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# Sonoclot Indicated a Risk of Immediate Postoperative Hypercoagulability

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**Abstract**

Several adverse responses may do after intravenous protamine administration for rapid-fire reversal of heparin anticoagulation. Respiratory(gasping), cardiovascular (pulmonary vasoconstriction, pulmonary roadway hypertension, hypotension, dropped cardiac contractility, bradycardia, cardiac arrest and ventricular fibrillation), skin (flushing, urticaria, and angioedema) and hematological (bleeding) have been reported . Protamine reactionsare both immunologically intermediated and a result of direct toxin. Contrary to cardiopulmonary bypass (CPB) which activates the indispensable complement pathway, especially through face contact in the oxygenator, protamine activates the complement system through the classical pathway. After cardiopulmonary bypass (CPB), administering protamine in an advanced cure given over a shorter time (<5 twinkles) increases the threat for pulmonary and hemodynamic adverse responses.

**Keywords:** Protamine; complement activation; C3a; sonoclot; cardiopulmonary bypass surgery

## Introduction

Several adverse responses may do after intravenous protamine administration for rapid-fire reversal of heparin anticoagulation (1). Respiratory(gasping), cardiovascular (pulmonary vasoconstriction, pulmonary roadway hypertension, hypotension, dropped cardiac contractility, bradycardia, cardiac arrest and ventricular fibrillation), skin (flushing, urticaria, and angioedema) and hematological (bleeding) have been reported (1). Protamine reactionsare both immunologically intermediated and a result of direct toxin (,2). Contrary to cardiopulmonary bypass (CPB) which activates the indispensable complement pathway, especially through face contact in the oxygenator (3- 5), protamine activates the complement system through the classical pathway. After cardiopulmonary bypass (CPB), administering protamine in an advanced cure given over a shorter time (<5 twinkles) increases the threat for pulmonary and hemodynamic adverse responses (6). The optimal cure of protamine for hemostasis has achieved great interest an inordinate cure of protamine after CPB can protract ACT and drop platelet function (7), but it has not been verified that this leads to increased postoperative bleeding (,9). Khan et al. (8) demonstrated a hypocoagulative thrombelastography pattern when redundant protamine was added in- vitro to blood samples from heparinized cases witnessing cardiac surgery with CPB, but didn't probe whether this had any significance for factual postoperative bleeding. Free protamine together with heparin in tube seems to affect platelet function less than free protamine without heparin (10). Thromboelastography has the stylish pungency/ delicacy so far amongst routine tests forpost-CPB bleeding (,12). The goods of different protamine tablets on complement activation and viscoelastic coagulation tests postoperative bleeding, haven't been studied. The end of this prospective, randomized and open study was to estimate a reduced cure of protamine, invested over 20 twinkles with a hype motorist on complement activation, Sonoclot coagulation analysis and clinical bleeding parameters in cases witnessing CABG. Our thesis was that a reduced protamine cure would drop complement activation without increased postoperative drainage bleeding. Material and styles. The study was prospective, open study, with no recessions or drop- outs. Following an airman study on different situations of complement activation after cardiac surgery with two different cure administrations of protamine, whose cases aren't included in this study, we anticipated a sample size of 40 cases to reach a power of>0.80 in a study with 2 different protamine tablets. Forty cases with stable angina pectoris, listed for primary optional CABG surgery were prospectively randomized into two groups, 20 cases in each group. Cases were eligible for addition if they were planned for optional CABG for stabile angina and had given written concurrence. Cases with known coagulation or bleeding diseases were barred, as were cases sharing in other clinical studies. An informed and spoken concurrence was attained preoperatively from each case for the use of their particular data for scientific purposes according to the Helsinki Declaration. The study was approved by the original ethics commission (Örebro University Hospital) and conducted at that same sanitarium. Cases entered one of two schematic protamine chloride (porcine mucine heparin, Leo Pharma, Sweden) tablets of either 2mg/ kg or 4mg/ kg bodyweight (BW). The 4mg/ kg BW protamine cure corresponds to the generally recommended protamine cure for heparin reversal after CPB/ CABG of 1mg/ 100 IU heparin. A study nanny broke the successionally numbered opaque sealed randomization envelope for each case at the time of the operation. Infusion was achieved using a hype motorist over 20 twinkles after the end of CPB. The study nanny also collected blood samples at the listed time intervals. fresh protamine was permitted in tablets of 25 mg first 1h after the protamine infusion, and was indicated by increased drainage bleeding (> 100 ml/ h during each of the following 3 hours and> 50 ml/ h later). Hemochron ® JR- ACT (International Technidyne Corp, NJ, USA) was measured before and after fresh protamine. Postoperative drainage blood loss

was estimated up to 25 h after the protamine infusion. Blood was autotransfused from the oxygenator force up to 5 h after the protamine in emulsion. The safety monitoring comported of enrollment of heart rate, blood pressure, respiratory pressures, respiratory volume/ pressure circles dynamic compliance and adverse events (with special consideration of postoperative bleeding. An original full cure of heparin (porcine- grounded standard heparin, Leo, Sweden), 300 IU/ kg body weight was given to allpatients.However, redundant heparin was administered before cardiac cannulation in repeated boluses of 5000 IU up to 500 IU/ kg BW, If inadequate heparinization with ACT< 480 seconds wasn't achieved. ACT was maintained> 480 s during CPB according to recommendations from the manufacturer of the oxygenator. 10 000 IE heparin was added to the pump florescence of the heart- lung machine. CPB was conducted with moderate hypothermia of 30 – 32 °C (rectal temperature) and a inflow rate of2.4 L/ min/ m2. Pulsative blood inflow wasn't maintained during the CPB period. The cases entered standard anaesthesia with fentanyl, thiopentone, isoflourane and pancuronium, and were covered using arterial and central venous catheters and respiration circles (AS3, Datex, Finland). Blood was tried from indwelling arterial catheters with vacutainer fashion ( Venoject, UK) into EDTA glass test tubes containing0.38 M EDTAK3( Becton Dickinson, USA). Blood was tried previous to induction, after sternotomy, after CPBstart, before protamine,0.3 hours (h), 1h, 3h, 6h and 24h after protamine infusion. Actuated complement, C3a- desArg and C4a- desArg were analysed from tube firmed to-70 C using radioimmunoassay styles from Kabi UpJohn Diagnostics (Kabi Upjohn Company, Kalamazoo, USA) as has been described in a former study (13). Arterial blood gas analysis (Radiometer, Denmark) also included hemoglobin( Hb). Routine laboratory analyses included platelet (plc) and leucocyte count ( LC), actuated partial thromboplastin time( aPTT), fibrinogen and antithrombin and were performed preoperatively, 2 h after Page 1 of 2 and 25 h after protamine. Individual changes from the starting values for arterial blood pressures, CVP, peak respiratory pressures, laboratory and Sonoclot coagulation data were anatomized by repeated ANOVAs with the factors time, treatment and case within treatment. The first two factors were considered as fixed factors and the last (case within treatment) as a arbitrary factor. Significant relations were tested by Tukey ´s test. Residuals were examined and metamorphoses were made if necessary. Bonferoni corrections were made for multiple comparisons. A statistical difference with a p0.05) in demographic data (coitus, age, body mass indicator (BMI)), heparin tablets, extracorporeal rotation (ECC), time aortic setting- time, cumulative protamine tablets, antithrombin, fibrinogen, aPTT, total blood loss and blood transfusion between the groups. Discussion With the preface of radioimmunosassays (RIA) in the early 1970's, complement activation during cardiopulmonary bypass could be detected at low situations (7). RIA- tests for C3a, C4a and C5a were made commercially available, and increased tube situations of these so called anaphylatoxins could be detected in a multitude of clinical and experimental settings. Complement may be actuated by either the classical (C4a, C3a) or alternate pathway (C3a) during CPB. The systemic goods of the anaphylatoxins are typically well regulated by the exertion of carboxypeptidase and by the rapid-fire affluence to spots of complement activation of neutrophils and monocytes, whose receptors act as a Gomorrah for C5a, which is internalized and inactivated by proteolysis (15). Although C5a is the strong estanaphylatoxin and chemoattractant, increased tube situations have infrequently been detected during CPB due to this internalization (16). All of these peptides have anaphylatoxic exertion, they beget smooth muscle compression and degranulation of mast cells and basophils, with consequent release of histamine and other vasoactive substances that induce capillary leakage. C5a is the most potent of these anaphylatoxins. C5a and C3a also have immunoregulatory goods on T cell function, either stimulating or inhibiting aspects of cell- intermediated impunity (17). Due to a 100 cross reactivity between C3a, C4a and C5a and their separate desarginated inactive declination products C3a-desArg, C4a- desArg and C5adesArg (C5a- desArg retains 10 anaphylactoid exertion) the pathophysiological meaning of the increased tube situations of the anaphylatoxins haven't always been clear (18). Species differences in the complement system and its commerce with neutrophils monocytes macrophages and their release responses of intracellular enzymes, free revolutionaries, leukotrienes and thromboxanes have been clarified (19). With preface of new and more specific monoclonal, neoantigenic antibody assays for complement activation/ complement spilt products (ELISA), terminal complement complex (TCC), complement receptors and preface of antibody- designed antagonists of different activation products and receptors, a better understanding of the complement system and its pathophysiology has evolved (21). There were no differences in C3a and C4a between the groups intraoperatively previous to the protamine infusion. A significant increase in C3a and for C4a (numbers 3 and 4) could be seen as compared to preoperative values. C3a generally starts to increase shortly after the onset of CPB with a continuing rise during the bypass. Membrane oxygenators appear to dwindle the degree of complement activation (22). The preface of heparin carpeted ECC systems has also dropped complement activation during CPB ( 3). Significantly advanced tube situations of C3a- desArg were seen with the 4mg/ kg BW protamine lozenge up to0.6 hpost-protamine compared to the 2mg/ kg BW lozenge. Protamine can drop carboxy peptidase (CPN) and thereby enhance complement activation effects2. This has been opposed by Rabito etal.,( 23) who only set up the drop in CPN during CPB to be caused by dilution and not to changes in CPN conflation, catabolism or protamine. Cardiac, pulmonary, renal and hematological dysfunction after CBP, longer ceased times of bypass and youngish age at operation have been identified to increased situations of C3a/ C3a-desArg (24). No similar correlations were set up in this study. likewise, no deterioration in hemodynamics or pulmonary function could be identified to the advanced complement activation in cases with the 4mg/ kg protamine cure governance. Current CBP pathophysiology focuses on other immunologic labels than complement and more sophisticated tests of organ dysfunction presumably need to be used rather of the routine hemodynamic monitoring, Servo 300C- deduced respiratory parameters and blood gas analyses (25). A rapid-fire protamine injection/ infusion can induce hypotension. This rate or free- attention-dependent hypotension may affect from several causes. Proposed explanations include stimulation of endothelium- deduced comforting factor release, inhibition of tube carboxypeptidase N, inactivation of colorful vasoactive peptides, and anon-immunologic release of histamine from mast cells. Histamine can be released by protamine from insulated mortal cutaneous mast cells at high attention but not from lung mast cells. Some protamine responses may be associated with complement activation via the classical pathway, either through protamine- heparin complexes or through protamine andanti-IgG-antibody commerce. The generation of anaphylatoxins may induce middleman release from mast cells and can also stimulate the generation of new intercessors, similar as thromboxane A2 from membrane phospholipids of actuated leucocytes. Other responses presumably represent classical immunoglobulin E(IgE)-intermediated mislike and present as classical anaphylactic responses with rash, urticaria, bronchospasm, and systemic vasodilation. A pronounced increase in pulmonary roadway pressure from pulmonary vasoconstriction with secondary right heart failure is seen in some cases. This response is presumably intermediated by release of thromboxane A2 into the tube, since its metabolite, thromboxane B2 attention correlates to the degree of vasoconstriction (1).

Previous exposure to protamine from protamine containing insulin (now uncommon) increases the threat of severe protamine response during CPB (1). Only one case in our study had insulin treated diabetes and there were no signs of anaphylactic response in this case nor exaggerate complement activation. None of our cases had entered heparin before.

The presence ofcross-reacting antibodies in cases with fish disinclinations or former vasectomy has also been intertwined as a threat factor for severe protamine response, but the substantiation is limited to case reports and has not been vindicated in a series of similar cases (1). None of our cases had fish mislike or had experienced vasectomy. Diabetes, valvular surgery, and antedating pulmonary hypertension have been suggested to be threat factors for pulmonary vasoconstriction but the data doesn't support these suggestions (2). Only one of

our cases was diabetic, and no pulmonary response or difference in complement activation could be detected. Although the infusion rate may not affect IgG or IgE- intermediated anaphylactic responses, it attenuates responses that may depend on the attention of free protamine and circulating heparin- protamine complexes (1). A slow infusion rate is always judicious (6). Protamine excess may increase ACT, drop platelet aggregation and worsen thrombin function in vitro (9). The tube position of free protamine needed for these marvels to reach clinical significance remains uncertain one kindly aged study suggests that large surpluses of protamine are clinical insignificant (26) but only tests of tube coagulation and not platelet function or bleeding issues were used. ACT is anon-specific test for discovery of heparin answer (9). Anintra-group hypercoagulative Sonoclot response was seen with the advanced protamine cure in the present study with advanced clot rate and stronger platelet function, but also as compare to preoperative birth values. Increased platelet exertion and high fibrin deposit rates in viscoelastic tests have been associated with venoarterial thrombosis, TIA/ stroke, graft occlusion after aortofemoral-bypass surgery and in cancer (,28). Protamine infusion may both stimulate platelet- cranking factor (PAF) biosynthesis by leukocytes in the lung and accelerate the exposure of PAF in the arterial bed. An imbalance in similar mechanisms may favour platelet aggregation, explaining stronger platelet exertion as indicated by the shorter time to peak in the Sonoclot. Complement activation may play a part in this hypercoagulative response, due to its several islands to the coagulation water fall (29). Leucocyte count( LC) was advanced after protamine in the 4 mg/ kg BW protamine group and this may also induce a hypercoagulative response. The significantly dragged ACT in both the Sonoclot and Hemochron (not shown) with the lower cure of protamine presumably indicate unblocked heparin with inhibition of fibrin and platelets as indicated by the drop in CR and extension of time to peak. The most generally used protamine protocols determine the reversal cure of protamine grounded on the total cure of heparin given during bypass, using a reversal rate of 1 to1.5 mg protamine per 100 U heparin. These styles don't regard for the elimination of heparin during bypass and may affect in substantial overdose of protamine. The protamine boluses calculated from the heparin cure- ACT response wind, heparin position dimension (heparin- protamine titration- Hemotec Â®), or protamine cure- ACT response in vitro( Hemochron) all affect in lower boluses( 9) as the more advanced Hepcon HMS. Reduced- cure protamine protocols should be used since they've been associated with lower bleeding (9). Fresh small boluses of protamine may be warranted after reinfusion of blood remaining in the CPB circuit after decannulation. There was no difference in redundant boluses of protamine in our two groups. The absoluteness of the heparin reversal is assessed 5 to 10 twinkles after the end of infusion by measuringACT.However, heparin position dimension can also be helpful in catching on whether the cure of protamine has been sufficient (9), If the ACT has returned to birth. ACT will be constantly dragged only after heparin attention exceeding0.1 U/ ml. A normal ACT doesn't avert the presence of a significant quantum of heparin( 9) since the reagent phrasings being used are designed for high cure heparin operation and are less responsive to residual situations of heparin. Heparinase coupled to ACT methodology seems to be a promising and practical way to uncover residual unneutralized heparin (9). We didn't give redundant protamine during the first hour as we wanted to easily separate the degree of complement activation in the two groups. ACT was advanced and Sonoclot indicated unblocked heparin in the group entering the lower cure of protamine. The transfusion of ERC, hourly drainage bleeding and autotransfusion were each advanced in the low protamine lozenge group â€“ and would presumably come significant with further study cases. Especially the nearly 50 advanced transfusion rate in the low protamine lozenge group and this difference still being nonsignificant indicates that our study is underpowered. Although original neutralization of heparin with all of the preliminarily described styles is acceptable, small quantities of free heparin can be detected with chromogenic substrate assay or reprise protamine titration between 1 and 5 hours after neutralization (9). Heparin position dimension at the end of bypass may be the most practical of these protocols. In the absence of a heparin position measuring bias, a cure of 1 mg protamine for each 100 U heparin given before CPB will nearly always affect in complete reversal of heparin (30). There are several limitations of our study. First the power was calculated on protamine activation of C3a, and then we saw a significant cure response.

**Competing interests**

The authors declare that they have no competing interests.

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