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The use of activated partial thromboplastin time versus antifactor Xa assay in monitoring continuous unfractionated heparin infusion therapy in obstetric intensive care unit

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Abstract

Background: Unfractionated heparin (UFH) infusion therapy needs accurate tight control to prevent overanticoagulation that may result in hemorrhagic complications and also to prevent sub therapeutic level that may result in thrombotic complications. The aim of this study was to compare the most popular monitoring tool activated aPTT versus antifactor Xa to reach accurate monitor to UFH therapy in critically ill pregnant females.

Results: Time to reach therapeutic level as well as total heparin dose required to reach this therapeutic level were much lower in the anti-Xa group when compared to aPTT group.

Conclusion: The use of anti-Xa-based protocol to monitor UFH infusion therapy resulted in better therapeutic control as it resulted in earlier achievement of therapeutic level and lower heparin dose requitments.

Keywords: Unfractionated heparin, Antifactor Xa, Activated partial thromboplastin time, Pregnancy

Background

Anticoagulation is required during pregnancy and/or postpartum period for prophylactic and treatment of deep vein thrombosis, females with prosthetic heart valves, cerebral venous sinus thrombosis, atrial fibrillation, and some patients with fetal losses (Bauer 2016).

Unfractionated heparin (UFH) is an acceptable alternative to low-molecular weight heparin (LMWH) and less expensive (Bauer 2016; Casele 2006). It may be more appropriate during stages of the pregnancy when rapid temporal control of anticoagulation is required (e.g., near the time of delivery, if surgery is required) especially in critical care settings and it is the preferred agent for patients with severe renal insufficiency (e.g., creatinine clearance ≤ 30 mL/min). It does not cross the placenta and no harmful effects on the fetus were detected (Howie 1986; Rutherford and Phelan 1986; Ginsberg et al. 1989).

However, the anticoagulant properties of UFH vary among patients as well as pregnant patients, as a consequence of the binding of UFH to various plasma proteins (Hylek et al. 2003). Studies demonstrated that the pharmacokinetics of UFH is different in pregnancy and that higher and possibly more frequent dosing is needed (Brancazio et al. 1995; Barbour et al. 1995). Due to the unpredictable anticoagulant response among patients given UFH, close monitoring is required (Caprini et al. 2005).

The most common two laboratory tests used to monitor UFH are the activated partial thromboplastin time (aPTT) and antifactor Xa (anti-Xa) analysis (Tahir 2007; Francis et al. 2004).

The aPTT is the most widely used test to determine the degree of anticoagulation with UFH when usual therapeutic doses are used. It is inexpensive, automated, and usually available 24 h a day (Olson et al. 1998). However, the aPTT test is also affected by numerous pre-analytic and analytic variables making the clinical validity of the test questionable (Eikelboom and Hirsh 2006).

Anti-Xa effect monitoring has been suggested as an alternative to the aPTT because the assay is based on

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enzymatic inhibition (Vandiver and Vondracek 2012), thus reflects the UFH activity more directly than the aPTT. It demonstrates less variability and exhibits minimal interference from the presence of biological factors, such as acute phase reactants (Rosenberg et al. 2010), and drawbacks of this assay are its relative high cost and limited availability. Barbour et al. (Barbour et al. 1995) study suggested that ideally anti-Xa levels should be used to monitor thromboprophylaxis with UFH in pregnancy.

The aim of this study is to compare the aPTT versus anti-Xa assay in monitoring continuous UFH infusion therapy in critically ill obstetric patients as monitoring in such group is considered challenging due to the physiological changes, the hypercoagulable state, and the critical illness per se.

Methods

After obtaining the approval of research ethical committee of Faculty of Medicine, Ain Shams University and informed consent from patients and/or her first degree relatives, this prospective, randomized observational study was conducted at Ain Shams University gynecology and obstetrics hospital in the obstetric intensive care unit (ICU) from January 2014 to January 2016.

One hundred patients were enrolled in this study and they were randomly assigned into one of two equal groups using a computer-generated random number table and sealed opaque envelops:

- Group P ($n = 50$): where aPTT was used for controlling heparin infusion therapy.
- Group X ($n = 50$): where anti-Xa assay was used for controlling heparin infusion therapy.

Inclusion criteria included nulliparous or multiparous females with single intrauterine pregnancies, aged 18–45 years in the antepartum or immediately postpartum period while *exclusion criteria* included age less than 18 years or more than 45 years, platelet count less than 50,000/mm^3, UFH infusion therapy for less than 24 h, and heparin resistance defined as the need for more than 35,000 units per day without reaching therapeutic level of anticoagulation as assessed by aPTT and anti-Xa assays.

All patients enrolled in our study received loading dose of heparin in a dose of 80 IU/kg that was followed by infusion rate of 18 IU/kg/h (Bergqvist et al. 1983). All doses and rates were calculated based on total body weight (TBW), except for patients weighing more than 125 kg; adjusted body weight (ABW) [ideal body weight (IBW) plus 40% of the difference between TBW and IBW)] was used in that population (Khan et al. 2005).

The aPTT and anti-Xa assay results were collected at 6-h intervals after initiation and subsequent rate adjustments until therapeutic anticoagulation was achieved. For aPTT, a therapeutic range of 1.5 to 2.5 times the control value and for anti-Xa activity therapeutic range is 0.3–0.7 IU/mL for UFH is accepted (Basu et al. 1972; Chiu et al. 1977).

According to the test results, the infusions adjusted to the following weight-based heparin dosing nomograms used in obstetric ICU Ain Shams University which are based on the previously published guidelines of clinical practice with some modifications (Raschke et al. 1993; Smith and Wheeler 2010).

In group P, the following weight-based nomogram was used (Table 1) While in group X, the following weight-based nomogram was used (Table 2):

While in group X, the following nomogram was followed (Table 2):

Patients were observed over the period of the study for development of minor or major hemorrhage. Major hemorrhage was defined as overt bleeding with either hemodynamic instability, decrease in the hemoglobin ≥ 2 g/dl, need for transfusion of ≥ 2 units of blood, need of surgical intervention, development of retroperitoneal hematoma, or development of intracranial hemorrhage. Minor hemorrhage was defined as overt bleeding but without other criteria mentioned previously (Hull et al. 1986).
Also, they were observed for the development of heparin-induced thrombocytopenia (HIT). HIT was defined as an absolute drop in the platelet count less than 150,000 mm^3 or a relative decrease of 30% from the baseline count after exclusion of other causes of thrombocytopenia (Greinacher et al. 2005).

All patients enrolled had demographic information including age, weight, and indications for UFH, the total dose of heparin were calculated. The primary endpoint of the study was number and percentage of patients who reached therapeutic level in each group. Secondary endpoints of the study were the development of heparin-induced adverse effects as hemorrhage or heparin-induced thrombocytopenia.

Table 1 Weight-based nomogram for continuous intra-vascular UFH infusion

aPTT	Dose adjustment
Less than 35 s	80 U/kg re-bolus and increase infusion rate by 4 U/kg/h
35–49 s	40 U/kg re-bolus and increase rate by 2 U/kg/h
50–70 s	No change
71–90 s	Decrease infusion rate by 2 U/kg/h
More than 90 s	Hold infusion for 1 h and decrease infusion rate by 4 U/kg/h

Table 2 Weight-based nomogram for continuous intra-vascular UFH infusion

Anti-Xa	Dose adjustment
Less than 0.2	80 U/kg re-bolus and increase infusion rate by 4 U/kg/h
0.2–0.29	40 U/kg re-bolus and increase rate by 2 U/kg/h
0.3–0.7	No change
0.7–0.9	Decrease infusion rate by 2 U/kg/h
More than 0.9	Hold infusion for 1 h and decrease infusion rate by 4 U/kg/h

Statistical analysis

Sample size calculation Epinfo version 6 guided by the following data: power of the test 80%, confidence level 95%, alpha error 5%, risk ratio 2, odds ratio 3.5, and total sample 100 on 2 equal groups. Statistical analysis was performed using a standard SPSS software package version 17 (Chicago, IL). Data were expressed as mean values ± SD, numbers (%). Student's t test was used to analyze the parametric data, and discrete (categorical) variables were analyzed using the χ^2 test, with p values < 0.05 considered statistically significant.

Results

Both groups were comparable regarding age, weight, and indications for UFH at time of admission to the intensive care unit. No statistically significant differences between the two groups were found as shown in Table 3.

Baseline platelet count showed no significant difference between the two groups as shown in Table 4. Baseline platelet functions and kidney functions showed no abnormalities in both groups.

The number (and percentage) of patients who reached therapeutic level was higher in group X (where anti-Xa was used in heparin monitoring) than in group P (where aPTT was used in heparin monitoring) during the first 12 and 24 h of therapy (76% vs. 46%, $p = 0.007$), (88% vs. 70%, $p = 0.045$) respectively. After 36 h of heparin therapy, patients who reached therapeutic level in group X were still higher than group P, but this was not statistically significant (100% vs. 96%, $p = 0.25$). After 48 h, all patients in both groups reached therapeutic level as shown in Table 5 and Fig. 1.

Total heparin dose required to reach this therapeutic level was significantly lower in group X when compared with that in group P at 12-, 24-, 36-, and 48-h interval (Table 6).

Regarding heparin-related adverse effects, no cases of minor or major hemorrhage reported in either group over the period of the study. Also, heparin-induced thrombocytopenia was not observed in either group. Table 4 shows platelet count at 24 h and at 48 h from time of initiation of the heparin treatment.

Table 3 Comparison between the two groups as regards the age (in years), weight (in kilograms), and indication for UFH (in numbers)

Parameter	Group P ($n = 50$)	Group X ($n = 50$)	p value
Age (years)	26.65 ± 4.5	24.84 ± 3.4	0.4776
Weight (kg)	83.2 ± 6.7	83.2 ± 8.6	0.98
Indications for UFH:			
Valvular heart disease	22	24	0.5277
Atrial fibrillation	17	16	0.4807
Anti-phospholipid syndrome	7	4	0.3305
Venous thromboembolism	4	6	0.625

Data presented as mean ± SD and numbers as appropriate, p value < 0.05 was considered statistically significant

Table 4 Comparison between the two groups as regards the platelet count

Time	Group P ($n = 50$)	Group X ($n = 50$)	p value
Baseline	249.6 ± 31.6	259.9 ± 35.35	0.98
At 24 h	233.5 ± 21.77	236.2 ± 23	0.54
At 48 h	216.93 ± 20.6	213.6 ± 16.3	0.38

Data presented as mean ± SD, p value < 0.05 was considered statistically significant

Discussion

The current study showed that the use of antifactor Xa heparin assay in monitoring of unfractionated heparin intravenous infusion resulted in faster achievement of therapeutic levels and lower doses of heparin required when compared to the use of PTT.

The balance of under- and overanticoagulation requires strict laboratory monitoring to ensure therapeutic dosing especially in vulnerable group of critically ill pregnant females. Physiological changes of pregnancy such as increased plasma volume, production of placental heparinase, and increased glomerular filtration rate can result in alteration of the pharmacokinetics of the drugs (Ensom and Stephenson 2004).

Although the use of anti-Xa is more expensive when compared to aPTT, the rapid achievement of target therapeutic level, the fewer doses of heparin needed to

Table 5 Comparison between the two groups as regards the number (percentage) of patients who reached therapeutic level

Time	Group P, ($n = 50$)	Group X, ($n = 50$)	p value
After 12 h	23 (46%)	38 (76%)	0.007*
After 24 h	35 (70%)	44 (88%)	0.045*
After 36 h	48 (96%)	50 (100%)	0.25
After 48 h	50 (100%)	50 (100%)	1

Data expressed as n (%), *p value < 0.05 was considered statistically significant

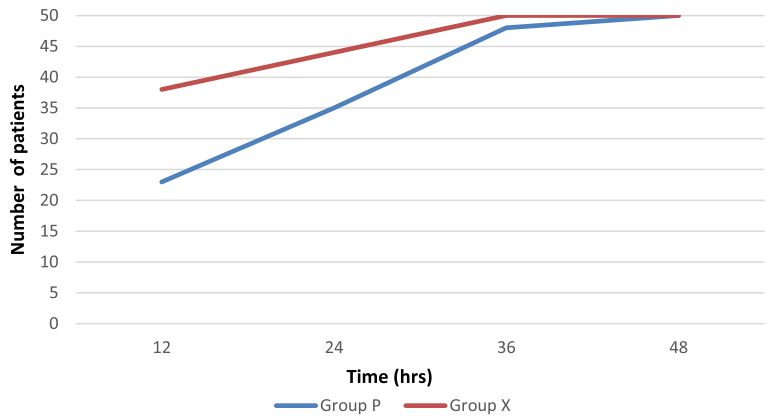

Fig. 1 Comparison between the two groups as regards the number of patients who reached therapeutic level over time

reach the therapeutic level when using anti-Xa for heparin monitoring can justify its relatively higher cost.

Considering the consequences of not maintaining patients in the therapeutic range, improved monitoring of patients receiving heparin represents an important issue for patient safety (Li et al. 2004).

In a study done by Hull et al. (Hull et al. 1997) showed that failure to reach an aPTT therapeutic level in the first 24 h during treatment with UFH, led to a significant increase in the risk of developing venous thromboembolism (25% vs. 2–4%, $p = 0.02$).

Many studies showed challenges in the standardization of aPTT-based protocols; it may be better to use the anti-Xa to avoid the risk of inaccuracy as it demonstrated less variability in measurement of heparin concentrations (Eikelboom and Hirsh 2006; Rosenberg et al. 2010; Rosborough 1999).

This study demonstrates that the use of the anti-Xa-based protocols for monitoring of UFH in pregnant females results in achieving therapeutic levels earlier than aPTT-based protocols within 12 and 24 h. The results of the current study came in agreement with other studies including a study by Guervil et al. which demonstrated that an anti-Xa protocol reached therapeutic goals quicker and required fewer lab tests and dose adjustments compared to an aPTT protocol. They found that the odds of reaching therapeutic anticoagulation at 24 h were 3.5 times higher for anti-Xa-based protocol than for aPTT-based protocol, and at 48 h the likelihood of reaching therapeutic anticoagulation level increased to 10 (Guervil et al. 2011).

Table 6 Comparison between the two groups as regards the mean total heparin dose used^

Time	Group P ($n = 50$)	Group X ($n = 50$)	p value
After 12 h	20,072 ± 5364	17,068 ± 2580	0.0006*
After 24 h	32,684 ± 9528	27,604 ± 6672	0.0026*
After 36 h	43,928 ± 13,332	36,484 ± 10,152	0.0022*
After 48 h	54,368 ± 16,728	44,764 ± 13,320	0.002*

Data presented as mean ± SD, *p value < 0.05 was considered statistically significant

^Mean total heparin dose calculated by measuring the total heparin dose required per patient divided by the number of patients

Frugé and Lee (2015) study also concluded that anti-Xa assay should be used to monitor UFH. This protocol demonstrated that patients were at the target therapeutic levels in all studied time points up to 24 h. Also, anti-Xa protocol usage led to fewer dosage adjustments within 24 h.

Another study was done by Samuel et al. (Samuel et al. 2016) showed in their pilot study that when comparing aPTT and anti-Xa, results showed that therapeutic range (> 50–100% of the time) was achieved in only 5 (10%) patients in the aPTT group vs. 21 (57%) in the anti-Xa group; $P < 0{\cdot}01$.

In this study, 88% of pregnant females on an anti-Xa-based protocol for monitoring of UFH had reached therapeutic levels within 24 h. These results came with an agreement with other studies such as Smith and Wheeler (Smith and Wheeler 2010) study which demonstrated that 92% of the subjects on an anti-Xa-based protocols for monitoring of UFH had reached therapeutic levels within 24 h. Other study done by Rosborough and Shepherd reported that 87% of patients on an anti-Xa UFH protocol were within therapeutic range at the 24-h mark. However, these studies did not compare their anti-Xa-based protocols to an aPTT-based protocols (Rosborough and Shepherd 2004).

This study showed another significance of usage of anti-Xa-based protocols to monitor UFH infusions over aPTT-based protocols as total heparin dose required to reach this therapeutic level was significantly lower in anti-Xa group at 12-, 24-, 36-, and 48-h interval. In a randomized trial done by Levine and colleagues in patients with venous thromboembolic disease, requiring more than 35,000 U per 24 h of UFH, dose adjustments

according to anti-Xa levels allowed for significantly lower daily dose of heparin as compared with aPTT (Levine et al. 1994).

Regarding heparin-related adverse effects, there were no reported cases of minor or major hemorrhage in either group over the period of the study. This may be to the close observation and early adjustment of UFH infusion. Also, there were no recorded cases for early HIT in either group. We believe that patients should be observed for more time for detection of such complication. Some studies revealed that HIT could occur up to 10 days after the start of the treatment (Warkentin and Kelton 1991).

The main difference between this study and others is that they were retrospective and performed on general population receiving heparin infusion therapy while this study was prospective and performed on pregnant patients only.

One limitation of the current study that we reported the secondary outcomes over the period of the study only which last for the first 48 h from initiation of the UFH infusion. Also, we did not estimate the incidence of thromboembolic manifestations. Another limitation is that we did not measure the length of ICU stay or the mortality rate in the studied groups.

Conclusion

This study concludes that although the use of anti-Xa is more expensive, it would be better to use anti-Xa-based protocols to achieve therapeutic anticoagulation more rapidly and to use lower doses of heparin to reach this therapeutic level in pregnant patients who are admitted to ICU.

Abbreviations

ABW: Adjusted body weight; anti-Xa: Antifactor Xa; aPTT: Activated partial thromboplastin time; HIT: Heparin-induced thrombocytopenia; IBW: Ideal body weight; ICU: Intensive care unit; LMWH: Low-molecular weight heparin; TBW: Total body weight; UFH: Unfractionated heparin

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HZ designed the study, revised the literature, followed the patients, and critically reviewed the manuscript. ME designed the study, analyze the data, and wrote and critically revised the manuscript. AS revised the literature, followed the patients, collected the data, performed the analysis, and wrote the manuscript. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

Approval of research ethical committee of Faculty of Medicine, Ain-Shams University was obtained (code number: FMASU 1528/2013) and informed conscent was obtained from paients and/or her first degree relatives.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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