202
Hemoglobin perioperative (g/dl)	T1	12.0 ± 0.97
	T2	9.7 ± 1.0
	T3	10.1 ± 0.97
	T4	11.2 ± 0.98
		median (min-max) mean ± SD

Results

Twelve patients were enrolled in this study. One did not transfuse autologous blood because of little bleeding, therefore he was excluded, leaving eleven patients for analysis in this study. Tables 1 and 2 shows patients' demographic and perioperative characteristics: the median age and body mass index (BMI) were 67.0 years and 23.3 kg m^{-2}, respectively. The average blood loss was 1635 g. After induction, CT, CFT and MCF on EXTEM were 57.1 seconds, 90.8 seconds and 61.2 mm, respectively, MCF in FIBTEM was 10.7 mm. In EXTEM, CT was slightly but significantly different between baseline and prior to transfusion (Figure 4). However, values were not significantly different among the other points. CFT was significantly prolonged and MCF was significantly reduced prior to transfusion compared with baseline (Figure 5, 6). However, these impairments were not below the normal levels. Although these parameters were not significantly different at the end of surgery compared with prior to transfusion of

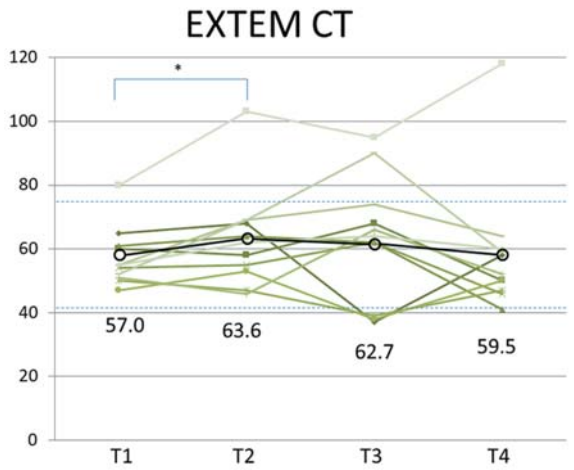

Figure 4. CT on EXTEM (* p<.05). The black line represents mean. The dotted lines represent the upper and lower normal limit.

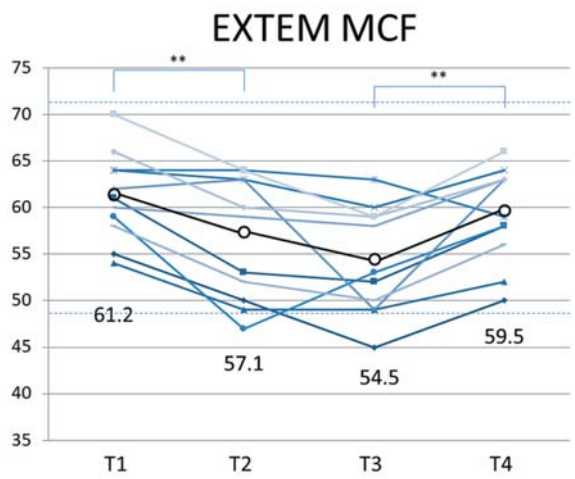

Figure 6. MCT on EXTEM (**p<.01). The black line represents mean. The dotted lines represent the upper and lower normal limit.

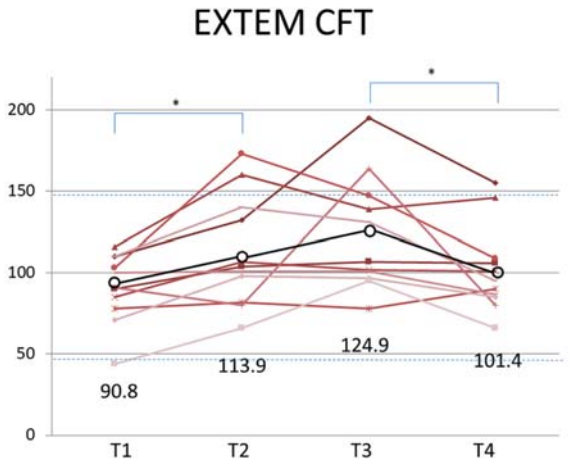

Figure 5. CFT on EXTEM (*p<.05). The black line represents mean. The dotted lines represent the upper and lower normal limit.

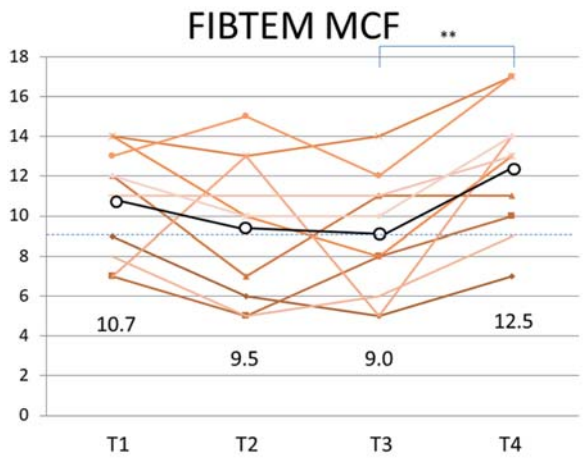

Figure 7. MCF on FIBTEM (**p<.01). The black line represents mean. The dotted line represents the lower normal limit.

autologous whole blood, CFT and MCF were significantly improved by the next morning. In FIBTEM, there were no significant differences among samples obtained baseline, prior to transfusion of autologous whole blood and at the end of surgery. In contrast, MCF was significantly improved the morning after surgery compared with the end of the surgery (Figure 7). None of the patients needed transfusion of homologous blood products.

Discussions

In this study, we showed that ROTEM parameters in patients undergoing radical prostatectomy were impaired by bleeding during the procedure. Transfusion of autologous whole blood did not improve these parameters by bleeding during the intraoperative period. These parameters, except CT on EXTEM, improved the next morning after surgery.

When bleeding occurred during surgery, the initial treatment is usually volume replacement with

crystalloids or colloids to maintain systemic circulation. In addition, allogeneic red cell concentrates are often transfusing to increase hemoglobin. However, these treatments consequently contribute to hemodilution, which can lead to coagulopathy.[12] Hiippala et al. showed that the critical level of hemostatic factors (platelets, fibrinogen, prothrombin, coagulation factors) was observed after more than 150% blood loss of calculated blood volume, and that fibrinogen was the first factor that reaches low level.[14] In a porcine model, approximately 65% of estimated blood loss volume and replacement with the same amount of gelatin solution made both of fibrinogen concentrations and platelet count reduce, but only fibrinogen concentration reached critical level.[15] These results represent that fibrinogen concentrations are the key factor for dilutional coagulopathy.

Although conventional coagulation tests are common screening tests for coagulation dysfunction, they are not always useful for perioperative coagulopathy. They require a long turn-around time because the sample was transferred to the laboratory and centrifuged to separate plasma from whole blood. Furthermore, both tests do not provide any information on *in vivo* interaction of platelets with coagulation factors due to using only plasma.[16] In this regard, ROTEM® can synergistically assess differential parts of hemostasis such as the initiation of clot formation, the propagation, the stiffness of clot, and the fibrinolysis because the whole blood sample from patient is investigated. It is beneficial for earlier recognition of a coagulopathy, because it can be performed at the bedside by using whole blood sample. Further, these results were visually displayed the graphic date in real-time and represented various parts of hemostasis. Thereby early checkup and appropriate treatment are enabled during surgery. The ROTEM parameters and the definition were express in Figure 1. CT is the onset of clotting and means the initiation of coagulation. CFT is the initial rate of fibrin polymerization and means the propagation of coagulation (the interaction between fibrin and platelets). Alpha-angle is same as CFT. The maximum amplitude of waveform represents MCF, which means the clot strength.[12] The EXTEM assay is performed by addition of tissue factor, and represents coagulation through the contact of extrinsic pathway. The FIBTEM assay is performed by addition of tissue factor and cytochalasin D, that is a platelet antagonist, and represents the effect of fibrin(ogen) on coagulation.[2] Ogawa et al. have investigated the correlations between ROTEM parameters and conventional coagulation tests. There were significant correlations between PT and CT on EXTEM ($r=0.55$; $p<0.001$) and between PT and CFT on EXTEM ($r=0.53$; $p<0.001$). MCF on EXTEM correlated with both fibrinogen levels and platelet counts ($r=0.69$ and $r=0.69$, respectively; $p<0.001$). Excellent correlation was observed between MCF on FIBTEM and fibrinogen levels ($r=0.85$; $p<0.001$).[17]

In our study, the average blood loss was 1635 g, which seemed to be not great amount of blood loss, in fact, our results were normal level. Especially, MCF on FIBTEM which represents fibrinogen concentrations was 9.5mm prior to transfusion. There is a correlation between fibrinogen concentrations and MCF in FIBTEM, and the critical level of fibrinogen concentrations is generally 2.0 g L^{-1}, and that of MCF on FIBTEM is 8 mm.[18] MCF on FIBTEM was 9.5 mm in our study, which represents the dilutional coagulopathy caused by bleeding in our procedure did not reach the critical level.

A radical prostatectomy is one of operations that may result in massive hemorrhage. The bleeding more than the circulation blood volume occurred few frequently in all operation, and 2.8% were prostatectomy.[19] Therefore, patients undergoing this procedure often prepared PABD as an aim of increasing RBC to maintain circulating oxygen-carrying capacity. The potential benefits of PABD are not only the increment of RBC but also including the components of coagulation system. As mentioned above, Minatoguchi et al. have investigated coagulation factors in whole blood stored at 4°C for five weeks.[8] In this study, fibrinogen and factor Ⅶ were maintained above the critical level through the stored period although factor Ⅴ, Ⅷ, and von Willebrand factor significantly decreased. On the other hand, factor Ⅹ Ⅲ slightly but significantly increased after the storage. In our study, the preservation period of blood was the range from one to four weeks. Although the preserved whole blood included fibrinogen in

theory, MCF on FIBTEM have not changed after transfusion. In conclusion, our study suggests the transfusion of the preserved autologous whole blood during surgery has a small effect on coagulation activity *in vivo*.

When compared with parameters intraoperative period, all parameters after surgery improved. The improvement in the postoperative period may indicate homeostatic reactions after surgery. ROTEM® can capture the reaction correctly.

Our study has some limitations. First, sample size was small. Radical prostatectomy has recently been reduced because robotic-assisted laparoscopic radical prostatectomy (RALP) was brought in our hospital from August September 2012, after that RALP rapidly became mainstream. Because RALP hardly bled and did not prepare autologous transfusion, patients undergoing this procedure excluded from this study. Second, we did not have a protocol about the timing of transfusion. Third, hydroxyethyl starch has been found to affect ROTEM parameters.[20] However, it was not influenced to the coagulopathy because the amount of it was equal to 1000ml or less. Finally, platelet count was not investigated in our study. The platelet activity plays the important role in hemostasis. Interestingly, platelet count reached the critical level (which was $50\times10^3/mm^3$) at 230% blood loss of calculated blood volume. In our study, we supposed the platelet count was maintained during surgery because MCF on EXTEM was not below normal level. In addition, there were not platelets in preserved whole blood at all because of low temperature preservation and anaerobic metabolism. Therefore, we did not investigate the effect of platelet activity in this study.

Conclusion

In conclusion, ROTEM parameters in patients undergoing radical prostatectomy were impaired by bleeding during the procedure. Transfusion of autologous whole blood did not alter these parameters during the intraoperative period.

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References

1. Bolliger D, Szlam F, Levy JH, Molinaro RJ, Tanaka KA: Haemodilution-induced profibrinolytic state is mitigated by fresh-frozen plasma: implications for early haemostatic intervention in massive haemorrhage. Br J Anaesth 2010; 104(3): 318-325
2. Larsen OH, Fenger-Eriksen C, Christiansen K, Ingerslev J, Sorensen B: Diagnostic performance and therapeutic consequence of thromboelastometry activated by kaolin versus a panel of specific reagents. Anesthesiology 2011; 115(2): 294-302
3. Oh AY, Seo KS, Lee GE, Kim HJ: Effect of preoperative autologous blood donation on patients undergoing bimaxillary orthognathic surgery: a retrospective analysis. International journal of oral and maxillofacial surgery 2016; 45(4): 486-489
4. Dzik WH, Fleisher AG, Ciavarella D, Karison KJ, Reed GE, Berger RL: Safety and efficacy of autologous blood donation before elective aortic valve operation. The Annals of thoracic surgery 1992; 54(6): 1177-1180
5. Martin K, Keller E, Gertler R, Tassani P, Wiesner G: Efficiency and safety of preoperative autologous blood donation in cardiac surgery: a matched-pair analysis in 432 patients. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2010; 37(6): 1396-1401
6. Lewis CE, Hiratzka LF, Woods SE, Hendy MP, Engel AM: Autologous blood transfusion in elective cardiac valve operations. Journal of cardiac surgery 2005; 20(6): 513-518
7. Bouchard D, Marcheix B, Al-Shamary S, Vanden Eynden F, Demers P, Robitaille D, et al: Preoperative autologous blood donation reduces the need for allogeneic blood products: a prospective randomized study. Canadian journal of surgery Journal canadien de chirurgie 2008; 51(6): 422-427
8. Minatoguchi M, Itakura A, Miki A, Kajihara T, Sasaki S, Takase Y, et al: Coagulation factors in whole blood collected from pregnant women and stored at 4 degrees C. Nagoya journal of medical science 2016; 78(1): 1-7
9. Weber DmChristian F, Görlinger DmK, Meininger

PDDmD, Herrmann PDrnE, Bingold DmT, Moritz PDmA, et al: Point-of-Care TestingA Prospective, Randomized Clinical Trial of Efficacy in Coagulopathic Cardiac Surgery Patients. Anesthesiology 2012; 117(3): 531-547

10. Trzebicki J, Flakiewicz E, Kosieradzki M, Blaszczyk B, Kolacz M, Jureczko L, et al: The use of thromboelastometry in the assessment of hemostasis during orthotopic liver transplantation reduces the demand for blood products. Annals of transplantation 2010; 15(3): 19-24
11. Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK: Effect of thromboelastography (TEG(R)) and rotational thromboelastometry (ROTEM(R)) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Critical care (London, England) 2014; 18(5): 518
12. Bolliger D, Gorlinger K, Tanaka KA: Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology 2010; 113(5): 1205-1219
13. Ganter MT, Hofer CK: Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesthesia and analgesia 2008; 106(5): 1366-1375
14. Hiippala ST, Myllyla GJ, Vahtera EM: Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesthesia and analgesia 1995; 81(2): 360-365
15. Fries D, Krismer A, Klingler A, Streif W, Klima G, Wenzel V, et al: Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model. Br J Anaesth 2005; 95(2): 172-177
16. Tanaka KA, Key NS, Levy JH: Blood coagulation: hemostasis and thrombin regulation. Anesthesia and analgesia 2009; 108(5): 1433-1446
17. Ogawa S, Szlam F, Chen EP, Nishimura T, Kim H, Roback JD, et al: A comparative evaluation of rotation thromboelastometry and standard coagulation tests in hemodilution-induced coagulation changes after cardiac surgery. Transfusion 2012; 52(1): 14-22
18. Ogawa S, Szlam F, Bolliger D, Nishimura T, Chen EP, Tanaka KA: The impact of hematocrit on fibrin clot formation assessed by rotational thromboelastometry. Anesthesia and analgesia 2012; 115(1): 16-21
19. Irita K, Inada E, Yoshimura H, Warabi K, Tsuzaki K, Inaba S, et al: Present status of preparatory measures for massive hemorrhage and emergency blood transfusion in regional hospitals with an accredited department of anesthesiology in 2006. Masui The Japanese journal of anesthesiology 2009; 58(1): 109-123
20. Weiss G, Lison S, Spannagl M, Heindl B: Expressiveness of global coagulation parameters in dilutional coagulopathy. Br J Anaesth 2010; 105(4): 429-436