Effects of protamine sulfate in off-pump coronary bypass surgery

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Abstract

Aims: Hypercoagulation has been shown to exist postoperatively in off-pump coronary surgery patients. The aim of this study was to determine whether protamine sulfate administration adversely affects the postoperative coagulation status in these patients.
Material and Methods: Forty consecutive patients who underwent off-pump coronary bypass surgery between December 2005 and February 2007 were randomized into two groups depending on whether (group A) or not (group B) they received protamine sulfate. Coagulation status was measured on the first and third postoperative days using thromboelastography (TEG). Postoperative blood loss was also compared between the groups.
Results: On the third postoperative day all patients in both groups showed an increase in the TEG maximal amplitude (MA), confirming the presence of hypercoagulation. The MA was greater in group A than in group B (76.6 vs. 73.3 mm, respectively), but did not reach statistical significance (ANOVA *p=0.40*). The total blood loss did not differ significantly between groups A and B (828 vs. 878 ml, respectively).
Conclusions: The results of this study suggest that the routine use of protamine sulfate in off-pump coronary surgery may not be necessary.
Key words: CABG, off-pump, coagulation.

Streszczenie

Wstęp: Nadmierna krzepliwość krwi była opisana po operacjach *off pump* u pacjentów z chorobą wieńcową. Celem pracy było zbadanie, czy podanie protaminy sulfatu może niekorzystnie wpłynąć na pooperacyjną krzepliwość krwi u tych pacjentów.
Materiał i metody: 40 pacjentów, u których były naszyte pomosty wieńcowe, randomizowano (podzielono) na dwie grupy w zależności od tego, czy otrzymali protaminę (grupa A), czy też nie (grupa B). Stan krzepliwości krwi był mierzony za pomocą tromboelastografii (TEG) w pierwszym i trzecim dniu pooperacyjnym. Porównywane było również krwawienie pooperacyjne między grupami.
Wyniki: W trzecim dniu pooperacyjnym wszyscy pacjenci w obu grupach wykazywali na TEG zwiększenie maksymalnej amplitudy (MA), co potwierdziło istnienie nadmiernej krzepliwości. MA było większe w grupie A niż w grupie B (76,6 *vs* 73,3 mm), ale wynik ten nie osiągnął statystycznego znaczenia (ANOVA p=0,40). Całkowite krwawienie pooperacyjne nie różniło się w obu grupach A i B (828 *vs* 878 ml).
Wnioski: Wyniki tej pracy sugerują, że rutynowe podawanie protaminy sulfatu w *off pump* w wieńcowej chirurgii nie musi być konieczne.
Słowa kluczowe: CABG, *off pump*, krzepliwość.

Introduction

Patients who undergo off-pump coronary surgery require so-called partial heparinization, in contrast to those operated on in extracorporeal circulation. The anticoagulant protocol that is used during beating-heart surgery varies between cardiac surgery units. Generally an activated clotting time (ACT) of over 300 s during the procedure is recommended, with some authors advising a lower threshold (≥250 s) [1]. Moreover, there is no consensus about the dosage of protamine sulfate that should be administered to reverse the effects of heparin at the end of the operation. Some authors have even advised against using any protamine sulfate in off-pump surgery [2, 3].

Hypercoagulation has been shown to exist postoperatively in off-pump patients [4], and this increases the risk of early bypass closure [5, 6]. We hypothesized that giving protamine sulfate to this group of patients to reverse the effects of heparin could affect their postoperative procoagulant status. We used thromboelastography (TEG) to assess the effects of protamine sulfate administration on the post-

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Tab. I. Preoperative profiles and results of preoperative coagulation tests in 40 consecutive patients

	Group A	Group B
LM (*N*)	6	5
hypertension	17	17
dyslipidaemia	10	17
diabetes	9	10
stroke	3	0
EF (%)	51.2 (20–65)	56.2 (40–65)
fibrinogen [g/l] mean±SD	3.82±0.83	3.82±1.3
TT [s]	13.36±1.6	13±1.0
aPTT [s]	27.75±2.7	27.5±4.0
INR	1.12±0.1	1.19±0.1

LM – left main disease; EF – ejection fraction of the left ventricle; TT – thrombin time; aPTT – activated prothrombin time; INR – international normalized ratio.

operative coagulation status in patients undergoing beating-heart surgery.

Material and Methods

Forty consecutive patients with ischaemic heart disease who underwent elective off-pump coronary bypass surgery performed by the same surgeon in our department between December 2005 and February 2007 were prospectively randomized into two groups based on whether (group A) or not (group B) they received protamine sulfate at the end of the operation. Randomization was performed a day before surgery by a physician who was not involved in the investigation, using an envelope method. The surgeon was not blind to the protamine administration. Group A comprised 8 (40%) men and 12 (60%) women, and group B comprised 14 men (70%) and 6 women (30%). The mean ages of the patients were 67.0 and 68.5 years in groups A and B, respectively. The clinical data of the patients are listed in Table I. This study was approved by the Institutional Review Board of University Hospital Olomouc, and informed consent was obtained from all patients.

A median sternotomy was used for surgical access in all cases. Systemic heparinization was introduced before cardiac manipulation, with the dose of heparin (ranging from 5,000 to 10,000 U) adjusted to the patient's weight so as to achieve an ACT of 300 s. The ACT calculation was performed using a Hemochrome device and tubes with a cellite activator. In our experience the ACT values are 50 s lower when using vials with a kaolin activator than when using a cellite activator.

The heart was stabilized using two mechanical suction-based tissue stabilizers and a single modified "Lima" pericardial traction stitch. All anastomoses were performed on intraluminal shunts. After completion of the procedure, protamine sulfate was administered in a 1:1 ratio with the dose of heparin received (in group A only).

Tab. II. Laboratory results and blood loss in 40 consecutive patients

	Group A	Group B	*p*
Hb0	132±12.7	134±19.9	0.588
Hb ICU	113±0.03	114±0.05	0.957
Hb3	105±16.2	109±23.8	0.776
HCT0	0.4±0.04	0.4±0.05	>0.99
HCT ICU	0.34±0.03	0.33±0.05	0.636
HCT3	0.32±0.04	0.32±0.06	0.935
PLT0	249±93.8	215±61	0.152
PLT ICU	221±115.5	186±55.8	0.256
PLT3	209±61.5	176±39.3	0.099
ACT0	169±25	173±19	0.715
ACT op	347±58	322±50	0.107
ACT ICU	159±33	179±36	0.012
blood loss, 12 h (ml)	420±128	520±176	0.051
blood loss, total (ml)	828±222	878±224	0.417

Hb – haemoglobin; HCT – haematocrit; PLT – platelet count; ACT – activated clotting time.
Suffixes: 0 – preoperative; op- – during operation; ICU – intensive care unit; 3 – third postoperative day.

The drainage system consisted of three to five 10-CH Redon drains (2-mm inner diameter) that were placed around the heart and into the pleural cavity. Postoperatively, blood loss was measured and compared between the groups 12 h after the procedure and on the second postoperative day when the drains were removed. The postoperative coagulation status was estimated on the first and third postoperative days using TEG. The results were compared with the preoperative TEG data.

The data are expressed as mean ± standard deviation and were statistically analyzed using Statistica 6.0 software (StatSoft, Tulsa, OK), with the recorded variables compared using the Mann-Whitney test and analysis of variance for dependent measurements (ANOVA). A p value less than 0.05 was considered statistically significant.

Results

The mean numbers of grafts per patient were 3.1 and 2.9 in groups A and B, respectively. The internal thoracic artery was used for one of the grafts in all but two patients in group B.

The preoperative values of haematocrit (HCT), haemoglobin (Hb), and platelet counts did not differ significantly (Table II). The mean amount of heparin used to evoke anticoagulation was 7,750 U, and did not differ significantly

either. The mean values of ACT after heparin administration were 347 and 322 s in groups A and B, respectively. There was a difference in ACT values obtained in the intensive care unit immediately after the procedure, with ACT being lower in group A (159 vs. 179 s, p=0.012). The blood loss was higher in group B (520 vs. 420 ml, p=0.051) in the first 12 h after the procedure. The total blood loss at the time of drain removal on the second postoperative day was 878 ml in group B and 828 ml in group A (p=0.48) (Table II). There was no significant difference between group A and group B in decline in HCT and Hb on the third postoperative day.

All patients who received transfusions after the procedure (3 patients in group A and 5 patients in group B) had some degree of anaemia preoperatively. However, the peri-operative and post-operative blood losses did not differ significantly between these patients and the other patients in each group.

The results of the preoperative laboratory coagulation tests were within the normal ranges in all patients included in this study. Two patients in each group received low-molecular-weight heparin (LMWH) preoperatively. Also, the results of preoperative coagulation tests were normal in these patients except for a prolonged reaction time (*R*) in TEG. Both groups also contained patients who showed an increased *R* (>7 min), despite not being on anticoagulant therapy.

The maximal amplitude (MA) in TEG expresses the absolute strength of the coagulum (maximal clot-shear elasticity), and its mean value before the procedure did not differ between the groups (70.4 and 69.6 mm in groups A and B, respectively) (Table III). MA decreased in both groups on the first postoperative day, with this being larger in group B. On the third postoperative day the MA was increased relative to its preoperative value in all patients in both groups, including the four patients on preoperative LMWH treatment (Fig. 1). The MA values were slightly higher in group A than in group B (75 vs. 73.7 mm). This difference was greater when only patients with a normal preoperative R (14 patients in group A and 15 patients in group B) were analyzed in both groups (76.6 vs. 73.3 mm, p=0.10) (Table III). Similarly, the increase in MA from preoperatively to the third postoperative day differed between groups A and B (6.14 vs. 3.8 mm, respectively, p=0.432). These results, however, did not reach statistical significance (ANOVA p=0.40).

None of our patients exhibited signs of fibrinolysis on TEG examination, or received platelet or fresh frozen plasma transfusion. No antifibrinolytics were administrated. No deaths occurred, and there were no myocardial infarctions, other signs of heart ischaemia, or coronary or other types of thrombosis. One patient in group A required repeat surgery owing to surgical bleeding from the edge of the sternum. His total blood loss was 920 ml and was calculated with the A group. One patient in group B suffered from pneumothorax requiring chest drainage. The postoperative course of the remaining patients was uneventful.

Tab. III. Results of thromboelastography examination in 29 consecutive patients with normal preoperative R (14 in group A, 15 in group B)

	Group A	Group B	*p*
*R*0	5.4±1.5	5.2±1.6	0.878
*R*1	8.1±3.0	9.3±5.6	>0.999
*R*3	6.8±2.8	6.2±1.9	0.585
*R*0→*R*3	1.4±2.8	0.9±2.1	0.760
MA0	70.4±7.0	69.6±5.9	0.776
MA1	69.4±6.7	66±11.4	0.471
MA3	76.6±3.8	73.3±6.3	0.150
MA0→MA3	6.14±7.75	3.8±7.34	0.432
alpha0	69.5±7.3	70.9±5.3	0.711
alpha1	64.5±11.0	59.5±15.8	0.407
alpha3	70.5±5.7	68.7±4.5	0.176
alpha0→alpha3	1±8.1	2.1±6.14	0.222

MA – maximal amplitude; R – reaction time; alpha, alpha angle; R0→R3, MA0→MA3, alpha0→alpha3, changes between preoperative and third-postoperative-day values. Suffixes: 0 – preoperative; 1 – first postoperative day; 3 – third postoperative day.

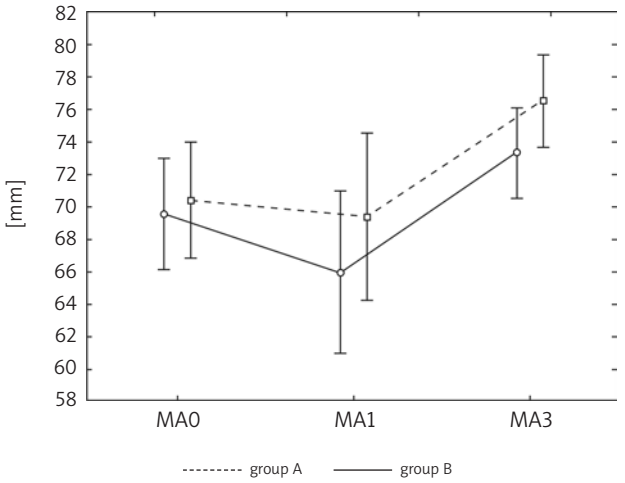

Fig. 1. Maximal amplitude (MA) in thromboelastography

Suffixes: 0 – preoperative; 1 – first postoperative day; 3 – third postoperative day.

Discussion

Heparin is used to prevent undesirable thrombosis during cardiac procedures. The effect of this drug is reversed at the end of the operation by administering protamine sulfate in order to return the haemostasis to normal. However, normal haemostasis involves a fine, autoregulated balance between endogenous anticoagulants and procoagulants, and is adversely affected by any interference with this balance. Surgery decreases the natural dominance of the anticoagulant

system over the procoagulant system. Previous studies have found that patients undergoing off-pump coronary surgery experience a state of hypercoagulation in their postoperative period [7, 8]. This suggests that the cascade of enzymatic activation in the coagulation system of an organism "overcompensates" for the risk of bleeding caused by surgical insult. This insight has led to increased interest in the risk of early bypass failure caused by thrombosis in cardiac patients.

The present study used TEG to analyze the effects of heparin reversal by protamine sulfate (which interferes with coagulation) on the postoperative coagulation state in patients undergoing off-pump coronary surgery. TEG is an excellent tool for assessing the instantaneous coagulation state [9, 10], and has proved to be indispensable in the postoperative care of cardiac patients, especially for distinguishing surgical from non-surgical bleeding [11]. It has also been used for assessing hypercoagulability. An increase in the MA on the TEG trace of >70 mm without a sudden decrease in its value (confirming fibrinolysis) indicates hypercoagulability of the blood sample. The TEG MA value has also been shown to be predictive of postoperative thrombotic complications [12].

Our study confirmed previous findings of the occurrence of a postoperative hypercoagulation state in patients receiving beating-heart surgery. TEG examinations showed an increased MA on the third postoperative day: 76.6 mm in group A and 73.3 mm in group B. This finding indicates that our standard postoperative anticoagulation management consisting of LMWH (0.2 ml of Clexane subcutaneously twice a day) and aspirin (100 mg once a day) was insufficient to maintain normal clotting. At the same time, a trend for a smaller increase in MA on the third postoperative day relative to the preoperative value has been shown in patients who did not receive protamine sulfate.

The number of platelets differed between the groups on the third postoperative day, which corresponded to the discrepancy in the preoperative platelet count between the groups. Although there was a gradual decrease in the number of platelets throughout the investigation in both groups, the initial decrease in MA on the first postoperative day was followed by an increase on day 3. This suggests that the absolute number of platelets as measured by laboratory tests does not correspond to the number of activated platelets that participate in the clot formation process and are expressed by the TEG MA value.

Since the activation of platelets has been identified as a major contributor to the hypercoagulable state during off-pump surgery [13] and because platelets represent a major component (86–90%) [14] of MA, we did not determine the postoperative level of fibrinogen in all patients. However, those patients in whom fibrinogen was measured on the third postoperative day showed that its value was abnormally high, independent of the group.

The results of this study failed to confirm the hypothesis that protamine sulfate increases the state of postoperative hypercoagulation in off-pump coronary surgery patients who are not exposed to the anticoagulant effect of extracorporeal circulation.

This study indicates, however, that routine use of protamine sulfate in off-pump coronary surgery may not be necessary.

References

1. Lo B, Fijnheer R, Castigliego D, Borst C, Kalkman CJ, Nierich AP. Activation of hemostasis after coronary artery bypass grafting with or without cardiopulmonary bypass. Anesth Analg 2004; 99: 634-640.
2. Mariani MA, Gu YJ, Boonstra PW, Grandjean JG, van Oeveren W, Ebels T. Procoagulant activity after off-pump coronary operation: is the current anticoagulation adequate? Ann Thorac Surg 1999; 67: 1370-1375.
3. Kim KB, Cho KR, Choi JS, Lee HJ. Right gastroepiploic artery for revascularization of the right coronary territory in off-pump total arterial revascularization: strategies to improve patency. Ann Thorac Surg 2006; 81: 2135-2141.
4. Quigley RL, Fried DW, Salenger R, Pym J, Highbloom RY. Thrombelastographic changes in OPCAB surgical patients. Perfusion 2002; 17: 363-367.
5. Poston R, White C, Read K, Gu J, Lee A, Avari T, Griffith B. Virchow triad, but not use of an aortic connector device, predicts early graft failure after off-pump coronary bypass. Heart Surg Forum 2004; 7: E428-E433.
6. Gwozdziewicz M, Němec P, Zezula R, Novotny J. Platelet mapping in postoperative management of acute postoperative aortocoronary bypass thrombosis. Kardiochirur Torakochir Pol 2006; 3: 214-216.
7. Poston R, Gu J, Manchio J, Lee A, Brown J, Gammie J, White C, Griffith BP. Platelet function tests predict bleeding and thrombotic events after off-pump coronary bypass grafting. Eur J Cardiothorac Surg 2005; 27: 584-591.
8. Silvay G. Risk management in major surgery III: myocardial injury following cardiac surgery. J Cardiothorac Vasc Anesth 2000; 14 (3 Suppl 1): 1.
9. Shore-Lesserson L. Evidence based coagulation monitors: heparin monitoring, thromboelastography, and platelet function. Semin Cardiothorac Vasc Anesth 2005; 9: 41-52.
10. Hobson AR, Agarwala RA, Swallow RA, Dawkins KD, Curzen NP. Thrombelastography: current clinical applications and its potential role in interventional cardiology. Platelets 2006; 17: 509-518.
11. Essell JH, Martin TJ, Salinas J, Thompson JM, Smith VC. Comparison of thromboelastography to bleeding time and standard coagulation tests in patients after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1993; 7: 410-415.
12. McCrath DJ, Cerboni E, Frumento RJ, Hirsh AL, Bennett-Guerrero E. Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. Anesth Analg 2005; 100: 1576-1583.
13. Gerrah R, Snir E, Brill A, Varon D. Platelet function changes as monitored by cone and plate(let) analyzer during beating heart surgery. Heart Surg Forum 2004; 7: E191-E195.
14. Mahla E, Lang T, Vicenzi MN, Werkgartner G, Maier R, Probst C, Metzler H. Thromboelastography for monitoring prolonged hypercoagulability after major abdominal surgery. Anesth Analg 2001; 92: 572-577.