Protamine has been shown to have adverse effects on coagulation at blood concentrations that are found clinically. Recent studies demonstrate that protamine alone can cause thrombocytopaenia, platelet dysfunction, impaired thrombin generation and fibrinolysis. In 1956, Perkins developed the technique of protamine titration that is predicated on the propensity of protamine to prolong clotting time. Mochizuki showed that protamine levels that exceed heparin levels by more than 1.3:1 prolong the ACT. Many recent studies document the adverse effects of small overdoses of protamine on thromboelastographic measures of coagulation.

Empirical dosing of protamine based on notional neutralization ratios of 1:1 mg or 1:100 IU can result in inappropriate and usually excessive protamine doses because of a number of factors. Reported activity ratios for heparin of 100 IU per mg may be quite variable despite efforts at international standardization. Better purification techniques mean that the current iteration of heparin preparations have higher mean molecular weights and specific activities than is traditionally referenced in the literature. Then also recommendations that 1 mg of protamine will neutralize 100 IU of heparin may not reflect the variety of possible interactions between these molecules. Further, the notion that the ratios of blood levels and doses can be used interchangeably fails to acknowledge the complex pharmacokinetics and pharmacodynamics of heparin itself, the inter- and intra-individual variations in these case by case, and the effect that CPB has on these factors.

Many investigations that report the titration of protamine dose to some sort of measured heparin level at the end of CPB suggest that the dose is lower than it might be on empirical grounds, without increases in bleeding, or perhaps with reductions in bleeding. In this session, I will review this body of literature, and try to come up with some effective, evidence-based practice tips for the management of protamine dosing for the reversal of heparin anticoagulation after on-pump cardiothoracic surgery.

8. Khan NU. The effects of protamine overdose on coagulation parameters as measured by thromboelastograph. EJA 2010; 27 (7) : pp. 624 – 627