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HAEMATOLOGY

The accuracy of a point of care measurement of activated partial thromboplastin time in intensive care patients

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Summary

Point of care (POC) devices are increasingly being used in intensive care units to obtain faster results. Data are limited on the performance of these devices in critically ill patients, especially those on heparin infusion. The objective of this study was to assess the agreement between POC activated partial thromboplastin time (APTT) and laboratory APTT results in patients on heparin infusion and to determine its impact on the clinical decisions regarding heparin dosage.

We screened all patients admitted to the intensive care unit (ICU) at St George Hospital, Sydney, over a 7-month period and enrolled those who were receiving intravenous heparin infusion. We measured APTT by two methods: bedside POC test (Hemochron Junior Signature Plus) and central laboratory method (STA analyser). We used the Bland–Altman method to test the statistical agreement between the two measurements and Cohen's kappa statistic to test the clinical agreement regarding heparin dosing decision.

A total of 176 paired samples from 44 patients (mean age 63 years, 64% males, mean APACHE 18) were analysed. The mean turnaround time for the point of care APTT result was significantly shorter than the central laboratory result (5.0±0.2 min vs 64.6±2.7 min, $p<0.0001$). Despite the statistically significant correlation, the overall agreement tested by the Bland–Altman method was poor. The 95% limits of agreement were widest (−27.266 to 64.791) and mean percentage bias was highest (24%) for the comparison between POC APTT using citrated blood and laboratory APTT. When POC APTT results of less than 90 seconds using whole blood were compared to laboratory APTT results, the limits of the agreement became narrower (−23.243 to 28.419), and the mean percentage bias decreased to 5%. The agreement between clinical decisions regarding heparin dosage based on the two methods was poor for plain and citrated blood (kappa 0.35 and 0.11, respectively).

The POC APTT results were not sufficiently accurate for use in patients on heparin infusion compared to laboratory APTT assay.

Key words: Point of care test; activated partial thromboplastin time; Hemochron Junior; intensive care patients; heparin infusion.

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INTRODUCTION

Monitoring of coagulation in high-risk patients on heparin infusion in intensive care unit (ICU) patients is a critical aspect of patient care. Activated clotting time (ACT), activated partial thromboplastin time (APTT), and prothrombin time (PT) are still the primary parameters for monitoring coagulation in the intensive care setting.[1]

There are delays encountered in the processing and reporting of the APTT samples by the hospital laboratory.[2] Therefore, it is essential to generate quick results to adjust heparin dosing and deliver optimal care to the patient. The point of care (POC) monitoring system of APTT is a new approach to optimise anticoagulation therapy in these patients. It requires only a small amount of blood when compared to laboratory testing. Furthermore, it provides immediate results allowing for rapid intervention in cases where the risk of bleeding is high.

Data on the accuracy of the POC device in critically unwell patients receiving heparin anticoagulation is limited. The use of a point of care system if found to be accurate, will help to adjust heparin dosing quickly and may improve patient care by optimising efficiency and permitting more timely and accurate clinical decision-making. Therefore, we conducted this study to assess the agreement between POC APTT and laboratory APTT results in patients on intravenous heparin infusion and to determine its impact on the clinical decisions regarding heparin dosage. We hypothesised that the two methods would produce similar APTT results.

METHODS

We conducted this prospective observational study in our ICU at St George Hospital, Sydney, Australia. The study was conducted over 7 months from February 2018 to August 2018. The study was approved by the hospital ethics committee. The need for patient consent was waived since the study was a quality improvement program.

We included all patients above the age of 18 years admitted to ICU who were receiving intravenous heparin infusion. Patients receiving any other type of anticoagulants were excluded. The treating clinician was responsible for determining the target APTT. The dose of heparin was adjusted according to laboratory APTT results.

Blood samples were collected by venepuncture, or from an existing indwelling arterial catheter or central venous cannula. We measured the APTT by two methods: (1) central laboratory method, and (2) bedside POC method.

POC APTT results can be obtained from the Hemochron Junior Signature Plus (International Technidyne Corporation, USA) using whole blood or citrated blood and different cuvettes for each. We performed the following

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three comparisons: (1) POC APTT (whole blood) versus laboratory APTT, (2) POC APTT (citrated blood) versus laboratory APTT, and (3) POC APTT (whole blood) versus laboratory APTT where POC APTT was less than 90 seconds.

Central laboratory method

We collected 4 mL of blood in vacutainers containing 3.2% trisodium citrate (0.109 M) and noted the collection time. The sample was sent to the central laboratory by a vacuum delivery system located in ICU. The sample was centrifuged, and the APTT was measured from the platelet poor plasma using a STA analyser (Stago International, France). The laboratory measures whole blood APTT time in approximately 4 minutes. The results were calibrated and maintained as per manufacturer standards and were entered into the hospital electronic medical record by laboratory personnel.

Bedside point of care method

For whole blood, we used a single drop of whole blood from the sample drawn from the patient for the central laboratory test before adding to the vacutainer, to measure APTT with the Hemochron Junior Signature Plus device. The plain cuvette was used to obtain these POC results.

For citrated blood, we aspirated a single drop of blood from the vacutainer (containing citrate) collected for the central laboratory test and used it in the Hemochron Junior Signature Plus device. The citrate cuvette was used to obtain these POC results.

The Hemochron Junior Signature Plus device was tested for quality control processes, and the tests were performed according to the manufacturer's recommendations. Only trained researchers performed APTT by the POC device. The system measures APTT using disposable single-use cuvettes. The cuvette contains reagents which mix with added blood sample to form clots. The time elapsed between the start of the test and clot formation is detected by optical detectors and the result is displayed on the screen. The APTT tests were performed at regular intervals as per unit protocol and as directed by the treating clinicians.

We collected the following data: age, sex, indication for heparin infusion, body weight, the severity of illness score (APACHE II and III), APTT by laboratory method, APTT by POC method and turnaround time for both methods.

Statistical analysis

We expressed the continuous variables as mean ± SD and categorical variables as proportions. We used an unpaired t-test to compare the turnaround time for POC APTT and laboratory APTT. We used the Bland–Altman method to determine the agreement between lab APTT and bedside APTT.[3] The association between POC APTT and mean percentage bias was analysed using simple linear regression. Cohen's kappa statistics were used to check the agreement between clinical decisions regarding the change in heparin dose based on APTT by two methods.[4,5] All statistical analyses were performed using Stata v14.2 (StataCorp, USA).

RESULTS

A total of 183 paired measurements were performed from blood samples collected from 44 patients on a heparin infusion. Four sample results were excluded from data analysis as being outside the range. The mean age of the patients was 63 years, 64% were males and mean APACHE II was 18 (Table 1). The main indication for the use of therapeutic anticoagulation with heparin infusion were pulmonary embolism and atrial fibrillation (Table 2). The mean turnaround time for the POC device APTT results was significantly shorter than the central laboratory results (5.0 ± 0.2 min vs 64.6 ± 2.7 min, $p<0.0001$).

Figures 1–6 show correlation and Bland–Altman plots. There was a moderate correlation between the APTT results by two methods (Fig. 1, 3 and 5, and Table 3). Despite the statistically significant correlation for all three comparisons, the overall agreement tested by the Bland–Altman method was poor. The 95% limits of agreement were widest (−27.266 to 64.791) and mean percentage bias was highest (24%) for the comparison between POC APTT using citrated blood and laboratory APTT. When POC APTT results of less than 90 seconds using whole blood were compared to laboratory APTT results, the limits of the agreement became narrower (−23.243 to 28.419), and the mean percentage bias decreased to 5% (Fig. 2, 4 and 6, and Table 4).

Figure 7 shows that for every 10 second increase in POC APTT using whole blood, the mean percentage bias increases by 4% [95% confidence interval (CI) 2.3%–5.4%, $p<0.001$]. This suggests that there is better agreement between the two methods for APTT values of less than 90 seconds when the whole blood is used for POC testing.

Agreement between clinical decisions based on the two methods

To assess the clinical impact of these differences, we analysed the number of POC APTT measurements (using whole blood and citrated blood) that would result in a change in heparin dosage when compared to the laboratory APTT measurements. For this analysis, we used the hospital protocol for therapeutic anticoagulation with heparin.

There was an agreement regarding heparin dosage in 144 of 176 measurements (κ=0.35). The discrepancies between POC APTT using whole blood and laboratory APTT was large enough to result in inadequate heparin dosing in 23 of 176 (13%) samples and excess heparin dosing in nine of 176 (5.1%) samples (Table 5).

There was an agreement regarding heparin dosage in 45 of 73 measurements (κ=0.11). The discrepancies between POC APTT using citrated blood and laboratory APTT was large enough to result in inadequate heparin dosing for 28 of 73

Table 1 Patient characteristics

Variables	All patients (n=44)
Males	28 (64%)
Age, years	63 ± 16
Weight, kg	82.9 ± 20
APACHE III	66.5 ± 20.8
APACHE II	18 ± 5.97

Table 2 Indications for heparin infusion (n=44)

Clinical condition	Patients, n
Pulmonary embolism (acute and chronic)	15
Atrial fibrillation	8
Deep vein thrombosis	2
Metallic valve	1
Myocardial ischaemia	2
Haemodialysis (CRRT)	3
Extracorporeal membrane oxygenation	2
Ischaemic limb	2
Temporary pacemaker	1
Miscellaneous indication (central line in carotid artery, flap thrombosis, SMV thrombosis, carotid artery dissection)	6
Cerebral venous thrombosis	2

CRRT, continuous renal replacement therapy; SMV, superior mesenteric vein.

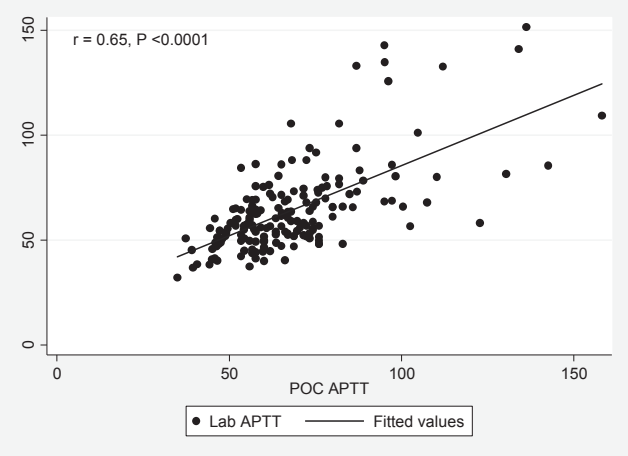

Fig. 1 Correlation between POC APTT using whole blood and laboratory APTT.

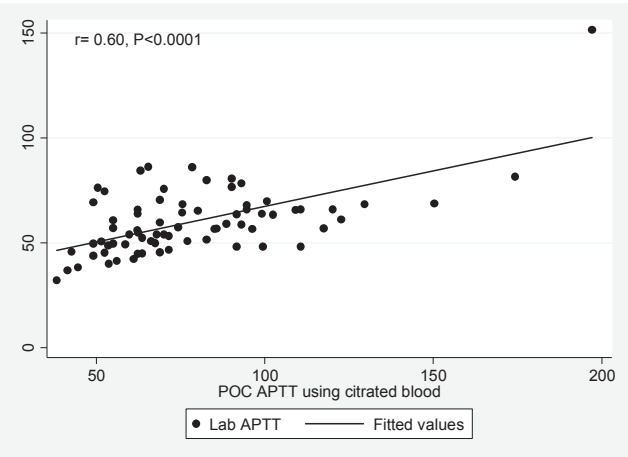

Fig. 2 Correlation between POC APTT using citrated blood and laboratory APTT.

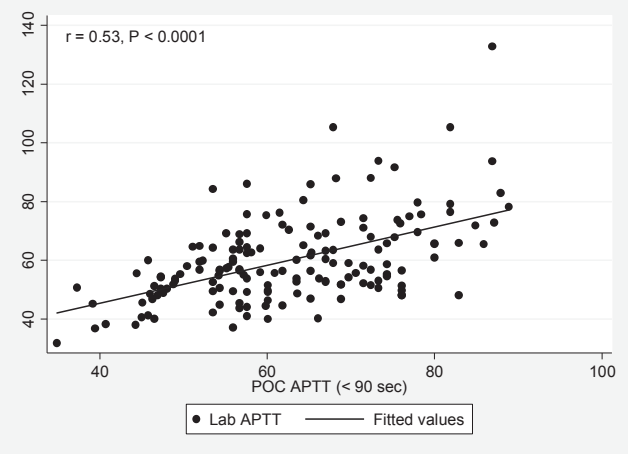

Fig. 3 Correlation between POC APTT (<90 s) using whole blood and laboratory APTT.

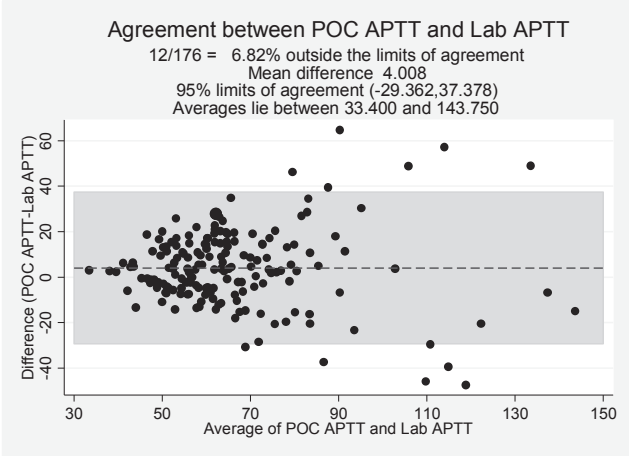

Fig. 4 Bland–Altman plot: POC APTT using whole blood vs laboratory APTT.

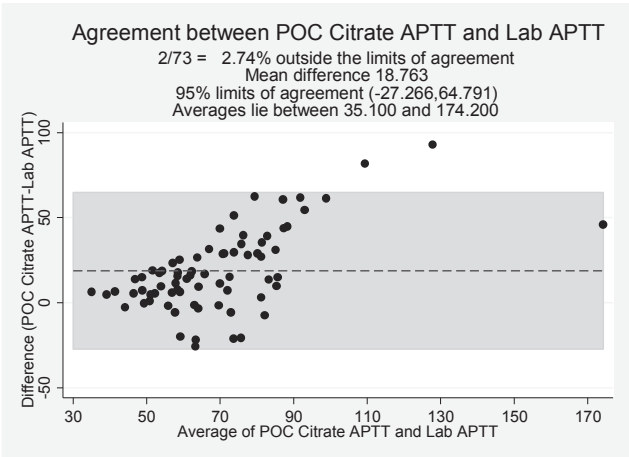

Fig. 5 Bland–Altman plot: POC APTT using citrated blood vs laboratory APTT.

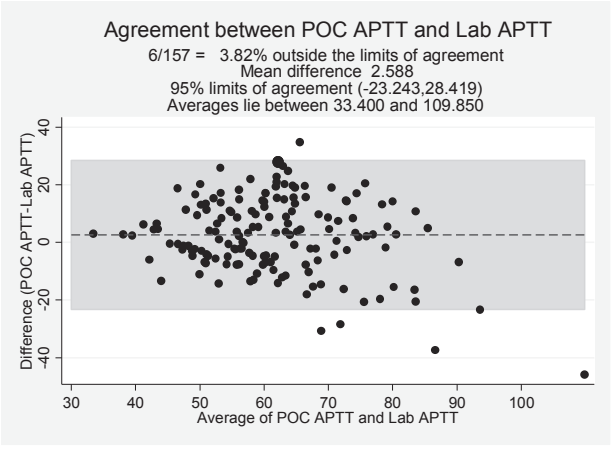

Fig. 6 Bland–Altman plot: POC APTT (<90 s) using whole blood vs laboratory APTT.

Table 3 Correlation between APTT results by two methods

Comparison	*n*	Correlation coefficient (*r*)	*p*
POC APTT using whole blood vs Lab APTT	176	0.65	<0.0001
POC APTT using citrated blood vs Lab APTT	73	0.60	<0.0001
POC APTT (<90 s) using whole blood vs Lab APTT	157	0.53	<0.0001

APTT, activated partial thromboplastin time; POC, point of care.

Table 4 Agreement between the APTT results by two methods

	n	95% Limits of agreement		Mean difference	Mean % bias
		Lower	Upper		
POC APTT using whole blood vs Lab APTT	176	−29.362	37.378	4.008	6.4
POC APTT using citrated blood vs Lab APTT	73	−27.266	64.791	18.763	24.0
POC APTT (<90 s) using whole blood vs Lab APTT	157	−23.243	28.419	2.588	5.0

APTT, activated partial thromboplastin time; POC, point of care.

(38.4%) samples and excess heparin dosing in 1 of 73 (1.4%) samples (Table 6).

DISCUSSION

Statement of principal findings

Despite faster turnaround time, the agreement between the APTT results by two methods was poor. Limits of agreements were wider, and the bias was higher with citrated blood POC APTT than with whole blood POC APTT. The agreement was better with POC APTT values of less than 90 seconds, and the bias increased with increasing values of POC APTT.

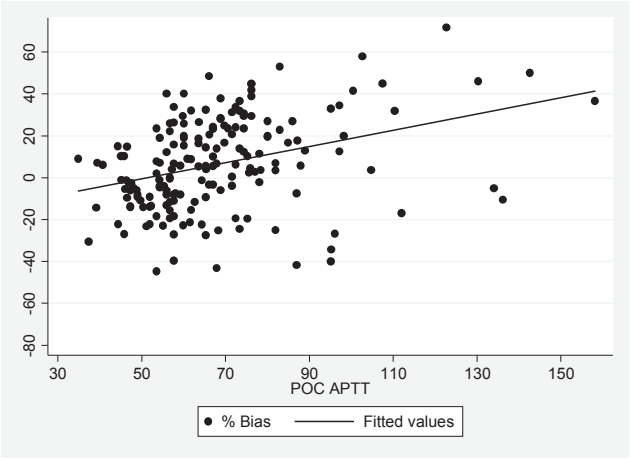

Fig. 7 Scatter plot: percentage bias vs POC APTT using whole blood (*n*=176).

Comparison with previous studies

Several studies have reported on the accuracy of POC test compared to the laboratory test. These studies used different POC devices (Hemochron 801, Hemochron Junior, Hemochron Response, Hemochron Signature Elite, etc.), and had different case mixes (ICU or non-ICU patients) with or without therapeutic anticoagulation using intravenous heparin infusion (Table 7). All of these studies had a wide range of limits of agreement and varying degrees of bias, which ranged from −8% to 15%. We used Hemochron Junior Signature Plus device in ICU patients who were on an intravenous heparin infusion. Therefore it is difficult to compare the results of our study with those of previous studies.

The data on the accuracy of the POC devices shows conflicting results. In a few studies carried out to validate different portable devices, the accuracy levels of POC tests were considered clinically acceptable.[1,6,7] On the other hand, some authors reported problems regarding the reliability of test results, pointing to the need for better calibration and use of external quality controls.[2,8,9]

Table 5 Clinical decision regarding heparin dose (POC APTT using whole blood vs laboratory APTT)

APTT POC whole blood results	APTT laboratory results			
	Heparin dose↓	No change	Heparin dose↑	Total
Heparin dose↓	8	11[a]	0	19
No change	6[b]	132	12[a]	150
Heparin dose↑	0	3[b]	4	7
Total	14	146	16	176

Kappa = 0.35.
APTT, activated partial thromboplastin time; POC, point of care.
[a] Inadequate heparin dosing on 23 occasions if APTT POC whole blood results were to be used.
[b] Excess heparin dosing on 9 occasions if APTT POC whole blood results were to be used.

Table 6 The clinical decision regarding heparin dose (POC APTT using citrated blood vs laboratory APTT)

APTT POC citrate blood results	APTT laboratory results			
	Heparin dose↓	No change	Heparin dose↑	Total
Heparin dose↓	1	22[a]	0	23
No change	0[b]	40	6[a]	46
Heparin dose↑	0	1[b]	3	4
Total	1	63	9	73

Kappa = 0.11.
APTT, activated partial thromboplastin time; POC, point of care.
[a] Inadequate heparin dosing on 28 occasions if APTT POC citrate blood results were to be used.
[b] Excess heparin dosing on one occasion if APTT POC citrate blood results were to be used.

Table 7 Comparison with previous studies

Author	Reich *et al.*[2]	Fitch *et al.*[14]	Douglas *et al.*[15]	Kok *et al.*[9]	Our study
Year	1993	1999	2009	2015	2018
Country/site	USA	USA	UK	Australia	Australia
Device	Hemochron 801	Hemochron Jr	Hemochron response	Hemochron Signature Elite	Hemochron Jr Signature Plus
Type of sample	Whole blood	Whole blood	Whole blood	Whole blood	Whole/citrated blood
No. of samples	76	65	39	28	176/73
Type of patients	Post-op CABG patients	CABG and vascular patients	Vascular surgical patients	Medical and surgical ICU patients	ICU patients
Heparin anticoagulation	No	No	Yes	No	Yes
Percentage bias	−8	5.5	15.2	4.11	6.4
Upper limit of agreement	3	8.7	58.2	42.13	−37.4
Lower limit of agreement	−19	2.3	−19.1	−33.91	−29.4
Conclusion	Not accurate	Accurate	Not accurate	Not accurate	Not accurate

CABG, coronary artery bypass grafting; ICU, intensive care unit.

In Australia, the magnitude of acceptable bias to determine if a POC device is accurate and therefore fit for purpose has not been defined. Evaluation of POC devices against an established reference method requires the testing of at least 40 samples covering a clinically meaningful range of the measurand, construction of a Bland–Altman plot and performance of a regression analysis of the results.[10] The Royal College of Pathologists of Australasia Quality Assurance Program (RCPAQAP) defines the allowable limits of performance for laboratory analysers,[11] but this does not specifically apply to POC devices. By contrast, acceptable performance limits for some measurands per the United Kingdom National External Quality Assessment Service (UK NEQAS) and United States Clinical Laboratory Improvement Amendments (CLIA) require that all results should be within 10–15% compared to the reference measurement.[12] An acceptable bias was defined as <10% between the measurements obtained by the POC device compared to the reference method in a study by Kok *et al.*[9]

The data on the performance of the Hemochron Junior Signature Plus device in critically ill patients is limited. Our study is the first to evaluate the accuracy of POC APTT in ICU patients on an intravenous heparin infusion. Our results showed acceptable bias when APTT POC using whole blood was compared to laboratory measurement. However, APTT POC using citrate blood showed a much higher bias.

Evaluations of POC devices should not necessarily be based on absolute values of the measurands but the clinical impact of the magnitude of the observed differences, as the methods that use percentage differences alone to assess agreement have been shown to correspond poorly with clinical decision-making.[13] Therefore, we looked at the clinical impact of the two measurements on heparin dosing. The results showed that adjusting the heparin dose based on POC APTT measurement would result in more patients receiving inadequate dosing than excess dosing.

The inadequate sample collection or management of the sample in the device may produce different results. We do not believe this was the case in our study as it was carried out by trained professionals to reduce the likelihood of errors during the pre-analytical phase.

Our results are consistent with the study by Kok *et al.*[9] which showed a lack of agreement between the Hemochron Signature Elite APTT results and laboratory measurement. Two other studies both in cardiac surgical patients[2,14] have also concluded that POC APTT results are not accurate. On the contrary, Fitch *et al.*[14] showed a significant correlation in data obtained using Hemochron Junior and standard laboratory for prothrombin time, international normalised ratio and APTT values in patients undergoing cardiovascular surgery. The disagreement in results between the two methods may be due to different

principles involved in the detection of time to clot (photoelectric versus viscoelasticity).

Our finding of significantly shorter turnaround time for the POC APTT test is consistent with previous studies.[7,14] These findings reinforce the fact that a central laboratory test is not suitable for quick APTT measurement.

Strengths and limitations

Our study has several strengths. We analysed a large number of samples, far more than the minimum recommended sample size of 40. The study was run by trained operators who had received one to one training from a company representative. We also looked at the clinical impact of using POC APTT results on heparin dosing. Our study is not without limitations. It was an observational study done in a single centre. Patients who were not on heparin infusion were not included.

Implications for future research

The accuracy of POC APTT results in patients not on heparin anticoagulation needs to be investigated. Future studies need to establish an APTT range over which the two results agree. The newer generation of POC devices coming into the market should be evaluated for their accuracy prior to their use.

CONCLUSION

The POC APTT test generates a faster result compared to the standard laboratory test. However, the results are not sufficiently accurate for use in critically ill patients on a heparin infusion. The risk of inadequate anticoagulation is high if the POC APTT result is used to titrate heparin infusion.

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