Whatever Happened to the Routine Use of Protamine?

Dr. Morton J. Kern, with contributions from Drs. Steven R. Bailey, Shreveport, Louisiana; Sam Butman, Cottonwood, Arizona; Mauricio G. Cohen, Miami, Florida; Kirk N. Garrett, Newark, Delaware; Steven L. Goldberg, Monterey, California; Farouc Jaffer, Boston, Massachusetts; Nils Johnson, Houston, Texas; Dean J. Kereiakes, Cincinnati, Ohio; Neal Kleiman, Houston, Texas; Jeff Marshall, Atlanta, GA; Jeffrey W. Moses, New York, New York; Kreton Mavromatis, Atlanta, Georgia; Pranav M. Patel, Irvine, California; Stephen R. Ramee, New Orleans, Louisiana; Chet Rihal, Rochester, Minnesota; Gurpreet S. Sandhu, Rochester, Minnesota: Bonnie H. Weiner, Worcester, Massachusetts

Early in the field of cardiac catheterization, heparin anticoagulation was required for almost every procedure in order to prevent thrombosis on the catheter, as the initial catheter materials, like Dacron, were highly thrombogenic. Often the anticoagulation with heparin required reversal with protamine as a routine. Over time, this practice faded into disuse as catheters and wires became less thrombogenic and the need for heparin reversal was only in patients thought to have a heparin-related bleeding complication. Protamine is currently used by surgeons after cardiac surgery, and by structural interventionalists. In the practice of coronary intervention, protamine reversal of heparin raises concern about promoting clot in a freshly implanted metal stent. Protamine is rarely used nowadays.

To this point, our colleague, Dr. Kreton Mavromatis, Director, Cardiac Catheterization Laboratory at the Atlanta VA Medical Center, asks our cath lab experts, "How widespread is the routine use of protamine immediately after coronary intervention to reduce femoral access complications? (Still need to use femoral access sometimes). Is the use of protamine considered safe after coronary intervention? Under all or some circumstances?"

Before getting into the practice and opinions of our experts, let's review what protamine is and what it does.

Protamine sulfate is a cationic peptide that binds to either heparin or low molecular weight heparin (LMWH) to form a stable ion pair without anticoagulant activity. The ionic complex is then removed and broken down by the reticuloendothelial system. In large doses, protamine sulfate has a weak anticoagulant effect. Protamine sulfate reverses the effects of heparin by direct binding. It is specifically useful in cases of heparin or LMWH overdose, or reverse heparin anticoagulation in patients during delivery or heart surgery. The onset of effects is typically <5 minutes.[1,2] Common side effects include low blood pressure, slow heart rate, allergic reactions, and vomiting. Protamine was originally made from the sperm of salmon (salmine, salmon protamine). It is now mainly made using recombinant biotechnology.

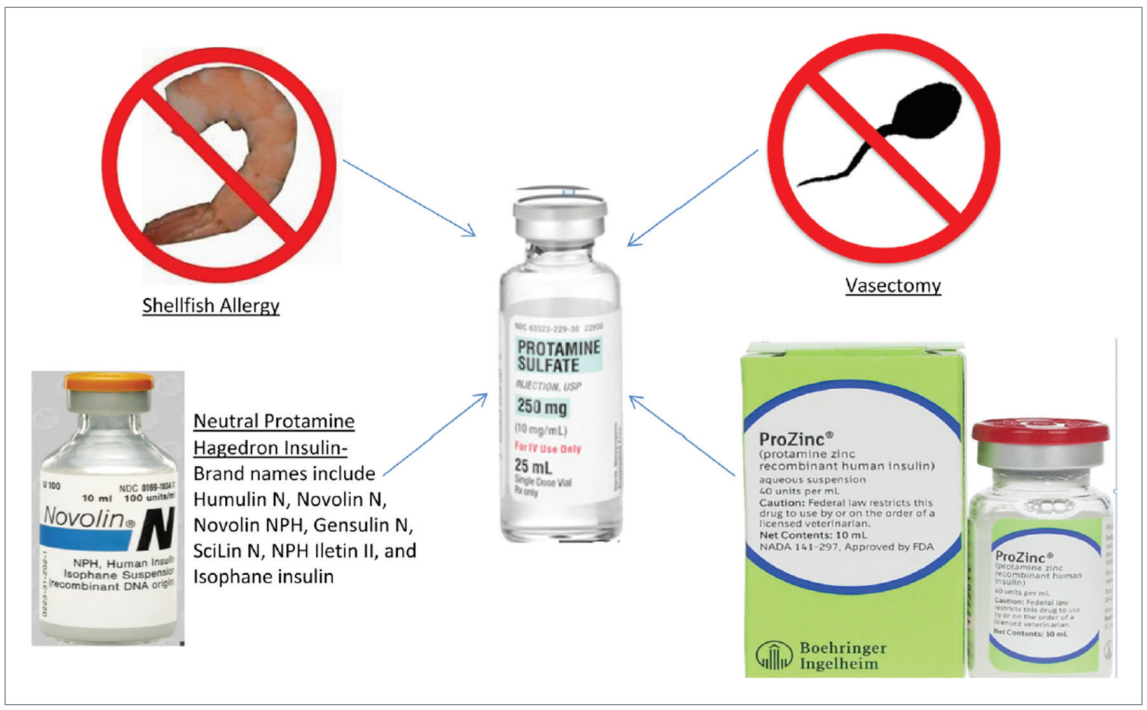


Figure 1. Risk factors for protamine anaphylaxis. **Reprinted with permission from Singh V, Song C, Woodbury A. The plight of protamine for heparin reversal in sensitized individuals. *Pol Ann Med*. 2017; 24(2): 264-267. doi: https://doi.org/10.1016/j.poamed.2017.02.003**

Protamine Reactions

While protamine is used widely for reversing systemic heparinization after cardiac catheterization, major reactions simulating anaphylaxis can occur, albeit rarely. Minor protamine reactions may appear as back and flank pain, or flushing with peripheral vasodilation and low blood pressure. Major reactions involve marked facial flushing and vasomotor collapse, which may be fatal. Patients taking NPH insulin have an increased sensitivity to protamine.[3,4] The incidence of major protamine reactions in NPH insulin-dependent diabetics is 27% compared with 0.5% in patients with no history of insulin use. Diabetic patients receiving NPH insulin and patients with allergies to fish should not be given protamine after cardiac catheterization. If use of protamine is necessary for these patients, it should be administered cautiously in anticipation of a major reaction.[5]

Is Protamine Routinely Used in Current Practice?

Mort Kern, Long Beach, California: Dr. Mavromatis, to your question, for routine PCI practice today, we rarely use protamine. I haven't given it in years. The rare occasion for use is a perforation not controlled by short-term intracoronary balloon tamponade in a fully heparinized patient or a suddenly discovered retroperitoneal hematoma from the femoral access before getting a covered stent in the femoral artery. I'm sure there may be a couple more indications (such as spontaneous retroperitoneal bleeding in radial access patient). I don't think protamine is dangerous when indicated, but in the diabetic patient, its use was thought to be dicey for those taking NPH (NPH stands for neutral protamine Hagedorn). I forgot who Hagedorn was. Let's see what our colleagues say.

Bonnie Weiner, Worcester, Massachusetts: I totally agree with the radial argument (my [radial] use is 80-90%, no protamine needed) but I do find that, almost by definition, any femoral cases that I end up doing are high risk (meaning there is no or limited upper extremity access options). Maybe we didn't know any better, but I don't remember using much protamine when we were entirely femoral access, even with 8-10 French (Fr) sheaths.

Kirk Garrett, Newark, Delaware: Routine use of protamine after coronary work vanished long ago in our practice. However, we use it regularly at the end of transcatheter aortic valve replacement (TAVR) procedures and even some large-bore venous procedures. The current protamine shortage has been a concern for the structural heart team.

Steven R. Bailey, Shreveport, Louisiana: Our experience is like that expressed by Kirk. We rarely use protamine post femoral or radial cases, with no cases in the last 2 years. Protamine is often used post TAVR and thoracic endovascular aortic repair (TEVAR). This is mostly given as vascular closure is occurring. We have not had any serious clinical events that have occurred. The current shortage of protamine and better access closure techniques have decreased the frequency of use post TAVR as well.

Chet Rihal, Rochester, Minnesota: There are a lot of practice variations, it seems. I routinely reverse all my structural procedures, TAVRs, valve-in-valves (VIVs), perivalvular leaks (mechanical valve or not), etc. There is not much need for reversal after percutaneous coronary intervention (PCI) with radial access, but occasionally it is helpful if a large-bore mechanical circulatory support (MCS) device is used. Dean [Kereiakes], I recall reading your paper. My alma mater in Canada would reverse after PCI and have published their data along with others.

Sam Butman, Cottonwood, Arizona: I gave protamine last week for the first time in I don't know how long, for a rare, enlarging groin hematoma after a vascular closure device that seemed fine until the patient became hypotensive a bit later. I had to look up the dose, checked that the patient was not insulin dependent, and gave him protamine, all the while worrying. His blood pressure was fine and as it turned out, he had no significant drop in hemoglobin. Hopefully, like the rest of us, with radial procedures now the norm, this [bleeding and use of protamine] has become an even rarer issue.

Nils Johnson, Houston, Texas: Likely the variation in practice arises from lack of data. Ghannam et al[7] reported in 150 patients undergoing atrial fibrillation ablations who were randomized 1:1 to protamine or control that the time to hemostasis favored protamine (123 vs 260 minutes). There are only two randomized, controlled trials that I could find on this topic.[6,7] Seems like low-hanging fruit for an interested investigator, given how many TAVR and MitraClip (Abbott Vascular) cases are being done via large-bore femoral access with vascular closure devices these days.

Regarding where protamine comes from, it is not often you see the phrase "semen of river trout" in the medical literature:

"Hans Christian Hagedorn (1888–1971) and August Krogh (1874–1949) obtained the rights for insulin from Banting and Best in Toronto, Canada. In 1923, they formed Nordisk Insulin laboratorium, and in 1926 with August Kongsted, obtained a Danish Royal Charter as a non-profit foundation. In 1936, Hagedorn and B. Norman Jensen discovered that the effects of injected insulin could be prolonged by the addition of protamine obtained from the 'milt' or semen of river trout."[8,9]

Gurpreet Sandhu, Rochester, Minnesota: In our lab, there is no routine use after coronary interventions, irrespective of access site. We use protamine after TAVRs, large-bore structural procedures, and after some femoral coronary diagnostics where intravascular ultrasound (IVUS)/ instant wave-free ratio (iFR)/spasm study, etc., necessitated heparin use.

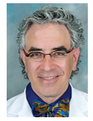
Steve Ramee, Ochsner Clinic, New Orleans, Louisiana: At Ochsner, we routinely reverse heparin after structural heart procedures, but only after coronary intervention for cause, i.e., bleeding.

Jeff Marshall, Atlanta, Georgia: I agree, protamine [should be given] for life-threatening bleeding post PCI.

Jeff Moses, New York, New York: When there are bleeding concerns, we use it without hesitation. These concerns don't need to be life-threatening as long as there was an optimal result, no evident thrombus, and equipment removed [without problems]. In the early days of stenting with just dual antiplatelet therapy (DAPT), Antonio [Colombo] would give it post procedure routinely, just to demonstrate the lack of thrombogenicity of well-deployed stents.

Farouc Jaffer, Boston, Massachusetts: For high activated clotting time (ACT) 300-350s cases during chronic total occlusion (CTO) PCI, we have reversed the last 400 cases with 10-30 mg protamine to get the ACT to 200s, without any thrombotic complications. For patients with insulin-dependent diabetes mellitus, we give 1 mg test dose and if well tolerated, give the rest slowly.

Dean Kereiakes, Cincinnati, Ohio: We were the first to describe partial heparin reversal with protamine in glycoprotein (GP) IIb/IIIa treated patients undergoing PCI.[10] If patients have adequate platelet inhibitor therapy on board (includes bolus-only tirofiban), this is a very safe and effective way to reduce access-site bleeding complications. I predict that Farouc will like his experience and will see fewer bleeding complications.



Steven L. Goldberg, Monterey, California: Antonio [Colombo] presented some data looking at predictors of stent thrombosis at Columbus Hospital in Milan. The use of protamine increased the risk of stent thrombosis, even though most patients tolerated it well. Based upon that, I would think it should be avoided, except when necessary.

Mauricio Cohen, Miami, Florida: I don't use protamine even after structural heart disease cases. After learning from advanced CTO operators, well versed in the management of perforations, I haven't even used protamine with coronary perforations that can be managed with balloon occlusion and a covered stent. I haven't used protamine in years.

Pranav Patel, Irvine, California: It looks like there is a wide variance of protamine use after coronary and structural heart cases. We tend to use it after every TAVR case at University of California Irvine. My confusion has always been how different individuals and institutions are dosing protamine. It seems [the practice] varies from place to place. I've seen the dose vary from 10 mg to 80 mg depending on the ACT, heparin dose, or even an individual physician's clinical acumen. Our cardiothoracic surgeons use very high doses compared to what we use in the cath lab. It would be interesting to know the dosing protocols that people have and use. I pulled Table 1 on dosing from Theheart.org/Medscape.

Neal Kleiman, Houston, Texas: I think we have all used it when there is life-threatening bleeding. I'm not aware of any stents clotting as a result.

Table 1. Protamine dose for heparin neutralization.

1-1.5 mg per 100 USP units of heparin; not to exceed 50 mg
Dose of protamine (mg) to neutralize 100 units of heparin:
• <1/2 hour: 1-1.5 mg/100 units of heparin
• 30-120 minutes: 0.5-0.75 mg/100 units of heparin
• >2 hours: 0.25-0.375 mg/100 units of heparin

Source: protamine (Rx). Drugs & Diseases. Dosing and Uses. Adult. Accessed July 13, 2021. Available online at https://reference.medscape.com/drug/protamine-343746

The Bottom Line

Protamine is rarely used for coronary interventions unless the bleeding is extreme and associated with heparin. However, there is practice variation in both indications and thresholds for use after PCI. Protamine is commonly used in heparinized patients who have had large-bore access, TAVR, or other structural heart interventions. While conventional wisdom cautions against protamine use in diabetics, experience from large centers suggests its benefits outweigh its risks. ■

References

1. Wikipedia. Protamine sulfate. Accessed July 12, 2021. Available online at https://en.wikipedia.org/wiki/Protamine_sulfate
2. Drugbank Online. Protamine sulfate. Accessed July 12, 2021. Available online at https://go.drugbank.com/drugs/DB09141
3. Levy JH, Zaidan JR, Faraj B. Prospective evaluation of risk of protamine reactions in patients with NPH insulin dependent diabetes. *Anesth Analg.* 1986; 65(7): 739-742.
4. Kimmel SE, Sekeres MA, Berlin JA, et al. Risk factors for clinically important adverse events after protamine administration following cardiopulmonary bypass. *J Am Coll Cardiol.* 1998; 32(7): 1916-1922.
5. Kern MJ. *The Interventional Cardiac Catheterization Handbook E-Book*. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2012; 131. ISBN 9781455740420.
6. Pan M, Suárez de Lezo J, Medina A, et al. In-laboratory removal of femoral sheath following protamine administration in patients having intracoronary stent implantation. *Am J Cardiol.* 1997; 80(10): 1336-1338. doi: 10.1016/s0002-9149(97)00676-0
7. Ghannam M, Chugh A, Dillon P, et al. Protamine to expedite vascular hemostasis after catheter ablation of atrial fibrillation: a randomized controlled trial. *Heart Rhythm*. 2018; 15(11): 1642-1647. doi: 10.1016/j.hrthm.2018.06.045
8. NPH Insulin. Wikipedia. Accessed July 21, 2021. Available online at https://en.wikipedia.org/wiki/NPH_insulin
9. Hans Christian Hagedorn. Wikipedia. Accessed July 21, 2021. Available online at https://en.wikipedia.org/wiki/Hans_Christian_Hagedorn
10. Kereiakes DJ, Broderick TM, Whang DD, Anderson L, Fye D. Partial reversal of heparin anticoagulation by intravenous protamine in abciximab treated patients undergoing percutaneous intervention: rationale, safety and clinical outcomes. *Am J Cardiol.* 1997; 80: 633-634. doi: 10.1016/s0002-9149(97)00437-2

Morton J. Kern, MD, MSCAI, FACC, FAHA
Clinical Editor; Chief of Cardiology, Long Beach VA Medical Center, Long Beach, California; Professor of Medicine, University of California, Irvine Medical Center, Orange, California

Disclosures: Dr. Morton Kern reports he is a consultant for Abiomed, Abbott Vascular, Philips Volcano, ACIST Medical, and Opsens Inc.

Dr. Kern can be contacted at mortonkern2007@gmail.com On Twitter @drmortkern

SOCIETY UPDATE

From the Society for Cardiovascular Angiography and Interventions (SCAI)

SCAI Government Relations

CMS Releases Proposed CY 2022 Physician Fee Schedule (PFS)

The Centers for Medicare & Medicaid Services (CMS) released the Proposed Rule on the Physician Fee Schedule (PFS) for the calendar year (CY) 2022. Society for Cardiovascular Angiography and Interventions (SCAI) staff will be reading and drafting comments on some of the highlights below in the coming weeks.

Conversion Factor

Conversion Factor for CY 2022 will be 33.58. The CCA ("Consolidate Appropriations Act") approved a 3.75% payment increase for 2021 that will expire at the end of the year. As a result of this anticipated 3.75 decrease for 2022, there will also be the usual budget neutrality adjustment which will be a decrease of $1.31. This brings the conversion factor to $33.58 for 2022. It is estimated that the whole of Cardiology will have a combined impact of -2%. This will mean that the conversion factor will affect practices in different ways. Staff will be looking this over to provide more information. SCAI will urge Congress and the Administration to make a critical investment in the nation's healthcare delivery system by maintaining the 3.75% increase to the Conversion Factor through at least calendar years 2022 and 2023.

Practice Expense

CMS is seeking comments on the practice expense for new Current Procedural Terminology (CPT) codes. CMS agreed with Relative Value Update Committee (RUC) recommendations for new CPT codes for Percutaneous Cerebral Embolic Protection and Exclusion of Left Atrial Appendage that go into effect on January 1, 2022. CMS recommended values for Endovascular Repair of Aortic Coarctation and Cardiac Catheterizations for Congenital Defect CPT codes that are lower than the RUC recommended values. Staff will be reviewing the logic of and drafting comments on these values.

National Coverage Determination (NCD)

CMS is soliciting comments on the removal of the NCD for Myocardial positron emission tomography (PET). When the NCD is removed, then payment is not automatic. The decision of payment is left to each local Medicare Administrator Contractor.

Cardiology Rehabilitation and Evaluation and Management (E/M) Telehealth Services

CMS is seeking comments on what telehealth services should be extended after the end of 2021 (i.e., presumably the end of the public health emergency). SCAI will need to seek input from our members on these services to see if we want to extend them after the year-end for 2021. Staff is seeking member input in order to comment on Inpatient, Observation Care, Office/Outpatient Services, Critical Care Services, and the G codes for Cardiac Rehabilitation.

Fractional Flow Reserve Computed Tomography (FFR_{CT})

CMS is seeking comment on whether other codes would provide a more appropriate crosswalk in terms of resource costs (i.e., a code of similar time and intensity). CMS is also more broadly soliciting public comment to help us better understand the resource costs for services involving the use of innovative technologies, including but not limited to software algorithms and artificial intelligence.

Quality Programs

Staff will be reviewing quality programs, such as Merit-Based Incentive Payment System (MIPS), Accountable Care Organization (ACO), and Appropriate Use Criteria (AUC). CMS is going to provide clarifications and proposals around the scope of the AUC program pertaining to updates or modifications to orders and CMS is proposing a flexible effective date for AUC program claims processing edits and payment penalty phase to being the later of January 1, 2023, or the January 1 of the year after the year in which the public health emergency (PHE) for COVID-19 ends. ■

Additional analysis and commentary will be provided soon. If you have questions, please contact: Debra Mariani, Director, Regulatory Affairs, at dmariani@scai.org