

Correspondence

To the Editor:

The recent report by Johnson et al. (1) concluded that the Hemochron® 8000 Rx/Dx system was not a justifiable improvement to patient management in light of the system cost. However, the conclusions must be viewed in light of the authors' assumptions, which may be inconsistent with current clinical practice.

Johnson et al. targeted a 480 second ACT and chose to initiate cardiopulmonary bypass (CPB) with a minimum ACT of 450 sec. As noted by Johnson, many clinicians use a 400 second ACT limit as the critical CPB value. In a multicenter study by Zucker et al. (1), the 400 sec critical value demonstrated accuracy of the HRT dosing test. Using a critical value of 400 sec, only 7 of the 56 patients (13%) required additional heparin prior to initiating CPB. This study employed unmatched heparin solutions and thus the predictive accuracy of the Rx/Dx system was not optimal.

Gravlee et al. (3) concluded that the Bull (4) recommended 480 sec target time is appropriate due to an ACT coefficient of variation of approximately 8% at clotting times above 400 sec. Assuming a normal distribution in clotting times, this suggests that the target ACT be set at least 16% (2 SD) above the critical clotting time. Thus, at 400 sec, the target should be at least 465 sec, but if 450 sec is the critical value, a target time of 520 sec is more appropriate. The Hemochron 8000 allows centers to set a customized target time. The expectation is that with proper target time selection, adequate anticoagulation is obtained 90% of the time. Many centers prefer the 520 sec target rather than the 480 sec target for optimal performance of the dosing system within the limits of accuracy of the ACT test.

Skewed objective and statistical parameters to evaluate the applicability of the Rx/Dx system is not unprecedented. A recent article by Clark et al. appearing in this journal compared the Medtronic HMS system, the HEMOCHRON Rx/Dx system, and empirical dosing. This study purported to claim that the HMS was "the most reliable predictor of heparin loading doses to reach a target ACT for cardiopulmonary bypass." The data presented, said to demonstrate a smaller post-heparin ACT standard deviation using the Medtronic HMS, only supported this claim in part. While the HMS standard deviation (105 sec at a mean post bolus ACT of 474 sec) was statistically lower than the empirical (135 sec at a mean post bolus of 487 sec), it was statistically indistinguishable from the Rx/Dx data (111 sec standard deviation at a mean post bolus ACT of 472 sec). The minor six second difference between the HMS and Rx/Dx systems translates to a 1.26% ACT difference at the post heparin bolus clotting time across the study population. Close examination of the histogram distribution of the three study groups, provided in the paper,

yields a significant observation. The HMS and Rx/Dx systems had an equivalent percentage of patients with post heparin ACTs of 400-500 sec (63.2% HMS versus 65.7% Rx/Dx), and the sole reason for the 1.26% standard deviation difference is a single Rx/Dx patient with a post-bolus ACT of greater than 900 sec. Such data cannot justify the conclusions drawn by the authors.

Together these papers demonstrate the need for authors, journal editors, and readers to carefully review data presentation and analysis before accepting conclusions. Failure to do so may result in inappropriate clinical use decisions based upon minimal data. The statistically demonstrated clinical utility of the Rx/Dx system [Jobes et al. (6); Delaria et al. (7)] must be viewed together with these current reports to describe the appropriate clinical application of in vitro dosing.

Sincerely,
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 Frank M. LaDuca, PhD
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1. Johnson HD, Morgan MS, Koenig GR, et al. Evaluation of the Hemochron 8000 Rx/Dx system for heparin management. *J Extra-Corpor Technol.* 1997; 29(2): 83-7.
2. Zucker ML, Barrett CL, Bennett K, LaDuca FM. Utility of in vitro heparin and protamine titration for dosing during cardiopulmonary bypass surgery. *J Extra-Corpor Technol.* 1997; 29(4): 176-180.
3. Gravlee GP, Haddon WS, Rothberger HK, et al. Heparin dosing and monitoring for cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1990; 99: 518-27.
4. Bull BS, Korpman RA, Huse WM, Braur FS. Heparin therapy during extracorporeal circulation. II: The use of a dose-response curve to individualize heparin and protamine dosage. *J Thorac Cardiovasc Surg.* 1975; 69: 685-9.
5. Clark TD, Ecklund J, McCall MM, Wolk DR, Riley JB. Comparison of three methods to estimate heparin loading dose for cardiopulmonary bypass. *J Extra-Corpor Technol.* 1996; 28(2): 67-70.
6. Jobes DR, Aitken GL, Shaffer GW. Increased accuracy and precision of heparin and protamine dosing reduces blood loss and transfusion in patients undergoing primary cardiac operations. *J Thorac Cardiovasc Surg.* 1995; 110: 36-45.
7. DeLaria GA, Tyner JJ, Hayer CL, Armstrong BW. Heparin-protamine mismatch: a controllable factor in bleeding after open heart surgery. *Arch Surg.* 1994; 129: 945-51.

To the Editor:

The letter from Dr. Marcia L. Zucker and Dr. Frank M. LaDuca concerning the article "Evaluation of the Hemochron 8000 Rx/Dx System for Heparin Management" has some validity. However, I must respectfully disagree with their statement that our assumption "may be inconsistent with current clinical practice".

Yes, there was a notation in the article that "many centers may choose to go with an ACT of 400 sec as acceptable to initiate cardiopulmonary bypass (CPB)." While that is what was said, we did NOT say that "many clinicians use a 400 sec ACT limit as the critical CPB value," as stated by Drs. Zucker and LaDuca. There is a slight difference... going on CPB with an ACT of 400 sec and maintaining an ACT of 400 sec are two different techniques. Going on with an ACT of 400 sec may frequently be done by the perfusionist, under the assumption (or hope), that the ACT will not stop at 401 sec!

Drs. Zucker and LaDuca explained very nicely normal distribution, along with 1 and 2 standard deviations of the 480 sec mark of the ACT. They went on to say that the "expectation is that with proper target time selection, adequate anticoagulation is obtained 90% of the time." This is exactly why we were anxious to evaluate the machine, in hopes that our first loading dose of heparin would result in an ACT of greater than 450 sec.

While we did choose an acceptable ACT of 450 sec, and not 400 sec, we did not state that we could condone the practice of maintaining an ACT of 400 sec. Further discussion was given to this..."we feel more comfortable with an ACT of 450 sec based on previous study slides showing gross deposits of platelets and fibrin on arterial filters at 400 sec, and much less of an effect was seen at 450 sec. Thus, we feel inclined to make every effort to have the ACT greater than 450 sec." If ITC condones the use of 400 sec, why then is it not put in as part of the software program (instead of 300 and 480 sec)?!

Again, we wanted to see if we could come up with better results in achieving an ACT greater than 450 sec after the first loading dose. Thirty-seven samples (patients) were compared (37 Rx/Dx, and 37 control patients); the Rx/Dx failed to get the ACT up to 480 sec in 62% of the patients, compared to our 30% with just our standard loading dose. While that was for 480 sec, what then can it do to achieve an ACT at other various levels (depending various acceptable levels for CPB, at different hospitals)? When trying to get the ACT over 450 sec (where we want it as an acceptable level to not have to give an additional dose of heparin) the Rx/Dx failed to get the ACT over 450 sec in 57% of the patients, compared to 22% in our standard loading dose population. If we say it only needs to get to 400 sec (for those that do use this endpoint), the Rx/Dx failed to get over 400 sec in 32% of the patients, and 8% in our standard loading dose population.

As you can see, our standard loading dose, while it did have cases where it did not get over 480, 450, or 400 sec, the number of times it did not get over those values was much more so in

the Rx/Dx system. How can we show those numbers to our administrators, and ask them to buy the machine?! Yes, I do agree with Drs. Zucker and LaDuca's statement, that the readers "need to carefully review data presentation and analysis before accepting conclusions." I agree so much so, that the statement was put into the article that "everyone should evaluate their own heparin dose protocol," and that "One must carefully evaluate the efficiency in every aspect of surgical technique and individual products...." We even noted that if the standard heparin loading dose of 300 IU/kg had been used (rather than our standard dose of 400 IU/kg), the numbers could possibly have been different (which could make the Rx/Dx look better). However, we don't use 300 IU/kg, and our loading dose resulted in fewer patients needing extra heparin before initiating CPB.

I feel the numbers in our study were complete. The machine calculated the heparin dose and gave us an ending ACT. Again, the failure rates were: did not get up to 480 sec in 62% (30% with our control), did not get over 450 sec in 57% (22% with our control), and did not get over 400 sec in 32% (8% with our control). While the "Hemochron 8000 allows centers to set a customized target time," the "expectation is that with proper target time selection, adequate anticoagulation is obtained 90% of the time" (as stated by Drs. Zucker and LaDuca with ITC). Our results show that this is a far cry from the 90% of adequate anticoagulation, at any desired level (480, 450, or even 400 sec). Therefore, we cannot justify this machine to our surgeons and/or administrators.

The whole purpose of scientific study is to see if the results are reproducible, and to validate the results. While we could not obtain the results ITC would have liked, obviously others have, and possibly others yet will in the future, and we certainly hope so. We would love to see refinements and advances in our perfusion technology. Thank you.

Sincerely,
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