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Retrospective Evaluation of Dosing Body Weight for Unfractionated Heparin in Obese Patients

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ABSTRACT

Purpose: Using adjusted body weight (AdjBW) for heparin dosing in obese patients is a common but not validated clinical practice. The purpose of this study was to evaluate whether using AdjBW in obese patients would lead to quick achievement of therapeutic activated partial thromboplastin time (aPTT) and low bleeding risk with heparin therapy.

Methods: A retrospective cohort study was conducted in patients that received heparin before and after implementation of a revised heparin protocol that utilized AdjBW for obese patients. The primary outcome was percentage of first aPTT values within the therapeutic range. Secondary outcomes included time to first therapeutic aPTT and clinically significant bleeding.

Results: There was no difference in the primary outcome in obese compared to non-obese patients in the pre-implementation group (11% vs. 15%) or post implementation group (17% vs. 21%). No difference was seen in time to first therapeutic aPTT between obese and non-obese patients in either group. However, obese patients in the post-implementation group achieved therapeutic aPTT significantly faster than obese patients in pre-implementation group (14 vs. 24 hours, $p = 0.002$). Clinically significant bleeding was higher in obese than non-obese patients prior to implementation (11% vs. 1%, $p = 0.01$), but no difference was seen after implementation.

Conclusion: Although there was no difference in the first aPTT values, more bleeding was seen in obese patients when actual body weight was used for heparin dose calculation. When AdjBW was used for dosing in obese patients, it was associated with faster achievement of therapeutic aPTT.

Introduction

Despite the availability of newer anticoagulants, unfractionated heparin (heparin) remains a mainstay anticoagulant for atrial fibrillation, acute coronary syndrome with or without percutaneous intervention, treatment and prevention of deep vein thrombosis (DVT), pulmonary embolism (PE), and other thromboembolic disorders.[1] For the past two decades, weight-based heparin dosing nomogram has become the standard practice for treatment of thrombosis, as it has been shown to achieve rapid anticoagulation and reduce risk of recurrent thrombosis.[2] Although the guidelines endorse the weight-based strategy, they do not specify what dosing weight should be used or whether a maximum bolus dose or initial infusion rate is recommended for the treatment of DVT, PE, or atrial fibrillation.[3,4,5]

The lack of guidance on dosing weight presents a challenge for the obese population, which comprises one-third of United States adults and correlates to approximately 78.6 million individuals.[6] The weight-based heparin dosing nomogram has not been well studied in these patients. In addition, literature suggests that using actual body weight (ABW) for heparin dose calculation in these patients may lead to supratherapeutic activated partial thromboplastin time (aPTT).[7–11] This observation is most likely attributed to the difference in heparin pharmacokinetics in obese patients. Although the volume of distribution of heparin is similar to that of blood volume, heparin does not distribute into the less vascular adipose tissue, thus making it difficult to estimate the volume of distribution for heparin in obese patients.[12,13] Therefore, dosing requirements for heparin in obese patients are not directly proportional to their ABW.

Several strategies have been suggested to account for the difference in heparin dosing requirements in obese patients. Some studies recommended reducing the initial infusion rate

with or without reducing the initial bolus dose,[14–16] setting a maximum limit for the initial bolus dose and/or infusion rate,[8,10,11] or a combination of both strategies.[17,18] In addition, a few case reports suggested using an adjusted body weight (AdjBW) for heparin dose calculation in obese patients, although the definition of obesity and formulas to calculate AdjBW varied.[19–22] Furthermore, none of the suggested AdjBW had been validated as the most appropriate heparin dosing weight in obese individuals to achieve quick anticoagulation without increasing risk of bleeding.

A retrospective evaluation of 79 patients at a 900-bed community teaching hospital concluded that when a high-intensity heparin protocol (80 units/kg initial bolus followed by 18 units/kg/hour initial infusion rate) was calculated using ABW without a maximum dose limit, patients who weighed more than 30% above their ideal body weight (IBW) had more first post-dose aPTT values above the therapeutic range than those with ABW within 30% above their IBW.[23] When evaluating the mean heparin infusion rate required to achieve a therapeutic aPTT, the mean infusion rate (units/kg/hour) in obese patients based on AdjBW was similar to the mean infusion rate in non-obese patients using their ABW. This finding suggested that a dosing weight using the formula AdjBW = IBW + 0.4 * (ABW-IBW) might be more appropriate for obese patients. As a result, the high-intensity heparin protocol at this institution was revised to utilize AdjBW for dose calculation in patients weighing greater than 100 kg. This definition of obesity was used in the modified protocol instead of ABW more than 30% above IBW, because ABW is more readily available in the medical charts without the need for manual calculation.

An informal survey to hospitals nationwide showed that many have also made adjustments to their institutional heparin protocols for obese patients, but the practice varied from various maximum dose limits to using AdjBW calculated using various formulas (Manny

Saltiel, Pharm.D, FASHP, FCCP, Regional Clinical Director, Comprehensive Pharmacy Services, Los Angeles, CA 90036, 2014 March 24). Although a few studies evaluated the impact of reducing heparin infusion rate and/or setting maximum dose limits in obese patients,[11,14,15,18] to the best of our knowledge no studies have been published to evaluate whether the use of AdjBW as heparin dosing weight provides better laboratory or clinical outcomes in this population. The purposes of this study was to 1) confirm the previous finding that patients who weigh more than 30% above IBW are more likely to be supratherapeutic at their first aPTT when using ABW for dosing; 2) evaluate whether AdjBW for heparin dosing in obese patients would lead to quick achievements of anticoagulation and few bleeding events.

METHODS

This retrospective cohort study was conducted at the same 900-bed community teaching hospital, where the high-intensity heparin protocol was revised to use AdjBW for obese patients. Prior to data collection, the study was approved by the institutional review boards at the community teaching hospital where the study was conducted and the university with which the investigators were affiliated.

Patients

All patients who received the high-intensity heparin protocol from January 2010 to June 2011 and January 2013 to July 2014 were evaluated for eligibility. There was no data collection between July 2011 and December 2012 to allow time for implementation of the revised high-intensity heparin protocol. Patients in the pre-implementation group (January 2010 to June 2011) received high-intensity heparin dose based on ABW regardless of their weight. Those in the post-implementation group (January 2013 to July 2014) received the revised protocol, where

AdjBW calculated from IBW + 0.4 * (ABW-IBW) was used for dose calculation in patients weighing greater than 100 kg.

Inclusion criteria included age 18 years or older, received high-intensity heparin protocol with a therapeutic aPTT range of 68-95 seconds, and had at least one aPTT measured 6 hours after the heparin infusion was started. In addition to these inclusion criteria, during the time period following the implementation of the revised heparin protocol, patients must also receive heparin dose based on the AdjBW if they weighed more than 30% above their IBW. Due to the discrepancy in definitions of obesity in the revised heparin protocol and this study, patients were excluded from the analysis if ABW was used for dosing even though they met the study definition of obesity (usually due to ABW less than 100 kg). Patients were also excluded if AdjBW was used for dosing when patients weighed greater than 100 kg even though they did not meet the study definition of obesity (i.e. ABW within 30% above IBW). Additional exclusion criteria included pregnancy during heparin treatment, continuation of heparin therapy from another institution, transition from low-intensity heparin therapy (mainly for cardiac indications, with lower dosing, a maximum dose limit, and a different aPTT goal) or subcutaneous low-dose heparin within preceding 48 hours, having received other anticoagulants that could potentially affect aPTT within 48 hours prior to the initiation of heparin (e.g. argatroban, bivalirudin, dabigatran), and any violation of the high-intensity heparin protocol (e.g. receiving a customized heparin regimen, using a weight different from what the protocol specifies) although omission of the initial bolus dose was allowed.

Eligible patients in both pre-implementation and post-implementation groups were further categorized into obese and non-obese, which gave the study a total of four cohorts. The

definition of obesity, for the purpose of this study, was ABW more than 30% above IBW. This definition was chosen to be consistent with the previous retrospective evaluation.[23]

Data Collection and Outcomes

The following data were collected for each eligible patient: basic demographic information (age, sex, height, and weight), indication for heparin use, heparin dosing information (actual dosing weight, initial bolus dose, infusion rate when therapeutic aPTT was achieved), baseline and subsequent aPTT values (drawn approximately 6 hours following heparin initiation and dose changes), baseline hemoglobin and the lowest hemoglobin values during and within 48 hours of discontinuation of heparin therapy, and any overt bleeding events.

The primary outcome was percentage of first aPTT values after initiation of heparin therapy that were within the therapeutic range. The secondary outcomes included the percentages of first aPTT values below and above the therapeutic range, percentage of second aPTT below, within and above the therapeutic range, percentage of patients achieving a therapeutic aPTT at any time during treatment, median time to first therapeutic aPTT, and infusion rate required to achieve first therapeutic aPTT. Primary safety outcome was clinically significant bleeding, which included both major bleeding and clinically relevant nonmajor bleeding. Major bleeding was defined as overt bleeding associated with a decrease in hemoglobin of 2 g/dL or more or required a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death.[24] Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but warranted treatment or heparin discontinuation.[25]

Statistical Analysis

Based on the previous evaluation, it was determined that 66 patients would be needed in each of the four cohorts to provide a power of 80% to detect a 20% difference in the primary outcome between the obese and non-obese cohorts, with a 2-sided alpha level of 0.05.[23] The demographic information was summarized using descriptive statistics and analyzed using t-test for continuous data and χ^2 test for nominal data. The primary outcome and other nominal data were analyzed using χ^2 test. T-test was also used to compare continuous data, such as bolus doses and aPTT values. The Kruskal-Wallis test was used to compare the median time to first therapeutic aPTT, while Fisher's exact test was used to compare clinically significant bleeding between cohorts. A p value less than 0.05 was considered to be statistically significant. The statistical analysis was performed with the MedCalc Statistical Software version 15.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015).

RESULTS

Patient Demographics

Overall, a total of 820 patients were identified as having at least one order for high-intensity heparin protocol during the defined time frames (315 patients during the pre-implementation period and 505 patients during the after-implementation period). After eligibility screening, 427 patients were excluded for various reasons (147 in pre-implementation period and 280 in post-implementation period). The most common reasons were violation of heparin protocol, received heparin therapy within 48 hours prior to initiation of the high-intensity heparin protocol, and using dosing weights different from the study definition (primarily in the post-implementation period). A more detailed breakdown of the excluded patients in both groups may be found in Figure 1. A total of 393 (168 in pre-implementation group and 225 in the post-implementation group) were included in the final analysis.

Other than weight and BMI, baseline characteristics were similar between the obese and non-obese cohorts in the pre-implementation group, whereas the obese patients in the post-implementation group were younger than the non-obese patients (Table 1). The most common indication for the high-intensity heparin therapy was venous thromboembolism (VTE), which included 29% PE, 24% DVT, and 7% both PE and DVT (Table 1). Heparin indications were similar among the 4 cohorts, except more non-obese patients in the pre-implementation group received heparin for *other* miscellaneous thrombosis such as apical thrombus, peripheral arterial disease, and carotid stenosis.

Pre-Implementation (ABW used for all patients)

Of all 168 patients who received high-intensity heparin protocol in the pre-implementation period, only 22 patients (13.1%) achieved therapeutic range with the first aPTT measurement (Table 2). Fewer obese patients had the first aPTT in the therapeutic range (10.5%) than non-obese patients (15.2%), but this difference was not statistically different ($p = 0.50$). This was not affected by whether patients received an initial bolus dose. No statistical difference was seen in the percentages of first aPTT values above or below the therapeutic ranges. Second post-dose aPTT values were available in 159 patients (94.6%); 35 of these (22%) achieved the therapeutic range. Only 7 of all 168 patients (4%) had two consecutive therapeutic aPTT values (both first and second aPTT values were within the therapeutic range). Although the second aPTT levels were significantly higher in value in the obese cohort, there was no statistically significant difference in the percentage of second aPTT below, within or above the therapeutic range compared to the non-obese cohort. During the course of treatment, 129 patients (76.8%) achieved at least one therapeutic aPTT, but no difference was seen between the two cohorts. It took less time for the non-obese cohort to obtain first therapeutic aPTT (19.9

hours), but again this difference was no statistically significant (23.8 hours in obese cohort; p = 0.11). To achieve the first therapeutic aPTT, those in the obese cohort required significantly lower infusion rate at 14 units/kg/hour whereas the non-obese cohort required 16 units/kg/hour (p=0.01) (Table 3). If AdjBW were used to calculate the heparin dose required to achieve the first therapeutic aPTT, the obese patients would require a mean infusion rate of 18.1 units/kg/hour, which is similar to the initial infusion rate for the high-intensity heparin protocol. Clinically significant bleeding occurred in 8 of 76 obese patients (11%) and in 1 of 92 patients (1%) in the non-obese cohort (relative risk of 9.7; 95% confidence interval, 1.2-75.7). This significant finding was driven primarily by major bleeding, 6 (8%) in obese cohort and 1 (1%) in the non-obese cohort (Table 4).

Post-Implementation (ABW for non-obese patients and AdjBW for obese patients)

Among the 225 patients who received high-intensity heparin after the protocol modification, 44 (19.6%) patients achieved the therapeutic range at the first aPTT measurement. Although no statistical difference was seen in the percentages of first aPTT values in the therapeutic range, significantly fewer obese patients had values above the therapeutic range (44.2% in obese vs. 59.5% in non-obese, p = 0.04) while more had subtherapeutic values (39% in obese vs. 19.6% in non-obese, p = 0.003) (Table 2). Second post-dose aPTT values were available in 204 patients (90.1%). Among these patients, 68 (33%) achieved the therapeutic range and 19 (8%) had two consecutive therapeutic aPTT values, although no difference was seen between the obese and non-obese cohorts. Overall, 168 patients (74.7%) achieved at least one therapeutic aPTT at any given time during the course of treatment, but no difference was seen between the two cohorts. Patients in the obese cohort achieved the first therapeutic aPTT more quickly (14 hours) than those in the non-obese cohort (17.3 hours), but this difference was

not statistically significant (p = 0.47). The infusion rate required to achieve the first aPTT in the obese cohort was 18.2 units/kg/hour compared to 16.5 units/kg/hour in the non-obese cohort (p=0.008). No difference was seen in clinically significant bleeding between the two cohorts. The breakdown of major and nonmajor bleeding is provided in Table 4.

Pre-Implementation versus Post-Implementation

The data from pre-implementation period were compared with those from the post-implementation period to evaluate whether the protocol modification improved heparin dosing in obese patients. When comparing the first aPTT values, obese patients had similar percentages of therapeutic values before and after the protocol modification. However, fewer patients had supratherapeutic values after the protocol modification, whereas more had subtherapeutic values (Figure 2). In addition, more obese patients in the post-implementation than the pre-implementation period achieved the therapeutic range at the second aPTT measurement (37.5% vs. 17.8%, p = 0.02). This was also reflected in more rapid achievement of therapeutic aPTT (< 24 hours) after protocol modification in the obese population (Table 5). However, the protocol modification did not result in a reduction of clinically significant bleeding in obese patients.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate whether using AdjBW in heparin dose calculation improves anticoagulation while minimizing bleeding risk in obese patients. Our study did not show a significant difference in aPTT values below, within, or above the therapeutic range between obese and non-obese patients when ABW was used for heparin dose calculation. Although we did not confirm the earlier findings that using ABW for heparin dosing in obese patients resulted in higher percentage of supratherapeutic aPTT, this is the first study to demonstrate that this dosing strategy was associated with a significant increase in

clinically significant bleeding. Our data from the pre-implementation group also suggested that using AdjBW to calculate the initial infusion rate in obese patients would result in a dose close to the infusion rate required to achieve the first therapeutic aPTT.

When the post-implantation group was analyzed, with AjBW used for heparin dosing in obese patients, it did not actually improve the percentage of patients achieving therapeutic range with the first or second aPTT measurements as expected. Interestingly, fewer obese patients had supratherapeutic aPTT while more had subtherapeutic aPTT at the first measurement, when compared to non-obese patients from the same time frame. This could be potentially concerning given the most common indication for heparin was VTE. This dosing strategy in obese patients may have led to underdosing, which could have resulted in a delay in therapeutic anticoagulation or even an increased risk of thrombosis. This result was a surprising finding; therefore the clinical implication was not collected in our study. However, an increased risk of thrombosis is unlikely given the fact that there is no difference in the second aPTT values below the therapeutic range or the time to achieve the first therapeutic aPTT between obese and non-obese patients. In addition, the mean infusion rate required to achieve the first therapeutic aPTT was closer to the initial infusion rate in obese patients than non-obese patients.

Although the time to first therapeutic aPTT was not different between the obese and non-obese cohorts, obese patients achieved therapeutic anticoagulation more rapidly when AdjBW instead of ABW was used for dose calculation. This improvement was also reflected in the higher percentage of obese patients who achieved therapeutic aPTT within 24 hours after protocol modification. Since achieving therapeutic anticoagulation within 24 hours of starting intravenous heparin for VTE was associated with decreased occurrence of recurrent thromboembolism[2,26], this improvement observed in our study is clinically relevant.

Several studies have been conducted to address heparin dosing in obese patients. Barletta *et al.* evaluated 101 patients who received the same high-intensity heparin protocol used in our study, dosed based on ABW without maximum dose limits.[8] The authors found that aPTT values at 6 and 12 hours were significantly higher and significantly more aPTT values at 12 hours were supratherapeutic in patients with BMI > 40 kg/m^2 compared to those with BMI < 40 kg/m^2. Despite the supratherapeutic aPTT values, no difference in bleeding was seen. The authors suggested a maximum dose limitation but did not recommend any specific dosing. A large prospective study by Riney *et al.* evaluated the mean infusion rate required to achieve therapeutic aPTT in 273 patients who received 3 different heparin protocols based on ABW.[10] The authors found that morbidly obese patients (BMI ≥ 40 kg/m^2) requires significantly lower infusion rate than overweight patients (BMI 25-39.9 kg/m^2) and normal/underweight patients (BMI < 25 kg/m^2). They also found that supratherapeutic aPTT occurred more frequently in morbidly obese patients. More clinical bleeding episodes were observed in the morbid obesity group, although the difference was not statistically significant. No difference was seen in time to therapeutic aPTT. The findings from both of these studies were consistent with our data before the heparin protocol modification, although we did not find a significant difference in aPTT values but found higher risk of bleeding when ABW was used for dosing in obese patients.

Spruill *et al.* evaluated a modified high-intensity heparin protocol (70 units/kg bolus followed by 15 units/kg/hour dosed based on ABW) and found no difference in time to first therapeutic aPTT or infusion rate required to achieve the therapeutic aPTT between obese and non-obese patients.[14] Although the definition of obesity in this study was the same as our study, it is difficult to extrapolate their results as the study used a lower dose, only had 20 patients in each group, and their obese patients weighed less (mean weight 95 kg). No information on

thrombosis or bleeding were collected. Bauer *et al.* evaluated 1054 patients who received a heparin protocol of 60 units/kg bolus followed by 12 units/kg/hour dosed based on ABW and found no difference in percentage of patients with a therapeutic initial aPTT or bleeding among four body mass index (BMI) quartiles.[9] They did find that patients in the highest BMI quartile (> 34.3 kg/m^2) are more likely to have an APPT > 110 seconds. Majority of the patients in this study received heparin for cardiac conditions, such as acute coronary syndrome, which makes it difficult to extrapolate their results as the guidelines recommend maximum dose limits in these patients.[27,28] A small retrospective study by Dee and Thomas evaluated another modified high-intensity heparin protocol, in which 10 obese patients (weighing more than 50% above IBW) received an initial infusion rate at 15 units/kg/hour and 45 non-obese patients received 18 units/kg/hour (all had a maximum initial infusion of 2100 units/hour); all patients received a bolus dose of 80 units/kg (maximum of 10,000 units).[18] The authors found no difference in percentage of patients achieving a therapeutic aPTT anytime during heparin treatment, time to therapeutic aPTT or bleeding. It is difficult to interpret data from this study given its small sample size and unusual definition of obesity. Gerlach *et al.* evaluated 62 critically ill patients who received heparin infusions without a bolus at 12 units/kg/hour if obese (BMI 30-39.9 kg/m^2) or morbidly obese (BMI ≥ 40 kg/m^2) and 16 units/kg/hour if BMI < 30 kg/m^2. The authors found 92% of all patients had at least one therapeutic aPTT, but only 55% reached steady state which was defined as three consecutive aPTT within target range. No difference was seen in time to first therapeutic aPTT, time to steady state or bleeding. Again the small sample size makes it difficult to extrapolate the data from this study.

Although reducing the initial infusion rate is a strategy recommended by some, others suggested using a modified dosing weight somewhere between the IBW and ABW. A

retrospective study of 213 patients by Yee and Norton evaluated the same high-intensity heparin protocol as our study and used a modified dosing weight (IBW + 0.3*[ABW-IBW]) in patients who weighed more than 10 kg above IBW.[17] The authors found that the mean first aPTT values were significantly lower in obese patients when a modified dosing weight was used for heparin dose calculation compared to non-obese patients in which ABW was used. This finding is similar to our study, although the authors did not report whether lower numeric values resulted in more subtherapeutic aPTT values. This study used 0.3 as the adjustment factor for a modified dosing body weight and obesity was defined as more than 10 kg above IBW with only 12% of the patients weighing more than 100 kg. The lower dosing weight and lower threshold for obesity likely explain the lower aPTT values seen in this study. Schwiesow *et al.* reported that using the average of IBW and ABW to dose heparin in a morbidly obese patient (BMI 75 kg/m^2, 182 kg) achieved therapeutic aPTT within 10 hours and was maintained for 6 days.[19] A case series by Khan *et al.* evaluated the average infusion rate required to achieve therapeutic aPTT in 8 patients and concluded that the infusion rate is close to the dose calculated based on AdjBW (same formula used in our study).[20] Myzienski *et al.* reported a case of under-anticoagulation when maximum initial bolus and infusion rate were used in a morbidly obese patient (BMI 134 kg/m^2, 388 kg). The authors indicated that the final infusion rate required to achieve therapeutic aPTT more closely resembled the dose calculated using AdjBW.[21]

The literature on heparin dosing in obesity patients is limited by small sample, mixed heparin dose protocols for various indications, disparity in definition of obesity, or inconsistency in the formula used to obtain a modified dosing body. Our study focused on only the high-intensity heparin protocol without maximum dose limits, as recommended by the guidelines based on a previous study by Raschke *et al.*[2–5] We also excluded violation of the protocol,

including those that transitioned from lower dose heparin protocol and those who received customized doses or had dosing weight different from what the protocol specifies. In addition to laboratory endpoints, we also evaluated clinically relevant endpoint such as time to therapeutic aPTT and clinically significant bleeding. Lastly, the study design allowed us a before and after look at the different dosing strategies to assess the impact of using AdjBW for dose calculation in obese patients, while still allowing comparison between obese and non-obese patients.

Several limitations of this study, however, should be highlighted. Although sample size was met in both the pre-implementation and post-implementation groups, it is possible that our study still did not have enough power for the primary outcome since the sample size analysis was done based on a previous small study. In addition, achieving one aPTT value in the therapeutic range does not necessarily mean that the full anticoagulation effect or steady state of heparin has been achieved, especially since a very low percentage of patients in our study had two consecutive aPTT values in the therapeutic range. One also has to interpret the results of this study with caution due to its retrospective nature. Two individuals collected data which may have introduced selection bias into this study. Additional confounders, inaccuracy in documentation, and other clinical variables may not have been evident during retrospective chart reviews. Although we compared data between the pre-implementation and post-implement periods, several factors other than the protocol modification could have contributed to the differences we observed. These may include increased nursing experience with the heparin protocol, improved monitoring and interventions from the pharmacy department, difference in patient populations in the two time periods. Therefore, we refrained from comparing too many endpoints between the two time periods and rather focused more on the comparison between obese and non-obese cohorts within the same time period. Furthermore, given the large number

of subtherapeutic aPTT values in the study, it would have been beneficial to collect data on adverse events associated with subtherapeutic aPTTs. Finally, using aPTT, a surrogate marker, as the primary outcome of our study may be a limitation in itself as some studies demonstrated that aPTT measurement does not correlate well with anticoagulation effect of heparin, especially in critically ill patients.[3,29,30] In addition, the association between supratherapetuic aPTT values and bleeding risk is unclear. Although our study did not show a significant difference in supratherapeutic aPTT between obese and non-obese patients, we did observe an increased incidence of clinically significant bleeding when ABW was used for dosing in obese patients. Due to these limitations of aPTT as a reliable monitoring parameter, using antifactor Xa level for heparin therapy may provide a better dose-response curve and require fewer blood samples and dose adjustments.[29]

In our study, AdjBW was calculated using IBW + 0.4 * (ABW-IBW) to determine a modified dosing weight for patients weighing 30% above their IBW. Other institutions have utilized a variety of methods to account for lower dose requirement in obese patients, such as using different formula to obtain a modified dosing weight, using ABW for dosing but reducing the initial infusion rate, and setting a maximum dose for the bolus and/or initial infusion rate. Future studies are needed to determine the appropriate weight for heparin dose calculation in the obese population, as well as comparing the different strategies for dose modification in heparin therapy. As more institutions transition from aPTT to antifactor Xa monitoring for heparin therapy, studies of heparin dosing in obese population also need to be updated to evaluate how the different dosing strategies affect antifactor Xa. Most importantly, larger studies need to be conducted to assess the clinical consequence of over-anticoagulating or under-anticoagulating obese patients, such as bleeding, recurrence of thrombosis, and length of hospital stay.

CONCLUSION

Given the increasing prevalence of obesity and the elevated risk of thrombosis in this population, it is important to determine an appropriate way to dose heparin in these patients to achieve prompt therapeutic anticoagulation without increasing the risk of bleeding. Our study demonstrated that using actual body weight in obese patients for heparin dosing resulted in increased bleeding, while using a modified dosing body weight in these patients led to quicker achievement of anticoagulation without increasing bleeding risk.

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Figure 1. Inclusion, Exclusion, and Group Assignments of Patients
aPTT = activated Partial Thromboplastin Time, IV = intravenous

Figure 2. Comparison of 1st Activated Partial Thromboplastin Time (aPTT) Values in Obese Patients

Table 1.
Baseline Characteristics[a]

Characteristics	Pre-Implementation			Post-Implementation		
	Obese (n=76)	Non-Obese (n=92)	p Value	Obese (n=77)	Non-Obese (n=148)	p Value
Age, yr, mean ± SD	63.4 ± 15.6	64.0 ± 18.8	0.82	59.2 ± 11.7	67.3 ± 17.5	<0.001
Male, n (%)	32 (42.1)	51 (55.4)	0.12	48 (62.3)	81 (54.7)	0.34
ABW, kg, mean ± SD	104.7 ± 11.5	71.9 ± 15.2	<0.001	138.7 ± 35.6	71.9 ± 14.9	<0.001
ABW range, kg	63.5 - 231	38.79 - 123		90.3 – 263.1	38.6 – 106.6	
BMI, kg/m^2, mean ± SD	36.1 ± 8.1	24.1 ± 3.5	<0.001	44.4 ± 10.4	24.4 ± 3.3	<0.001
BMI range, kg/m^2	26.4 – 70.9	16.4 - 40		30.2 – 77.1	12.6 – 31.7	
Baseline aPTT, sec, mean ± SD	37.7 ± 17.2	34.7 ± 10.0	0.25	31.3 ± 4.3	33.0 ± 7.3	0.09
Heparin Indication, n (%)						
VTE	48 (63.1)	50 (54.3)	0.32	53 (68.8)	88 (59.5)	0.22
PE	30 (39.5)	21 (22.8)		27 (35.1)	37 (25.0)	
DVT	17 (22.4)	25 (27.2)		18 (23.4)	35 (23.6)	
PE with DVT	1 (1.3)	4 (4.3)		8 (10.4)	16 (10.8)	
Atrial Fibrillation	13 (17.1)	12 (13.0)	0.60	14 (18.2)	27 (18.2)	0.86
Valve Replacement	9 (11.8)	5 (5.4)	0.22	4 (5.2)	14 (9.5)	0.39
Others	3 (3.9)	22 (24.0)	<0.001	5 (6.5)	13 (8.8)	0.73
≥ 2 indications	3 (3.9)	3 (3.3)	0.83	1 (1.3)	6 (4.1)	0.46

[a]ABW = actual body weight, BMI = body mass index, aPTT = activated partial thromboplastin time; VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis;

Table 2.
Activated Partial Thromboplastin Time (aPTT) Measurements

	Pre-Implementation			**Post-Implementation**		
Variable	Obese (n=76)	Non-Obese (n=92)	p Value	Obese (n=77)	Non-Obese (n=148)	p Value
First aPTT						
Sec, Mean ± SD	119.3 ± 40.2	109.7 ± 38.7	0.12	94.0 ± 41.5	110.1 ± 40.6	0.006
Therapeutic, n (%)	8 (10.5)	14 (15.2)	0.50	13 (16.9)	31 (20.9)	0.58
Subtherapeutic, n (%)	14 (18.4)	20 (21.7)	0.73	30 (39.0)	29 (19.6)	0.003
Supratherapeutic, n (%)	54 (71.1)	58 (63.0)	0.35	34 (44.2)	88 (59.5)	0.04
Second aPTT[a]						
Sec, Mean ± SD	112.0 ± 37.9	96.2 ± 41.4	0.01	90.7 ± 35.5	97.3 ± 35.7	0.20
Therapeutic, n (%)	13 (17.8)	22 (25.6)	0.32	27 (37.5)	41 (31.1)	0.44
Subtherapeutic, n (%)	14 (19.2)	24 (27.9)	0.27	21 (29.2)	31 (23.5)	0.47
Supratherapeutic, n (%)	46 (63.0)	40 (46.5)	0.06	24 (33.3)	60 (45.5)	0.20
Patients with ≥ 1 therapeutic aPTT, n (%)	59 (77.6)	70 (76.1)	0.96	59 (76.6)	109 (73.6)	0.75
Time to first therapeutic aPTT, hr, median (interquartile range)	23.8 (14.1-36.7)	19.9 (9.8-32.3)	0.11	14.0 (8.4-24.4)	17.3 (7.4-28.7)	0.47
Time to first therapeutic aPTT, hr, n (%)			0.58			0.74
< 24	31 (40.8)	43 (46.7)		44 (57.1)	76 (51.4)	
24-48	20 (26.3)	20 (21.7)		13 (16.9)	27 (18.2)	
> 48	8 (10.5)	7 (7.6)		2 (2.6)	6 (4.1)	

[a]2010: n=73 in obese vs. n=86 in non-obese; 2014: n=72 in obese vs. n=132 in non-obese

Table 3.
Dosing Characteristics

	Pre-Implementation			**Post-Implementation**		
Variable	Obese (n=76)	Non-Obese (n=92)	p Value	Obese (n=77)	Non-Obese (n=148)	p Value
Received bolus, n (%)	42 (55.3%)	59 (64.1%)	0.31	54 (70.1%)	103 (69.6%)	0.94
Bolus dose, units/kg, mean ± SD	76.5 ± 10	81.1 ± 14.5	0.08	79.3 ± 7.4[a]	78.8 ± 6.5	0.65
Absolute bolus dose, units, mean ± SD	8017 ± 2263	5834 ± 1335	<0.001	7848 ± 1382	5676 ± 1250	<0.001
Infusion rate at first therapeutic aPTT, units/kg/hr, mean (SD)[b]	14.0 ± 4.0	15.8 ± 4.1	0.01	18.2 ± 3.9[a]	16.5 ± 4.0	0.008

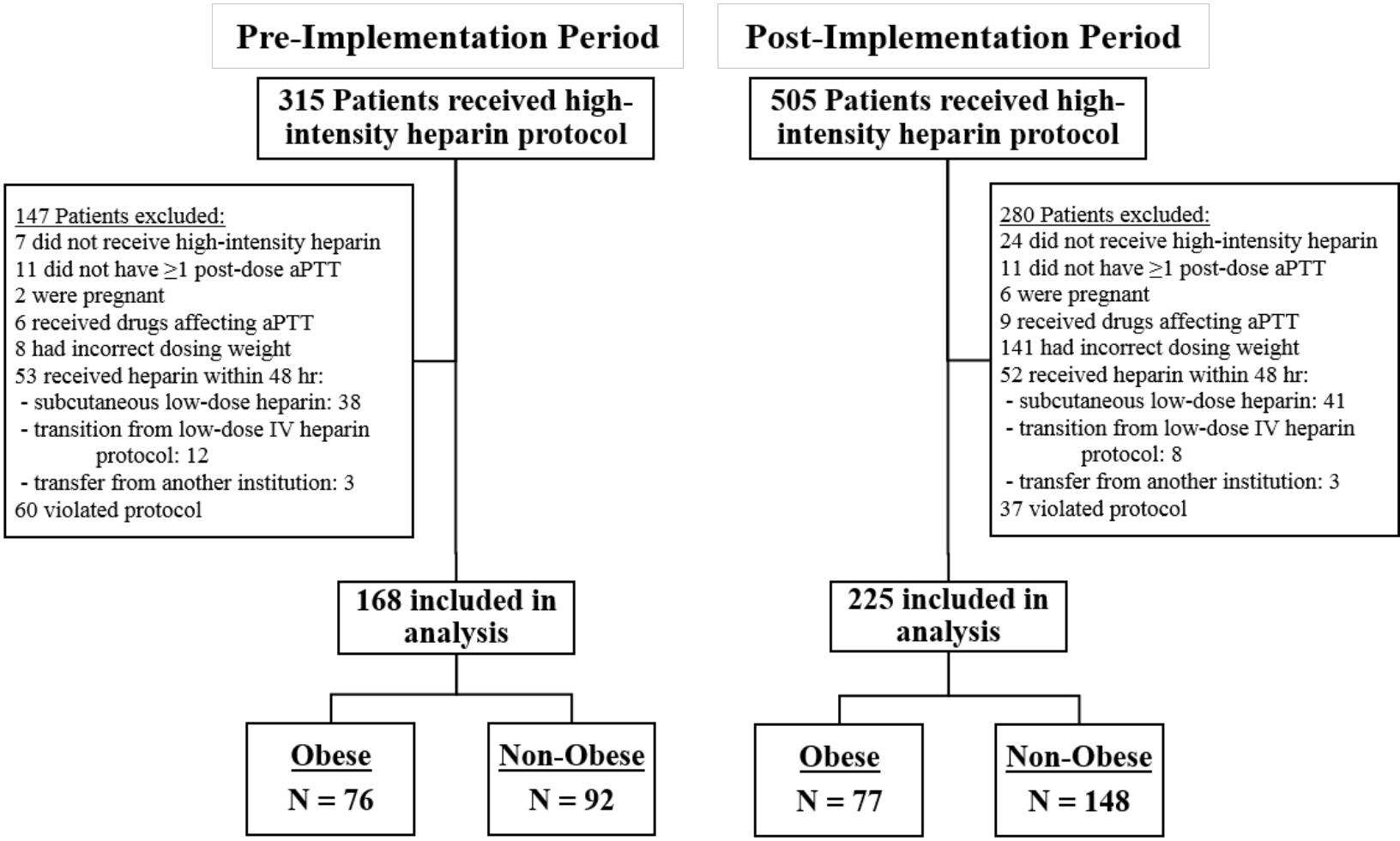
[a]Calculated based on AdjBW
[b]2010: n=59 in obese vs. n= 70 in non-obese; 2014: n=59 in obese vs. n=109 in non-obese

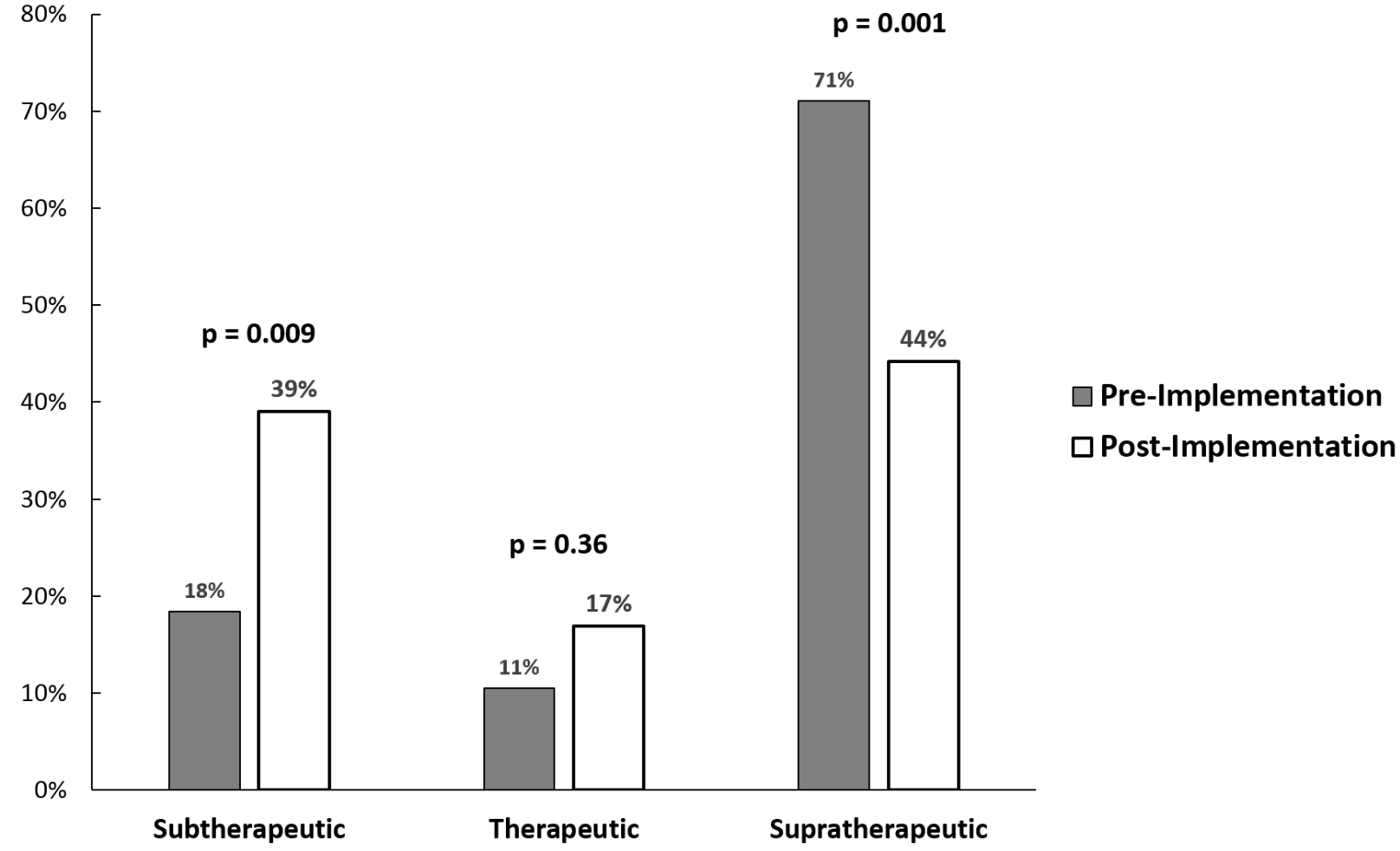
Table 4.
Bleeding Events

	Pre-Implementation			**Post-Implementation**		
Variable	**Obese (n=76)**	**Non-Obese (n=92)**	**p Value**	**Obese (n=77)**	**Non-Obese (n=148)**	**p Value**
Clinically Significant Bleeding, n (%)	8 (10.5)	1 (1.1)	0.01	7 (9.1)	18 (12.2)	0.66
Major Bleeding, n (%)	6 (7.9)	1 (1.1)	0.047	4 (5.2)	10 (6.8)	0.78
Clinically Relevant Nonmajor Bleeding, n (%)	2 (2.6)	0 (0)	0.20	3 (3.9)	8 (5.4)	0.75

Table 5.
Time to First Therapeutic Activated Partial Thromboplastin Time (aPTT)

Variable	**Pre-Implementation Obese (n=76)**	**Post-Implementation Obese (n=77)**	**p Value**
Time to first therapeutic aPTT, hr, median (interquartile range)	23.8 (14.1-36.7)	14.0 (8.4-24.4)	0.002
Time to first therapeutic aPTT, hr, n (%)			0.02
< 24	31 (40.8)	44 (57.1)	
≥ 24	28 (36.8)	15 (19.5)	


Pre-Implementation Period
315 Patients received high-intensity heparin protocol
147 Patients excluded:
7 did not receive high-intensity heparin
11 did not have ≥1 post-dose aPTT
2 were pregnant
6 received drugs affecting aPTT
8 had incorrect dosing weight
53 received heparin within 48 hr:
- subcutaneous low-dose heparin: 38
- transition from low-dose IV heparin protocol: 12
- transfer from another institution: 3
60 violated protocol
168 included in analysis
Obese
N = 76
Non-Obese
N = 92
Post-Implementation Period
505 Patients received high-intensity heparin protocol
280 Patients excluded:
24 did not receive high-intensity heparin
11 did not have ≥1 post-dose aPTT
6 were pregnant
9 received drugs affecting aPTT
141 had incorrect dosing weight
52 received heparin within 48 hr:
- subcutaneous low-dose heparin: 41
- transition from low-dose IV heparin protocol: 8
- transfer from another institution: 3
37 violated protocol
225 included in analysis
Obese
N = 77
Non-Obese
N = 148


80%
70%
60%
50%
40%
30%
20%
10%
0%
p = 0.009
p = 0.36
p = 0.001
18%
39%
11%
17%
71%
44%
Subtherapeutic
Therapeutic
Supratherapeutic
Pre-Implementation
Post-Implementation