Journal of
Cardio - Thoracic Medicine

http://jctm.mums.ac.ir

Effectiveness of Moderate Acute Normovolemic Hemodilution Combined with Tranexamic Acid on the Reduction of Allogenic Blood Transfusion in Patients Undergoing Off-pump Coronary Artery Bypass

Reza Jalaeian Taghaddomi[1], Masoomeh Tabari[1]*, Alireza Sharifian Attar[1], Ali Azari[2], Kambiz Alizadeh[2], Hengameh Rezaei Broujerdi[1]

[1] *Anesthesiologist, Department of Anesthesiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

[2] *Cardiac Surgeon, Department of Cardiac Surgery, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLEINFO

Article type:
Original Article

Article history:
Received: 27 Jul 2016
Revised: 20 Sep 2017
Accepted: 9 Oct 2017

Keywords:
Acute Normovolemic Hemodilution
Off-pump Coronary Artery Bypass
Tranexamic Acid

ABSTRACT

Introduction: There are different approaches to reduce the amount of blood loss and allogenic transfusion in cardiac surgery. Regarding this, the present study aimed to evaluate the blood sparing effect of acute normovolemic hemidilution (ANH) combined with intraoperative tranexamic acid in patients undergoing off-pump coronary artery bypass (OPCAB).
Material and Methods: This study was conducted on 80 consecutive patients scheduled for elective OPCAB. The patients were randomly subjected to tranexamic acid treatment (TA group) or to tranexamic acid plus ANH (ANH group). All data, including demographic information, allogenic transfusions (based on a prior defined criteria), amount of postoperative bleeding, and major complications, were recorded.
Results: According to the results, the two groups were comparable in terms of the demographic data and intraoperative variables. The mean values of postoperative bleeding were 483±125 and 580±201 mL in the TA and ANH groups, respectively, indicating no significant difference between them in this regard. Total transfused packed red blood cells (PRBC) used in the TA and ANH groups were 15 and 20 units, respectively, which revealed no significant difference between the two groups in this respect (P=0.23). Furthermore, 12 and 10 patients in the TA and ANH groups were transfused with PRBC, respectively. Moreover, the two groups showed no significant difference in terms of the postoperative hematological variables (P>0.05).
Conclusion: As the findings of the present study indicated, ANH was not effective in reducing postoperative bleeding and the need for allogenic blood products in the patients undergoing OPCAB.

► *Please cite this paper as:*
Jalaeian Taghaddomi R, Tabari M, Sharifian Attar A, Azari A, Alizadeh K, Rezaei Boroujerdi H. Effectiveness of Moderate Acute Normovolemic Hemodilution Combined with Tranexamic Acid on the Reduction of Allogenic Blood Transfusion in Patients Undergoing Off-pump Coronary Artery Bypass. J Cardiothorac Med. 2017; 5(4): 226-231.

Introduction

Blood products are a scarce resource, which can expose the patients to the risk of blood-borne diseases as well as graft-versus-host and acute hemolytic reactions, all of which increase patient morbidity or mortality (1). Bleeding and hemorrhagic complications and the consequent need for allogenic transfusions are still major problems occurring after cardiac surgery. There

**Corresponding author:* Masoomeh Tabari, Department of Anesthesiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985138417402; Email: tabarim@mums.ac.ir

are different strategies, including pharmacologic approaches and autologous blood transfusions, to reduce preoperative bleeding and allogenic blood transfusions (2).

The beneficial effects of tranexamic acid as an antifibrinolytic have been demonstrated during the cardiac surgery in a large number of controlled trials (1-15). The application of this agent is associated with less blood loss as well as requirement and shown to be effective both in on-pump and off-pump cardiac surgeries. Acute normovolemic hemodilution (ANH) is another blood conservation technique that was introduced into surgical practice in the 1970s to reduce the requirements for blood transfusion. The fundamental principle of ANH is the creation and tolerance of intraoperative anemia.

The preoperative dilution of circulating blood volume reduces the amount of red blood cells and plasma constituents that are lost during surgical bleeding (16). Based on the report of the American Society of Anesthesiologists Task Force on blood component therapy, ANH has been suggested as an inexpensive and effective means of reducing allogenic blood exposure (17). However, the efficacy of this technique is uncertain yet. According to the results of two meta-analyses conducted by Bryson et al. (18) and Segal et al. (19) on the role of ANH in reducing the perioperative allogenic transfusion, the systemic review and statistical summary of published trials of ANH were inconclusive.

Since the reduction of blood loss and perioperative transfusion are among the important priorities in a cardiac surgery, we decided to combine two different approaches to determine whether their combination is more beneficial or not. With this background in mind, the present study was designed to evaluate the effect of the combination of ANH and tranexamic acid on the reduction of blood loss and transfusion in the patients undergoing off-pump coronary artery bypass (OPCAB) graft surgery.

Materials and Methods

The present study was conducted on Eighty consecutive patients scheduled for OPCAB from January 2013 to August 2014. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran. Informed written consent was obtained from all the patients. The exclusion criteria were: 1) history of hematological disorders, 2) hemoglobin of < 12 g/dL, 3) advanced chronic renal insufficiency (i.e., serum creatinine of > 2 mg/dL), 4) active chronic hepatitis or cirrhosis, 4) left main coronary artery stenosis, 5) left ventricular ejection fraction of < 30%, 6) previous cardiac surgery, 7) myocardial infarction of < 30 days, and 8) withdrawal of clopidogrel or aspirin less than 5 days before surgery.

A total of four patients were excluded from the study due to conversion to on-pump surgery (two case) and the need for post-operative re-exploration for hemorrhage with an evident surgical source of bleeding. By using a computer-generated random number sequence, the patients were prospectively assigned into ANH and tranexamic acid (TA) groups, entailing 39 and 37 cases, respectively. The TA group was considered as the control group and no ANH was performed. All patients received intravenous bolus dose of 1 g of tranexamic acid 20 min before skin incision, followed by a continuous infusion of 400 mg/h until the end of the surgery. In the ANH group, 18±2% of the circulating blood volume was removed, as calculated using the body-surface area on the nomogram.

After the induction of anesthesia and before the administration of tranexamic acid, blood was drawn by gravity through a large-bore catheter placed into the internal jugular vein and collected into sterile bags containing CPDA (Citrate Phosphate Dextrose Adenine). The amount of removed blood was simultaneously replaced with an equivalent amount of hydroxyethyl starch (130/0.4). Each unit of blood was labeled with the patient's name and order of collection and kept in the operating room. Reinfusion of the collected blood was started at the end of the surgery after protamine administration.

Anesthetic and surgical procedure

All patients received premedication with intramuscular morphine at 0.1 mg/kg and oral diazepam at 0.15 mg/kg. The anesthetic technique was standardized to include fentanyl (20-30 μg/kg), propofol (50-80 μg/kg/min), midazolam (0.1 mg/kg), and pancrunium bromide. In both groups, lactated Ringer's solution (500 ml) was used for volume expansion, followed by 5 ml/kg for basic needs, and 7 ml/kg for third space loss. Replacement for intraoperative blood loss was three times the amount of bleeding. All patients were operated on through a full median sternotomy.

The left internal mammary artery (LIMA) was routinely harvested. Additionally, a tract of the great saphenous vein was harvested when required. A U-shaped stabilizer was used to dampen the movement of the beating heart. The verticalization of the heart was achieved by using a posterior pericardial suture. The initial dose of intravenous heparin (150 IU/kg) was administered after harvesting the LIMA within the target activated clotting time over 250 sec.

After the end of revascularization, the effect of heparin was neutralized by protamine with the ratio of 1:1. The threshold for the transfusion of allogenic red blood cells was hemoglobin (Hb) of < 9 g/dL and hematocrit (Hct) value of < 27%. Fresh frozen plasma transfusion was performed in case the prothrombine time (PT) was 1.5 times longer than the baseline with diffuse bleeding. The protocol for platelets transfusion was the presence of diffuse bleeding and a platelet count of < 50,000 per mm (3).

Patients' characteristics and intraoperative variables, including number of grafts, amount of bleeding, and infused blood, were recorded in a checklist by an independent research fellow. Intraoperative blood loss was determined by measuring the weight change of moistened surgical gauzes and observing the fluid level of suction reservoirs. During the surgery, Hct and Hb were monitored in the samples drawn for blood gas determination. Hematologic parameters (i.e., Hb, Hct, Platelet count, PT, partial thromboplastin time, and international normalized ratio), amount of chest tube drainage, and volume of infused blood products were recorded 6 and 24 h postoperatively. In addition, major complications, such as myocardial infarction (new Q waves on electrocardiogram, CK-MB of > 10% and troponin I of > 0.1 mg/L), acute renal failure (creatinine twice the baseline value or the need for dialysis), venous thrombosis, as well as minor and major neurological complications were registered.

Demography, clinical and paraclinical data was collected and analyzed using SPSS software. Descriptive statistical methods included center tendency, dispersion and frequency distribution analysis. Inductive statistics were applied, comprising of t-test and chi square test to compare categorical data and t-test to compare quantitative data of the two groups in case of Normal distribution, and non-parametric Mann-Whitney test in case of non-Normal distributions. Paired t-test was employed to compare variables before and after intervention in a group (in case of a Normal distribution), and non-parametric Wilcoxon signed-rank test (in case of non-Normal distribution). P value < 0.05 was considered statistically significant.

Results

Out of the 80 patients enrolled in this study, one patient in each group was excluded due to conversion to on-pump surgery during the course of the operation. In addition, in the TA group, two more patients were withdrawn owing to excessive bleeding and the need for postoperative re-exploration. The two groups showed no significant difference in terms of the demographic data, baseline preoperative variables, and surgical characteristics (Table 1).

Intraoperative data are illustrated in Table 2. There were no significant differences between the two groups regarding the number of anastomoses, surgical time, and intraoperative Hct. The mean values of intraoperative blood loss in the TA and ANH groups were 379±151 and 454±145 mL, respectively, indicating no significant difference between the two groups in this regard (P=0.45).

Postoperative bleeding and required allogenic transfusion were similar in the two groups (P=0.1) There was no significant difference in blood loss 6 and 24 h postoperatively in both groups (p-value=0.12). Although the total amount of postoperative bleeding (580±210 mL) was higher in the ANH group than that in the control group, the difference between the two groups was

Table 1. Demographic data and baseline preoperative variables of the study groups

Variable	Control group (n=37)	ANH group (n=34)	P-value
Age (year)	60.5 ±7.8	60.1±10.6	0.55
Gender (M/F)	28/9	28/11	0.91
Weight (kg)	67.8±10.6	67.5±9.2	0.93
Height (cm)	162.2±7.6	160.9±5.3	0.41
Baseline LVEF (%)	50.9±7.8	49.8±8.5	0.63
Hypertension (%)	64	66	0.85
Hemoglobin(gr/d)	13.4±1.4	13.5±0.97	0.7
Platelet count ($10^3/mm^3$)	219.5±67.5	221.3±58.5	0.92
Prothrombin time	13.2±1.1	13.1±1	0.96
PTT	30.5±3	30.9±3.7	0.74
INR	0.98±0.1	1±0.02	0.42
Creatinine (mg/dl)	1.13(1-1.2)	1.10(1-1.28)	0.81

LVEF: left ventricular ejection fraction, PTT: partial thromboplastin time, INR: international normalized ratio (t-test and chi square test)

Table 2. Intraoperative loss and ACT and surgical time between two group blood

Variable	Control group (Mean+SD) (n=37)	ANH group (Mean+SD) (n=39)	P value
Surgical time(h)	2.23±0.4	2.25±6.6	0.9
ACT during surgery (s)	305±19	300±24	0.52
ACT at the end of surgery(S)	154±12	160±16	0.79
The amount of bleeding (ml)	397±151	454±145	0.45

ACT: activated clotting time (t-test)

Table 3. Postoperative bleeding and perioperative allogenic transfusion

Variable	Control group (n=37)	ANH group (n=39)	P value
Bleeding 0-6h postoperative(means+_SD)	152±54	171±62	0.4
Bleeding 6-24h postoperative	422±110	501±174	0.12
Total postoperative bleeding (ml)	483±125	580±201	0.1
Number of patients transfused with PRBC postoperatively	12(32)	10(25.5)	0.46
PRBC in OR (units/ patients transfused)	3.3	1.1	0.35
Total PRBC (units)	20	15	0.23
FFP in OR (units/patients transfused)	0/0	0/0	1
Number of patients transfused with FFP Postoperatively	2	4	0.5
Total FFP (units)	6	13	0.46

PRBC: packed red blood cells, OR: operating room, FFP: fresh frozen plasma (t-test and chi square test)

Table 4. Postoperative hematological data in the study groups

Variable	Control group Mean+SD (n=37)	ANH group Mean+SD (n=39)	P-value
Hemoglobin (g/dL)	11.3±1.4	11.1±1	0.71
Hematocrit (%)	34.1±3.9	33.7±3.5	0.67
Platelet count (10^3/mm^3)	218.2±15	167.3±55.4	0.13
PT (sec)	14.3±1.1	14.6±1.4	0.4
PTT (sec)	32.2±4.3	40.2±3	0.2
INR	0.92±0.1	1±0.04	0.32
Creatinine (mg/dL)	1.04±0.26	1±0.23	0.48

PT: thromboplastin time, PTT: partial thromboplastin time, INR: international normalized ratio (t-test used to compare two groups)

not statistically significant in this regard (P=0.1).

Furthermore, there was no significant difference between the study groups regarding the amount of transfused PRBC units, number of patients received allogenic blood, and fresh frozen plasma transfused postoperatively. As indicated in Table 3, no platelet was transfused. Table 4 presents the postoperative hematological data, indicating that the two groups were identical in this respect. Additionally, there were no hospital mortality, myocardial infarction, stroke, renal failure requiring dialysis, and pulmonary embolism in both groups.

Discussion

Decreased use of allogenic blood product, especially PRBC, has been reported during the OPCAB surgery. The activation of fibrinolysis and platelet consumption are less frequent in OPCAB than those in cardiopulmonary bypass. Nevertheless, net consumption of antithrombin and fibrinogen as well as blood loss occur to a similar degree in the two types of surgery (18). Therefore, excessive bleeding requiring transfusion remains a major concern. For this reason, in the recent years, antifibrinolytic agents have gained widespread interest. Tranexamic acid has been studied in different cardiac surgeries. Its beneficial effects to minimize bleeding and reducing exposure to blood products have been determined in OPCAB surgeries (1, 2, 7-13, 21-23).

In addition, ANH is a technique that has been suggested as an inexpensive and effective means of reducing allogenic blood exposure. In our study, we assumed that the combination of ANH and tranexamic acid would further reduce the need for allogenic blood transfusion in comparison to the sole use of tranexamic acid. However, the efficacy of ANH is still controversial.

In a meta-analysis carried out by Bryson et al. (18), 24 trials (containing a total of 1,218 patients) were included. When all trials were pooled, ANH reduced the likelihood of exposure to allogenic blood transfusion as well as the total units of allogenic blood transfused. However, there was a marked heterogeneity in the results. In the mentioned trials, based on a protocol used to guide preoperative transfusion, ANH failed to reduce either the likelihood of transfusion or the administered units. In another meta-analysis, Segal et al. (19) reported that the efficacy of ANH was likely to be low.

It appears that ANH can modestly reduce bleeding and volume of allogenic blood requirements; nonetheless, the efficiency of this technique with regard to the avoidance of allogenic transfusion has not been demonstrated yet. In the present study, we did not find any beneficial effects regarding the combined use of ANH with tranexamic acid, which is in accordance with the findings of the aforementioned meta-analysis. Virmani et al. (16) also investigated the effect of ANH on primary elective valve surgery. They did not find any added advantages of low volume ANH as a sole method of reducing allogenic blood requirements in primary elective surgery.

In a study similar to our research, Casati et al. (20) investigated the effect of intraoperative moderate ANH associated with a comprehensive blood sparing protocol during OPCAB surgery. In addition to tranexamic acid, they reinfused the shed blood in excess of 250 ml, while we did not use intraoperative blood salvage. In the mentioned study, 2 patients in the ANH group versus 10 patients in the control group required the transfusion of significantly smaller number of PRBC units. However, in our study, there was no significant difference between the two groups regarding the amount of PRBC requirements.

Due to the moderate degree of hemodilution and the attention paid to maintain normovolemia, no patient in our study experienced intraoperative myocardial ischemia. Accordingly, the outcomes and postoperative complications did not differ between the two groups. During the treatment with antifibrinolytics, such as tranexamic acid, there is a theoretic risk of increased thrombotic events affecting cardiovascular, cerebrovascular, and renal outcomes. In the present study, we did not notice any thrombotic complications.

In another meta-analysis, Adler Ma et al. (1) mentioned that although the results of the different trials did not demonstrated any side effects for the use of tranexamic acid in OPCAB surgery, limitations of their analysis prevented them from concluding with any certainty that the side effects did not exist. Consequently, as suggested by Adler Ma et al. (1), further appropriately powered studies are needed in the future to investigate the side effects associated with tranexamic acid.

Conclusion

As the findings of the present study revealed, moderate ANH combined with tranexamic acid administration did not have a beneficial effect on the reduction of bleeding and PRBC requirements in the patients undergoing OPCAB surgery. Consequently, further large studies are necessary since the efficiency of ANH is still controversial.

Acknowledgments

We want to acknowledge the Vice Chancellor of research, Mashhad university of medical sciences for the Financial and material support. We also thank Dr Khajehdaluiee for methodological and statistical consult. And last, we appreciate the great works of all the nurses and staffs of Ghaem hospital's open heart operation room for their close cooperation in this study.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Adler Ma SC, Brindle W, Burton G, Gallacher S, Hong FC, Manelius I, et al. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: A systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2011; 25:26-35.
2. Taghaddomi RJ, Mirzaee A, Attar AS, Shirdel A. Tranexamic acid reduces blood loss in off-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2009; 23:312-5.
3. Barrons RW, Jahr JS. A review of post-cardiopulmonary bypass bleeding, aminocaproic acid, tranexamic acid, and aprotinin. Am J Ther. 1996; 3:821-38.
4. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: Meta-analyses using perioperative blood transfusion as the outcome. The international study of perioperative transfusion (ISPOT) investigators. Anaesth Analg. 1997; 85:1258-67.
5. Wong Bl, McLean RF, Fremes SE, Deemar KA, Harrington EM, Christakis GT, et al. Aprotinin and tranexamic acid for high transfusion risk cardiac surgery. Ann Thorac Surg. 2000; 69:808-16.
6. Andreasen JJ, Nielsen C. Prophylactic tranexamic acid in elective, primary coronary bypass surgery using cardiopulmonary bypass. Eur J Cardiothorac Surg. 2004; 26:311-7.
7. Casati V, Gerli C, Franco A, Torri G, D'Angelo A, Benussi S, et al. Tranexamic acid in off-pump coronary surgery: a preliminary, randomized, double-blind placebo-controlled study. Ann Thorac Surg. 2001; 72:470-5.
8. Casati V, Della Valle PD, Benussi S, Franco A, Gerli C, Baili P, et al. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: comparison between on-pump and off-pump techniques. J Thorac Cardiovasc Surg. 2004; 128:83-91.
9. Jares M, Vanek T, Straka Z, Brucek P. Tranexamic acid reduces bleeding after off-pump coronary artery bypass grafting. J Cardiovasc Surg. 2003; 44:205-8.
10. Vanek T, Jares M, Fajt R, Straka Z, Jirasek K, Kolesar M, et al. Fibrinolytic inhibitors in off-pump coronary surgery: A prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo). Eur J Cardiothorac Surg. 2005; 28:563-8.
11. Murphy GJ, Mango E, Lucchetti V, Battaglia F, Catapano D, Rogers CA, et al. A randomized trial of tranexamic acid in combination with cell salvage plus a meta-analysis of randomized trials evaluating tranexamic acid in off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2006; 132:475-80.
12. Mehr-Aein A, Sadeghi M, Madani-civi M. Does tranexamic acid reduce blood loss in off-pump coronary artery bypass? Asian Cardiovasc Thorac Ann. 2007; 15:285-9.
13. Wei M, Jian K, Guo Z, Wang L, Jiang D, Zhang L, et al. Tranexamic acid reduces postoperative bleeding in off-pump coronary artery bypass grafting. Scand Cardiovasc J. 2006; 40:105-9.
14. Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. J Thorac Cardiovasc Surg. 2004; 128:442-8.
15. Englberger L, Markart P, Eckstein FS, Immer FF, Berdat PA, Carrel TP. Aprotinin reduces blood loss in off-pump coronary artery bypass (OPCAB) surgery. Eur J Cardiothorac Surg. 2002; 22:545-51.

16. Virmani S, Tempe DK, Pandey BC, Cheema AS, Datt V, Garg M, et al. Acute normovolemic hemodilution is not beneficial in patients undergoing primary elective valve surgery. Ann Card Anaesth. 2010; 13:34-8.
17. Practice Guidelines for blood component therapy: a report by the American society of anaesthesiologists task force on blood component therapy. Anaesthesiology. 1996; 84:732-47.
18. Bryson GL, Laupacis A, Wells GA. Does acute normovolemic hemodilution reduce perioperative allogenic transfusion? A meta-analysis. Anesth Analg. 1998; 86:9-15.
19. Segal JB, Blasco-Colmenares E, Norris EJ, Guallar E. Perioperative acute normovolemic hemodilution: a meta-analysis. Transfusion. 2004; 44:632-44.
20. Casati V, Benussi S, Sandrelli L, Graddo MA, Spagnolo S, D` Angelo A. Intraoperative Moderate Acute Normovolemic Hemodilution associated with a comprehensive blood-sparing protocol in off-pump coronary surgery. Anesth Analg. 2004; 98:1217-23.
21. Wang G, Xie G, Jiang T, Wang Y, Wang W, Ji H, et al. Tranexamic acid reduces blood loss after off-pump coronary surgery: A prospective, randomized, double-blind, placebo-controlled study. Anesth Analg. 2012; 115:239-43.
22. Myles PS, Smith JA, Forbes A, Silbert B, Jayarjah M, Painter T, et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med. 2017; 376:136-48.
23. Sigaut S, Tremey B, Outtara A, Couturier R, Taberlet C, Grassin- Delyle S, et al. Comparison of two doses of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. J Am Soc Anesthesiol. 2014; 120:590-600.