Minimal Protamine Dosing during Drug Shortages: Comment

To the Editor:

We read with interest the contribution to the journal by Jain *et al.*, in which patients were allocated to receive a single 250-mg dose of protamine sulphate or a 1:1 (1 mg protamine:100 IU heparin) fixed-dose ratio after cardiopulmonary bypass (CPB).[1] We congratulate the authors for undertaking this trial.

The authors conclude that "a conservative heparin reversal strategy based on the initial administration of a single 250-mg dose of protamine is feasible and effective. It resulted in activated clotting time values that were not different from a heparin ratio-based strategy and allowed protamine conservation without worsening postoperative bleeding." However, the applicability of their results in contemporary clinical practice is limited: specifically, their choice of intervention, comparator, and primary outcome are inappropriate.

Protamine requires judicious dosing.[2,3] Previous studies have reported increased bleeding when higher fixed-dose ratios of protamine to heparin are used.[4,5] While guidance from 2019 recommends a fixed-dose ratio of between 0.8 and 1.0 (based on the initial dose of heparin required to establish a safe activated clotting time) be used when dosing protamine,[6] more recent guidance recommends explicitly against using a protamine-to-heparin ratio of 1.0.[7] This recommendation is classed 1B, suggesting equipoise for including this regimen in clinical trials is limited.

While no significant difference in 24-h chest tube drainage was reported in Jain *et al.*, the study was not powered to examine this outcome[8]; a −77 ml (95% CI, −220 to 65) mean difference in chest drain output favoring the intervention group was observed ($P = 0.28$). It is not surprising that this result did not achieve significance given the small sample size of the study (n = 125), and there is a risk of type II error. Previous studies suggest that patients who received fixed-dose ratios of 1.0 or greater are likely to have received excess protamine, leading to inferior coagulation parameters as a result.[8]

The authors' choice of activated clotting time after administration of protamine as their primary outcome muddies the waters further: while activated clotting time correlates well with heparin concentration before CPB, it is known to correlate poorly with heparin concentration both during[9] and after[10,11] CPB. This is because activated clotting time is affected by multiple factors in addition to heparin concentration once CPB commences. Furthermore, activated clotting time cannot differentiate between different causes of deranged coagulation.[12] In the absence of any other coagulation assessment (*i.e.*, kaolin/heparinase R-time ratio on thromboelastography, anti-Xa concentration, activated partial thromboplastin time, and others), it is not possible to state with any certainty whether the coagulation profile after protamine differed between the groups (although, again, lower doses of protamine have been shown to correlate with superior coagulation parameters on viscoelastic hemostatic assays), especially where a fixed-dose ratio of 1:1 or greater is used as the comparator.[5,8,13]

Our attention now turns to the intervention group, and whether a single 250-mg dose of protamine in all patients is appropriate. In the Optimal Protamine Dosing After Cardiopulmonary Bypass (PRODOSE) multicenter randomized controlled trial, our group assessed the performance of a pharmacokinetic algorithm of heparin metabolism to determine protamine dose. The algorithm was designed to account for variability in heparin requirement during CPB.[8] The median initial protamine dose in the algorithm group was 180 mg (interquartile range, 160 to 210 mg). This correlates to an initial fixed-dose ratio of 0.66 (interquartile range, 0.56 to 0.75). The median total protamine dose in the algorithm group (accounting for pump blood) was 210 mg (interquartile range, 180 to 250 mg). The variances of these results highlight the substantial interindividual variability in protamine requirement, itself a reflection of the size of the initial dose of heparin, the duration spent on CPB, and the size and timing of supplemental doses of heparin. It is not plausible that a single fixed dose of protamine can safely account for all these factors. The apparently satisfactory performance of the 250-mg dose reported by Jain *et al.* needs to be interpreted in the context of the high dose of protamine administered to the control group. As suggested by our results[8] and by others,[14,15] an initial dose of 250 mg protamine in all patients will be, for a substantial proportion, excessive.

To conclude, the impact of Jain *et al.* is limited by the choice of intervention and comparator dosing, and the choice of the primary outcome. Where pharmacokinetic algorithms are not available, fixed-dose ratios (based on the initial dose of heparin used to establish a therapeutic activated clotting time) of 0.7:1 are safe and effective in most patients, and this is discussed appropriately in best practice guidelines.[7] There is no one-size-fits-all protamine dose, and clinicians eager to minimize protamine wastage need not settle for an imprecise dosing strategy.

Competing Interests

The authors declare no competing interests.

Lachlan F. Miles, Ph.D.[1,2]*
Florian Falter, Ph.D.[3]
[1]Austin Health, Melbourne, Australia
[2]University of Melbourne, Melbourne, Australia
[3]Royal Papworth Hospital National Health Service Foundation Trust, Cambridge, United Kingdom
*lachlan.miles@unimelb.edu.au

DOI: 10.1097/ALN.0000000000005615

References

1. Jain P, Silva-De Las Salas A, Bedi K, Lamelas J, Epstein RH, Fabbro M: Protamine dosing for heparin reversal after cardiopulmonary bypass: A double-blinded prospective randomized control trial comparing two strategies. Anesthesiology 2025; 142:98–106. doi:10.1097/ALN.0000000000005256
2. Shore-Lesserson LJ, Baker RA, Ferraris VA, et al.: The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of ExtraCorporeal Technology: Clinical practice guidelines - Anticoagulation during cardiopulmonary bypass. Ann Thorac Surg 2018; 105:650–62. doi:10.1016/j.athoracsur.2017.09.061
3. Pagano D, Milojevic M, Meesters MI, et al.: 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. Eur J Cardiothorac Surg 2018; 53:79–111. doi:10.1093/ejcts/ezx325
4. Kunz SA, Miles LF, Ianno DJ, et al.: The effect of protamine dosing variation on bleeding and transfusion after heparinisation for cardiopulmonary bypass. Perfusion 2018; 33:445–52. doi:10.1177/0267659118763043
5. Meesters MI, Veerhoek D, de Lange F, et al.: Effect of high or low protamine dosing on postoperative bleeding following heparin anticoagulation in cardiac surgery. A randomised clinical trial. Thromb Haemost 2016; 116:251–61. doi:10.1160/TH16-02-0117
6. Kunst G, Milojevic M, Boer C, et al.; Authors/Task Force Members: 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. Br J Anaesth 2019; 123:713–57. doi:10.1016/j.bja.2019.09.012
7. Casselman FP, Lance MD, Ahmed A, et al.: 2024 EACTS/EACTAIC guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP. Eur J Cardiothorac Surg 2025; 67:ezae352. 10.1093/ejcts/ezae352.
8. Miles LF, Burt C, Arrowsmith J, et al.: Optimal protamine dosing after cardiopulmonary bypass: The PRODOSE adaptive randomised controlled trial. PLoS Med 2021; 18:e1003658. doi:10.1371/journal.pmed.1003658
9. Despotis GJ, Summerfield AL, Joist JH, et al.: Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. J Thorac Cardiovasc Surg 1994; 108:1076–82
10. Taneja R, Marwaha G, Sinha P, et al.: Elevated activated partial thromboplastin time does not correlate with heparin rebound following cardiac surgery. Can J Anaesth 2009; 56:489–96. doi:10.1007/s12630-009-9098-6
11. Galeone A, Rotunno C, Guida P, et al.: Monitoring incomplete heparin reversal and heparin rebound after cardiac surgery. J Cardiothorac Vasc Anesth 2013; 27:853–8. doi:10.1053/j.jvca.2012.10.020
12. Levy JH, McKee A: Chapter 30 in Bleeding, Hemostasis, and Transfusion Medicine, Cardiothoracic Critical Care. Edited by Sidebotham D, McKee A, Gilham M, Levy J. Philadelphia, Butterworth-Heinemann, 2007, pp 437–60
13. Ni Ainle F, Preston RJS, Jenkins PV, et al.: Protamine sulfate down-regulates thrombin generation by inhibiting factor V activation. Blood 2009; 114:1658–65. doi:10.1182/blood-2009-05-222109
14. Kjellberg G, Holm M, Fux T, Lindvall G, van der Linden J: Calculation algorithm reduces protamine doses without increasing blood loss or the transfusion rate in cardiac surgery: Results of a randomized controlled trial. J Cardiothorac Vasc Anesth 2019; 33:985–92. doi:10.1053/j.jvca.2018.07.044
15. Meesters MI, Veerhoek D, de Jong JR, Boer C: A pharmacokinetic model for protamine dosing after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2016; 30:1190–5. doi:10.1053/j.jvca.2016.04.021

(Accepted for publication May 29, 2025.)

Minimal Protamine Dosing during Drug Shortages: Comment

To the Editor:

We read with interest the study by Jain *et al.*, which adds a new contribution to the long-lasting tricky issue of unfractionated heparin neutralization after cardiac surgery with cardiopulmonary bypass (CPB).[1] The authors observed that the use of a fixed dose of 250 mg protamine, compared

with a 1 to 1 ratio of the initial unfractionated heparin dose to achieve an activated clotting time greater than 450 s, was not associated with an increased incidence of prolonged activated clotting time 3 min after protamine administration. However, the choice of the activated clotting time to assess the complete neutralization of unfractionated heparin is highly debatable and provides us an opportunity to recall a few methodologic concepts that clinicians often overlook.

The activated clotting time is performed in whole blood and measures the time until initial clot formation or thrombin generation after the addition of a high amount of a contact pathway activator (*e.g.*, celite or kaolin). The test was designed to monitor very high levels of unfractionated heparin administered during cardiac surgery with cardiopulmonary bypass (plasma anti-Xa levels: 3 to 5 U/ml, compared with the 0.3 to 0.7 U/ml targeted for venous thromboembolism treatment).[2] Using such high amounts of activator makes the test insensitive to low concentrations of unfractionated heparin: the instruction for use of the activated clotting time plus Hemochron cartridge (Werfen USA LLC, USA) used by the authors states that the test is sensitive to unfractionated heparin concentrations ranging from 1 to 6 U/ml. This means that a patient can still have "therapeutic" unfractionated heparin concentrations (*i.e.*, 0.3 to 0.7 U/ml) despite a normal activated clotting time. Therefore, an activated clotting time that has returned to the patient's baseline cannot be used to rule out clinically significant levels of unfractionated heparin.[3–5] Additionally, the sensitivity of the activated clotting time to residual heparin varies depending on the system used and should therefore be verified for each specific device and reagent.[6]

Other laboratory tests are more sensitive for assessing low concentrations of unfractionated heparin, *i.e.*, the activated partial thromboplastin time, the thrombin time, or the anti-Xa assay. These tests, which are performed with platelet-poor plasma obtained after centrifugation of whole blood, have a longer turnover time than the activated clotting time, around 30 min for an optimized laboratory.[7] However, they are useful in clinical practice for checking the complete reversal of unfractionated heparin in the workup of persistent bleeding despite normal activated clotting time. As the activated clotting time, the activated partial thromboplastin time uses a contact pathway activator, with a lower amount, to measure the time to inception of clotting and is sensitive to low coagulation factor levels. Because such factor deficiencies can prolong the activated partial thromboplastin time independently of residual heparin, this test is less appropriate than the thrombin time or the anti-Xa assay after CPB, particularly when surgery was prolonged and there is a risk of coagulopathy with low coagulation factor levels. In line with this, a previous study showed no correlation between activated partial thromboplastin time and residual heparin levels after cardiac surgery.[8] The thrombin time measures the conversion of fibrinogen to fibrin by an exogenous amount of added thrombin. This test is sensitive to the inhibition of thrombin by heparin–antithrombin complexes independently of the patient's coagulation factors level but is prolonged in case of hypofibrinogenemia.[9] Because it is highly sensitive to thrombin inhibitors, the thrombin time is useful for ruling out a residual unfractionated heparin, but not for its quantification.[10,11] In addition, the sensitivity of thrombin time to unfractionated heparin concentrations in the therapeutic range varies according to the reagent used.[12] Finally, the anti-Xa assay measures the inhibition of an exogenous amount of factor Xa added to the plasma sample by heparin–antithrombin complexes, independently of the patient's coagulation factor levels, and provides an estimate of heparin levels by prior calibration. Thus, the anti-Xa assay is the accepted standard to ensure adequate neutralization of unfractionated heparin and should be used in clinical trials, provided that the reagent does not contain dextran sulfate, which would displace heparin–protamine interactions *in vitro*.[13,14] Finally, it should be noted that the three tests are performed with plasma in the absence of platelets. This may lead to an overestimation of the heparin that is actually active *in vivo*, as platelets activated during the clotting process by generated thrombin release platelet factor 4, which neutralizes some of the heparin.[15]

Although the activated clotting time is the first-line test for checking the full neutralization of unfractionated heparin by protamine after cardiac surgery thanks to its short turnaround time, its sensitivity is insufficient to completely exclude residual heparin. More sensitive tests such as the anti-Xa assay or thrombin time are more appropriate for ensuring the absence of residual unfractionated heparin in cases of persistent microvascular bleeding after protamine administration despite an activated clotting time returned to its pre-CPB value, or as part of a research protocol.

Competing Interests

The authors declare no competing interests.

Michael Hardy, M.D., Ph.D.[1,2*]
Dominique Lasne, Prof.[3]
Maximilien Gourdin, Prof.[1,2,4]
Thomas Lecompte, Prof.[5,6]
Isabelle Gouin-Thibault, Prof.[7,8]
Francois Mullier, Prof.[1,2]
[1]Université catholique de Louvain, Louvain-la-Neuve, Belgium
[2]CHU UCL Namur, Yvoir, Belgium
[3]AP-HP, Hôpital Universitaire Necker-Enfants Malades, Paris, France
[4]University of Namur, Namur, Belgium
[5]University Hospital of Nancy, Nancy, France
[6]University of Lorraine, Nancy, France
[7]Pontchaillou University Hospital of Rennes, Rennes, France
[8]University of Rennes, IRSET-INSERM-1085, Rennes, France
*michael.hardy@uclouvain.be

DOI: 10.1097/ALN.0000000000005616

References

1. Jain P, Silva-De Las Salas A, Bedi K, Lamelas J, Epstein RH, Fabbro M II: Protamine dosing for heparin reversal after cardiopulmonary bypass: A double-blinded prospective randomized control trial comparing two strategies. Anesthesiology 2025; 142:98–106. doi:10.1097/ALN.0000000000005256
2. Bowers J, Ferguson JJ III: The use of activated clotting times to monitor heparin therapy during and after interventional procedures. Clin Cardiol 1994; 17:357–61. doi:10.1002/clc.4960170704
3. Magunia H, Schenk S, Schlensak C, et al.: Detection of early incomplete heparin reversal following congenital cardiac surgery: A single-center retrospective observational study. Thromb Res 2019; 182:33–8. doi:10.1016/j.thromres.2019.08.008
4. Tanaka KA, Thourani VH, Williams WH, et al.: Heparin anticoagulation in patients undergoing off-pump and on-pump coronary bypass surgery. J Anesth 2007; 21:297–303. doi:10.1007/s00540-007-0506-1
5. Taneja R, Szoke DJ, Hynes Z, Jones PM: Minimum protamine dose required to neutralize heparin in cardiac surgery: A single-centre, prospective, observational cohort study. Can J Anaesth 2023; 70:219–27. doi:10.1007/s12630-022-02364-4
6. Dirkmann D, Nagy E, Britten MW, Peters J: Point-of-care measurement of activated clotting time for cardiac surgery as measured by the Hemochron signature elite and the Abbott i-STAT: Agreement, concordance, and clinical reliability. BMC Anesthesiol 2019; 19:174. doi:10.1186/s12871-019-0846-z
7. Dincq AS, Lessire S, Pirard G, et al.: Reduction of the turn-around time for the measurement of rivaroxaban and apixaban: Assessment of the performance of a rapid centrifugation method. Int J Lab Hematol 2018; 40:e105–8. doi:10.1111/ijlh.12870
8. Taneja R, Marwaha G, Sinha P, et al.: Elevated activated partial thromboplastin time does not correlate with heparin rebound following cardiac surgery. Can J Anaesth 2009; 56:489–96. doi:10.1007/s12630-009-9098-6
9. Undas A: Determination of fibrinogen and thrombin time (TT). Methods Mol Biol 2017; 1646:105–10. doi:10.1007/978-1-4939-7196-1_8
10. LaDuca FM, Zucker ML, Walker CE: Assessing heparin neutralization following cardiac surgery: Sensitivity of thrombin time-based assays versus protamine titration methods. Perfusion 1999; 14:181–7. doi:10.1177/026765919901400305
11. Kortchinsky T, Vigué B, Samama CM: Reversal for heparins and new anticoagulant treatments. Ann Fr Anesth Reanim 2013; 32:37–49. doi:10.1016/j.annfar.2012.10.034
12. Flanders MM, Crist R, Rodgers GM: Comparison of five thrombin time reagents. Clin Chem 2003; 49:169–72. doi:10.1373/49.1.169
13. Hardy M, Cabo J, Deliege A, et al.: Reassessment of dextran sulfate in anti-Xa assay for unfractionated heparin laboratory monitoring. Res Pract Thromb Haemost 2023; 7:102257. doi:10.1016/j.rpth.2023.102257
14. Lasne D, Toussaint-Hacquard M, Delassasseigne C, et al.: Factors influencing anti-Xa assays: A multicenter prospective study in critically ill and non-critically ill patients receiving unfractionated heparin. Thromb Haemost 2023; 123:1105–15. doi:10.1055/s-0043-1770096
15. Gouin-Thibault I, Mansour A, Hardy M, et al.: Management of therapeutic-intensity unfractionated heparin: A narrative review on critical points. TH Open 2024; 8:e297–307. doi:10.1055/a-2359-0987

(Accepted for publication May 29, 2025.)

Minimal Protamine Dosing during Drug Shortages: Comment

To the Editor:

I read the article by Jain *et al.*[1] with interest. There have been new developments with both unfractionated heparin and protamine, and I hope this communication encourages further dialogue.

First, the authors imply that the protamine–heparin ratio is 1:1 (or 1:100). That these two ratios are synonymous with each other is a widely held belief and assertion. The 1:100 ratio assumes that 1 mg unfractionated heparin equals 100 U. However, recent developments indicate that each milligram of unfractionated heparin now contains not less than 180 U,[2] and this may come as a surprise to some. The question then arises whether anesthesiologists need to change their heparin dose the next time they need to administer it. *Per se*, this change in unfractionated heparin potency does not matter clinically since we have always referred to unfractionated heparin in units, not milligrams.[3] This is why unfractionated heparin vials from all manufacturers I am aware of do not contain any reference to unfractionated heparin in milligrams.

The authors also calculate the protamine–heparin ratio as "total mg of protamine per 100 U heparin administered before cardiopulmonary bypass (CPB)." To this end, one could argue not only the validity of the protamine–heparin ratio as has been traditionally accepted, but also that the protamine–heparin ratio incorporating the total dose of unfractionated heparin administered during surgery (rather than just the pre-CPB value) may be more reassuring. It might not be more informative in this study cohort with relatively short bypass times requiring low doses of unfractionated heparin on CPB but may be useful if anesthesiologists extrapolate the study data to other instances with longer CPB times.

Second, the authors are correct that protamine neutralization of just the initial dose of unfractionated heparin administered is based on an institutional culture, and not pharmacologic principles. It is quite possible that this historically just represents a very simplistic approach to not only homogenize but more importantly restrict the total dose of protamine on account of its anticoagulant potential. An interim announcement from the United States Pharmacopeia (Rockville, Maryland) on protamine indicates that each milligram of protamine neutralizes not less than 100 U unfractionated heparin.[4] Real-world data from various pharmaceuticals also suggest that different manufacturers report a wide range of its ability to neutralize unfractionated heparin; 1 mg protamine may neutralize anywhere from 66 to 144 U unfractionated heparin.[5]

This then highlights the age-old problem anesthesiologists encounter in the operating room routinely—it is unknown how much of the residual circulating unfractionated heparin needs neutralization at the termination of CPB, nor is there a clear understanding of how many unfractionated heparin units a particular dose of protamine dose will neutralize. Based on the information presented here, it is not unreasonable to start with a low dose of protamine initially, monitor the activated clotting time, and administer more protamine as needed to bring the activated clotting time back to baseline. How low one could go with the initial protamine dose still has to evaluated systematically, but there are limited data to date suggesting that protamine–heparin ratio can vary between patients.[6] Of course, activated clotting time may reflect adequate neutralization of anti-IIa levels (the accepted standard for quantifying unfractionated heparin activity),[2] but this perhaps needs validation in further studies conducted in different clinical settings. However, considering the data so far, it is quite possible that limiting the dose of protamine may not only help in the era of drug shortages but also be all that is required at the end of CPB.

Last, let us not forget the ubiquitous nature of "heparin rebound."[7,8] Exploration of how protamine dose in the operating room impacts further protamine and transfusion rates in critical care should be quantified in all trials exploring protamine–heparin interactions.

Research Support

Supported by grant No. S10–002 from the Academic Medical Organization of Southwestern Ontario (London, Canada).

Competing Interests

The author declares no competing interests.

Ravi Taneja, M.D.
London Health Sciences Centre, London, Canada
ravi.taneja@lhsc.on.ca

DOI: 10.1097/ALN.0000000000005618

References

1. Jain P, Silva-De Las Salas A, Bedi K, Lamelas J, Epstein RH, Fabbro M: Protamine dosing for heparin reversal following cardiopulmonary bypass: A double-blinded prospective randomized control trial comparing two strategies. Anesthesiology 2025; 142:98–106. doi:10.1097/ALN.0000000000005256
2. United States Pharmacopeia: Available at: https://www.nihs.go.jp/dbcb/Heparin/USP-heparin_Na.pdf. Accessed February 22, 2025.
3. Jerrold LH, Flood P, Rathmell JP, et al.: Anticoagulants, Stoelting's Pharmacology & Physiology in Anesthetic Practice, 5th edition. Philadelphia, Wolters Kluwer Health, 2015, pp 648
4. United States Pharmacopeia:Available at:https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/iras/protamine_sulfate_injection_2016-05.pdf. Accessed February 22, 2025.
5. Vandenheuvel M, Vandewiele K, De Somer F, Wouters PF: On the reporting of protamine dosage in cardiac surgery. J Cardiothorac Vasc Anesth 2024; 38:2123–5. doi:10.1053/j.jvca.2024.04.048
6. Taneja R, Szoke D, Hynes Z, et al.: Minimum protamine dose required to neutralize heparin in cardiac surgery: A single-centre, prospective, observational cohort study. Can J Anaesth 2023; 70:219–27. doi:10.1007/s12630-022-02364-4
7. Taneja R, Marwaha G, Sinha P, et al.: Elevated activated partial thromboplastin time does not correlate with heparin rebound following cardiac surgery. Can J Anaesth 2009; 56:489–96. doi:10.1007/s12630-009-9098-6
8. Teo K, Young E, Blackall M, Roberts R, et al.: Can extra protamine eliminate heparin rebound following cardiopulmonary bypass surgery? Thorac Cardiovasc Surg 2004; 128:211–9. doi:10.1016/j.jtcvs.2003.12.023

(Accepted for publication May 29, 2025.)

Minimal Protamine Dosing during Drug Shortages: Reply

In Reply:

Thank you for the opportunity to respond to the letters regarding our study.[1–3] We appreciate each of the authors' thoughtful comments.

As we noted in the Limitations section, the single-center, single-surgeon design may constrain the generalizability of our results.[4] Miles and Falter[1] highlight existing evidence and guidelines that support using lower heparin-to-protamine ratios (*i.e.*, less than 1 mg protamine per 100 U heparin). While we agree with this perspective, the primary objective of our study was not to evaluate heparin-to-protamine reversal ratios. Rather, we examined the use of a fixed-dose, single-vial protamine strategy in patients receiving large heparin doses as a response to national protamine shortages. Taneja further outlines many of the clinical and pharmacologic issues with ratio-based calculations, including variability in manufacturing practices.[3] This further emphasizes the need for practical conservation strategies, which our article supports in the studied patient population.

Our findings, alongside the evidence cited by Miles and Falter,[1] further support the safety and efficacy of a conservative protamine dosing approach. Notably, 25% of patients in our study received a heparin-to-protamine ratio less than 0.71, which is substantively lower than the dosing suggested in the referenced European guidelines. Those same guidelines also provide a Class I, Level A recommendation for activated clotting time–guided heparin management.[5] This is relevant to the concern raised about our use of activated clotting time as a primary endpoint by Hardy *et al.*,[2] as well as Miles and Falter.[1] Both letters underscore activated clotting time's imperfect correlation with heparin concentration during cardiopulmonary bypass and highlight more accurate tests such as the anti-Xa assay. However, activated clotting time remains the most widely used and accessible method for monitoring heparin effect and reversal in clinical practice.

With respect to concerns about the study being underpowered to detect differences in chest tube output, we emphasize that this was a secondary endpoint. The study was powered to assess differences in activated clotting time. The possibility of false-negative results (*i.e.*, type II errors) typically exists for secondary outcomes and suggests the need for a much larger study powered to detect these clinically relevant differences.

Regarding the commentary on the imprecision of fixed-dose protamine administration, as discussed in the viscoelastic testing–driven PRODOSE trial,[6] we commend Miles *et al.*, the authors of that important work, for their contributions to advancing coagulation management. However, we note that the recent multicenter FARES-II trial, published in the *Journal of the American Medical Association*, relied on point-of-care international normalized ratio testing to guide plasma and factor concentrate administration. This likely represents the limited availability of viscoelastic testing at many North American centers.[7] For this reason, we designed our study to be pragmatic and applicable to institutions with resource constraints and clinical workflows similar to our own.

We sincerely thank all the authors for their engagement with our work. It is through collegial dialogue such as this that we collectively advance the critical field of patient blood management.

Competing Interests

The authors declare no competing interests.

Michael Fabbro II, D.O.*
Pankaj Jain, M.D.
Richard H. Epstein, M.D.
Miller School of Medicine, University of Miami, Miami, Florida
*mxf790@med.miami.edu

DOI: 10.1097/ALN.0000000000005619

References

1. Miles LF, Falter F: Minimal protamine dosing during drug shortages: Comment. Anesthesiology 2025; 143:1127–8. doi:10.1097/aln.0000000000005615
2. Hardy M, Lasne D, Gourdin M, Lecompte T, Gouin-Thibault I, Mullier F: Minimal protamine dosing during drug shortages: Comment. Anesthesiology 2025; 143:1128–30. doi:10.1097/aln.0000000000005616
3. Taneja R: Minimal protamine dosing during drug shortages: Comment. Anesthesiology 2025; 143:1130–1. doi:10.1097/aln.0000000000005618
4. Jain P, Silva-De Las Salas A, Bedi K, Lamelas J, Epstein RH, Fabbro M: Protamine dosing for heparin reversal after cardiopulmonary bypass: A double-blinded prospective randomized control trial comparing two strategies. Anesthesiology 2024; 142:98–106. doi:10.1097/aln.0000000000005256
5. Casselman FP, Lance MD, Ahmed A, et al.: 2024 EACTS/EACTAIC guidelines on patient blood

management in adult cardiac surgery in collaboration with EBCP. Eur J Cardiothorac Surg 2024; 67:ezae352. doi:10.1093/ejcts/ezae352
6. Miles LF, Burt C, Arrowsmith J, et al.: Optimal protamine dosing after cardiopulmonary bypass: The PRODOSE adaptive randomised controlled trial. PLoS Med 2021; 18:e1003658. doi:10.1371/journal.pmed.1003658
7. Roytburd S, Shankar D, Bosch NA, Law A, Shi Z: Practice patterns of viscoelastic hemostasis testing use in US intensive care units: 2016-2022. Chest 2024; 166:A2151. doi:10.1016/j.chest.2024.06.1327

(Accepted for publication May 29, 2025.)

Race, Ethnicity, and Antiemetic Management: Comment

To the Editor:

We read with great interest the recent study by Goldson *et al.* titled "Does Management of Postoperative Nausea and Vomiting Differ by Patient Demographics? An Evaluation of Perioperative Anesthetic Management—An Observational Study."[1] The authors have made a valuable addition to the field by shedding light on differences in how postoperative nausea and vomiting (PONV) and postdischarge nausea and vomiting are handled across different demographic and socioeconomic groups. The findings highlight the essential need to address inequalities in surgical care related to the administration of antinausea medications.

The study offers key insights into demographic and socioeconomic differences, but we want to highlight hormone changes as another critical element for understanding PONV risk management. New research indicates that hormone shifts, like those tied to menstrual cycle stages and menopause status, play a big role in PONV likelihood.[2,3] For instance, premenopausal women experience higher PONV rates than postmenopausal women, and the luteal phase of the menstrual cycle seems to lower PONV risk compared to the follicular or ovulatory phases.[2,3]

Adding hormone-related factors to upcoming research might give us a better grasp on PONV risks and help customize strategies for managing patients before, during, and after surgery. For example, breaking down the data by menstrual cycle phase or whether someone has gone through menopause could uncover new differences or risk factors we are missing. This fits with the focus of the work by Goldson *et al.*[1] on using data segmentation as a method for identifying and addressing healthcare disparities. We applaud the researchers for their valuable work. We're hopeful that future studies will build on what they've found by looking into how demographic, socioeconomic, and biological factors work together to affect PONV risk and treatment.

Acknowledgment of AI Assistance

The manuscript was developed with the assistance of ChatGPT (OpenAI; USA). The AI tool was used for language refinement, grammatical corrections, and improvement of the clarity of the text. However, all conceptual development, data analysis, and interpretation were conducted by the authors.

Competing Interests

The authors declare no competing interests.

Mahmut Sami Tutar, M.D.*
Betul Kozanhan, M.D.
Munise Yildiz, M.D.
University of Health Sciences, Konya City Hospital, Konya, Turkey
*masatu42@gmail.com

DOI: 10.1097/ALN.0000000000005642

References

1. Goldson KV, Brennan E, Burton BN, et al.: Does management of postoperative nausea and vomiting differ by patient demographics? An evaluation of perioperative anesthetic management—An observational study. Anesthesiology 2025; 142:704–15. doi:10.1097/ALN.0000000000005367
2. Medina-Diaz-Cortés G, Brancaccio-Pérez IV, Esparza-Estrada I, et al.: Differences in postoperative pain, nausea, and vomiting after elective laparoscopic cholecystectomy in premenopausal and postmenopausal Mexican women. World J Surg 2022; 46:356–61. doi:10.1007/s00268-021-06367-y
3. Šimurina T, Mraovic B, Skitarelić N, Andabaka T, Sonicki Z: Influence of the menstrual cycle on the incidence of nausea and vomiting after laparoscopic gynecological surgery: A pilot study. J Clin Anesth 2012; 24:185–92. doi:10.1016/j.jclinane.2011.07.011

(Accepted for publication June 27, 2025.)