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Review Article

REVIEW ARTICLE

Anticoagulant and side-effects of protamine in cardiac surgery

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Abstract

Neutralisation of systemic anticoagulation with heparin in cardiac surgery with cardiopulmonary bypass requires protamine administration. If adequately dosed, protamine neutralises heparin and reduces the risk of postoperative bleeding. However, as its anticoagulant properties are particularly exerted in the absence of heparin, overdosing of protamine may contribute to bleeding and increased transfusion requirements. This review describes the mechanisms underlying the anticoagulant properties and side-effects of protamine, and the impact of protamine dosing on the activated clotting time and point-of-care viscoelastic test results, and explains the distinct protamine dosing strategies in relation to haemostatic activation and postoperative bleeding. The available evidence suggests that protamine dosing should not exceed a protamine-to-heparin ratio of 1:1. In particular, protamine-to-heparin dosing ratios >1 are associated with more postoperative 12 h blood loss. The optimal protamine-to-heparin ratio in cardiac surgery has, however, not yet been elaborated, and may vary between 0.6 and 1.0 based on the initial heparin dose.

Keywords: anticoagulants; cardiopulmonary bypass; haemostasis; heparin

Editor's key points

- In this narrative review, the authors describe the mechanisms underlying the anticoagulant properties and side-effects of protamine.
- They explore the available dosing strategies for protamine, and conclude that protamine dosing should not exceed a protamine-to-heparin ratio of 1:1.

Protamines are small, nuclear, basic, arginine-rich, positively charged proteins with similarities to histones that are involved in the compact folding and stabilisation of DNA in the sperm head.[1] Protamine was primarily isolated from salmon fish sperm (salmine), but is now increasingly produced through recombinant biotechnology. Protamine is available in a sulphate and chloride formulation, with the latter being the most resistant to breakdown by peptidases.

In the first half of the 20th century, protamine was mostly used in insulin preparations to prolong the hypoglycaemic action of insulin, such as Hagedorn insulin.[2] The haemostatic effects of protamine, including its neutralising influence on the anticoagulant properties of heparin, were first described in

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the beginning of the 20th century.[3–6] Moreover, it was shown that adding increasing quantities of protamine sulphate to fresh whole blood prolonged the clotting time,[7] which was appointed to interference with the conversion from prothrombin to thrombin.[8,9] From these studies, it became apparent that the dosing of protamine is crucial in the shift towards an anticoagulant effect.[7]

The number of publications focusing on protamine dosing is relatively small compared with studies on heparin dosing (Fig. 1), and evidence levels for protamine dosing strategies in available guidelines are low.[10,11] Protamine use and dosing are controversial, and are frequently based on local practices and individual experience rather than evidence, with a large range of protamine-to-heparin ratios reported in the literature. Moreover, it is still common to administer additional protamine in continuing oozing patients, whilst the origin of coagulopathy and microvascular bleeding is not related to residual heparin. The ignorance of the anticoagulant properties of excessive protamine may result in prolonged bleeding and increased transfusion requirements. The objective of this review was to present an overview of the anticoagulant properties and side-effects of protamine; the evidence for the unfavourable effects of protamine overdosing on patient haemostasis; and recent studies focusing on optimising protamine dosing using heparin monitoring, fixed protamine-to-heparin dosing strategies, or algorithm-based protamine dosing.

Mechanism of action

Protamine is a highly positively charged peptide consisting of about 32 amino acids, and neutralises the effect of heparin through electrostatic binding between the cationic arginine groups of protamine and the anionic heparin in a 1:1 ratio. The resulting neutral protamine–heparin salt aggregates are clearly visible as white suspension and are formed within seconds.[12] In parallel, the binding of protamine to heparin dissociates the anti-thrombin/heparin complex, leading to the recovery of the original anti-thrombin activity.[13–16] The neutralisation of heparin by protamine is further influenced by platelet factor 4 (PF4), a heparin-binding protein excreted by activated platelets. PF4 is complimentary to protamine regarding heparin neutralisation, and during extracorporeal circulation, PF4 release contributes to the stability of the protamine–heparin complex.[17]

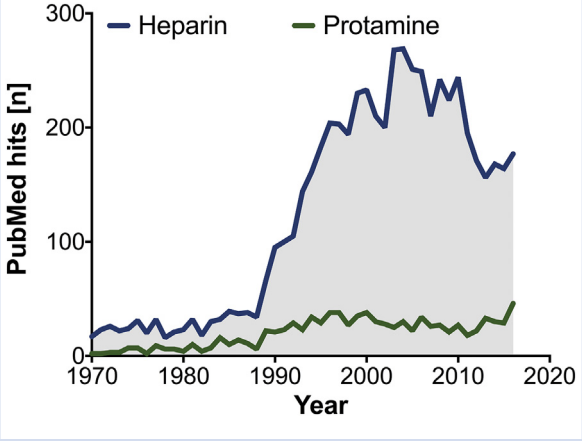

Fig 1. PubMed hits for [heparin] and [cardiac surgery] (blue line), and [protamine] and [cardiac surgery] (green line). Results of January 1, 2017.

Protamine has a rapid onset of action, a heparin-neutralising effect within 5 min for unfractioned heparin, and a relatively short half-life of about 10 min in healthy volunteers in the absence of heparin administration as determined by high-performance liquid chromatography.[18] In patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), 250 mg of protamine sulphate administered as infusion over 5 min in the presence of heparin showed a median plasma clearance of protamine of 1.4 litres min^{-1} (0.61–3.8) and a median half-life of 4.5 min (1.9–18), as estimated by a two-compartment exponential model with a volume distribution of 0.066 litres kg^{-1}.[19] Clearance of low-molecular-weight heparin by protamine depends on the molecular weight of heparin, with small heparin fragments being more difficult to neutralise than larger molecules.[20]

There is only little insight in the metabolism of the neutral protamine–heparin salt complex. One animal study using radiolabelled heparin showed that heparin–protamine complexes are mainly metabolised in the liver,[21] whilst infusion of radiolabelled protamine in the absence of heparin in a rat study showed that it is mainly metabolised and excreted by the kidneys.[22]

Anticoagulant properties of protamine

Whilst protamine primarily neutralises heparin, protamine has anticoagulant properties that are attributed to an interaction with platelet function, interference with coagulation factors, and stimulation of clot breakdown. The effects of protamine on different functions in the haemostasis system are summarised in Figure 2.

Effect of protamine on platelet count, activation, and aggregation

Exposure to protamine may result in thrombocytopenia,[23] reduced thrombin-induced platelet aggregation,[24] and decreased platelet responsiveness to thrombin receptor agonist peptide.[25] Using a protamine-dose range from 0 to 60 μg ml^{-1}, Shigeta and colleagues[26] showed in a small patient study that the inhibitory effects of protamine on platelet aggregation are dose dependent and can be minimised by adaptation of the protamine dose to the residual heparin concentration at the end of CPB. Moreover, high doses of protamine (200 μg ml^{-1}) reduced the glycoprotein Ib interaction with surface-bound von Willebrand factor (vWF) in platelet-rich plasma, and decreased the platelet–collagen adhesion under shear stress in an *in vitro* set up.[27]

Protamine reduced the platelet aggregation by 50% in heparinised patients undergoing cardiac surgery with CPB.[23] This study was, however, limited by a 1:1 protamine-to-heparin dosing ratio that was calculated for the initial heparin dose administered during CPB regardless of heparin consumption, and additional protamine dosing was allowed.[28] Similar findings were reported in patients undergoing pulmonary thromboendarterectomy with deep cooling receiving protamine-to-heparin ratios exceeding 1.[29] An *in vitro* study also showed that blood spiked with a protamine-to-heparin dosing ratio ranging from 1:1 to 10:1 reduces adenosine diphosphate (ADP)-induced platelet aggregation in a protamine-dose-dependent fashion.[30]

In summary, protamine reduces platelet activity and aggregation, but the underlying mechanism is multifactorial.