Introduction: Protamine sulfate is used to neutralize unfractionated heparin after cardiopulmonary bypass (CPB). The optimal protamine:heparin ratio (P:H) is difficult to individualize. Indeed, when in excess, protamine can induce hemodynamic instability, complement activation and platelet dysfunction. Using in vivo titration curves, our objective was to determine the optimal P:H, hoping it would translate into a safe and effective heparin neutralization.

Methods: With our Research Ethics Board approval, 118 patients admitted for elective primary cardiac surgery requiring CPB consented to participate in this prospective randomized controlled study. After weaning from CPB, protamine infusion was initiated and celite activated clotting time (ACT) values were measured every 3 minutes. The control group was given a standard protamine infusion of 1.3 mg:1 mg (100 U) of heparin. The test group was given an infusion of protamine until two consecutive celite ACT values were lower than 160 and had reached a plateau. Anti-Xa activity was determined pre-protamine, 15 minutes and 3 hours post-protamine. The P:H, blood losses and transfusion exposure were recorded.

Results are presented as mean ± standard deviation. Student T-test, Chi2 or Wilcoxon rank sum tests were used for analysis. Statistical significance was assumed for a P value lower than 0.05.

Results: Demographic data between the two groups were similar. At the end of the protamine infusion, the ACT was significantly lower in the test group (136 ± 28 sec vs. 151 ± 23 sec). Mean P:H was 1.31 ± 0.10 in the control group and 0.82 ± 0.22 in the test group (P < 0.0001). Residual heparin concentrations were higher in the test group 15 minutes (0.12 ± 0.12 U/ml vs. 0.04 ± 0.06 U/ml, P = 0.0002) and 3 hours (0.07 ± 0.12 U/ml vs. 0.01 ± 0.03 U/ml, P = 0.0005) post-protamine. Mean total blood losses in the control group were comparable to blood losses in the test group (1335 ± 1420 cc vs. 1275 ± 960 cc, P = 0.99).

Discussion: The lower ACT at the end of infusion in the test group suggests that excess protamine causes an elevation of ACT. The optimal P:H was 0.82 mg of protamine to 100 U of total heparin, consistent with the existing literature. Residual circulating heparin did not qualify for heparin rebound (i.e. > 0.3 U/ml). Optimized protamine dosing did not translate into increased blood losses and/or transfusion of allogenic blood products. The in vivo protamine titration method eliminates the need for estimating the blood volume and measuring the heparin concentration at the end of CPB. It individualizes the optimal protamine:heparin ratio and is safe and efficient in this low-risk population.