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Heparin dose calculated according to lean body weight during on-pump heart surgery

On-pump kalp cerrahisi sırasında heparin dozunun yağsız vücut ağırlığına göre hesaplanması

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ABSTRACT

Background: The aim of this study is to compare heparin dose regimen calculated based on the lean body weight with traditional heparin regimen in terms of ensuring adequate anticoagulation and complications associated with perioperative bleeding.

Methods: This prospective, single-blind, randomized study included a total of 100 adult patients (42 males, 58 females; mean age 52.7 years; range, 22 to 84 years) undergoing elective valve surgery with cardiopulmonary bypass between June 2016 and January 2017. Prior to cardiopulmonary bypass, heparin dose was adjusted as 4 mg/kg, according to the actual body weight (n=50) and lean body weight (n=50). The minimal activated clotting time target value was accepted as 480 sec for cardiopulmonary bypass initiation. Demographic and hemodynamic data, post-heparin activated clotting time, additional heparin and perioperative transfusion, postoperative drainage volumes, reoperations, and mortality were recorded.

Results: Demographic data, cross-clamp and cardiopulmonary bypass times, and intraoperative transfusion requirement were not significantly different between the groups. The initial and total doses of heparin, as well as the total dose of protamine, were significantly higher in the actual body weight group. Postoperative transfusion rates were also higher in this group. None of the patients in the lean body weight group required reoperation, while three patients in the actual body weight group underwent reoperation.

Conclusion: Our study results showed that adequate anticoagulation was achieved with the titration of heparin dose calculated according to the lean body weight during cardiopulmonary bypass and reduced total heparin and protamine doses decreased postoperative bleeding and blood product transfusion requirement.

Keywords: Actual body weight; blood management; cardiac anesthesia; cardiac surgery; cardiopulmonary bypass; heparin; lean body weight; protamine; tamponade.

ÖZ

Amaç: Bu çalışmada geleneksel heparin rejimi ile yağsız vücut ağırlığına göre hesaplanan heparin doz rejimi yeterli antikoagülasyonun sağlanması ve perioperatif kanama ile ilişkili komplikasyonlar açısından karşılaştırıldı.

Çalışma planı: Bu prospektif, tek kör, randomize çalışmaya Haziran 2016 - Ocak 2017 tarihleri arasında kardiyopulmoner baypas ile elektif kapak ameliyatı yapılan toplam 100 erişkin hasta (42 erkek, 58 kadın; ort. yaş 52.7 yıl; dağılım, 22-84 yıl) alındı. Kardiyopulmoner baypas öncesinde heparin dozu, aktüel vücut ağırlığına göre (n=50) ve yağsız vücut ağırlığına göre (n=50) olmak üzere 4 mg/kg olarak ayarlandı. Kardiyopulmoner baypasa başlanması için minimum aktive pıhtılaşma zamanı hedef değeri 480 sn. olarak kabul edildi. Demografik ve hemodinamik veriler, heparin sonrası aktive pıhtılaşma zamanı, ek heparin ve perioperatif transfüzyon, ameliyat sonrası drenaj miktarları, yeniden ameliyatlar ve mortalite kaydedildi.

Bulgular: Demografik veriler, kros klemp ve kardiyopulmoner baypas süreleri ve ameliyat sırası transfüzyon ihtiyacı gruplar arasında anlamlı düzeyde farklı değildi. Heparinin başlangıç ve toplam dozlarının yanı sıra toplam protamin dozu, aktüel vücut ağırlığı grubunda anlamlı düzeyde daha yüksekti. Ameliyat sonrası transfüzyon oranları da, bu grupta daha yüksekti. Yağsız vücut ağırlığı grubunda hiçbir hastada yeniden ameliyat gerekli olmaz iken, aktüel vücut ağırlığı grubunda üç hasta yeniden ameliyat edildi.

Sonuç: Çalışma sonuçlarımız kardiyopulmoner baypas sırasında yağsız vücut ağırlığına göre hesaplanan heparin doz titrasyonu ile yeterli antikoagülasyon sağlanabileceğini ve toplam heparin ve protamin dozlarının düşürülmesi ile ameliyat sonrası kanama ve kan ürünü transfüzyonu gereksinimin azaltılabileceğini göstermiştir.

Anahtar sözcükler: Aktüel vücut ağırlığı; kan yönetimi; kardiyak anestezi; kalp cerrahisi; kardiyopulmoner baypas; heparin; yağsız vücut ağırlığı; protamin; tamponad.

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In cardiac surgery, heparin administration is required to prevent tromboembolism during cardiopulmonary bypass (CPB); however, excess heparin doses may cause bleeding, tamponade, and bleeding-related reoperation during the postoperative period. At the end of CPB, protamine is used for heparin neutralization. Similar to heparin, protamine has also several side effects including hypersensitivity, systemic hypotension, pulmonary hypertension, right ventricular failure, angioedema, bronchospasm, and anticoagulation with overdoses. An increase in the dose of heparin would also increase the need for protamine. During CPB, there is no standard for clinical management of heparin administration. In clinical practice, due to heparin insensitivity, anti-thrombin-III deficiency, heparin binding proteins, and different heparin formulations, anticoagulation and heparin response may become complicated. In this respect, there is no universal consensus on the quantitative value of heparin and anticoagulation in CPB, that is, the ideal activated clotting time (ACT) value required for CPB. Most of the cardiac centers determine the target ACT value required for CPB as 400-480 sec.[1,2] Also, in most cardiac centers, heparin is administered at a dose of 300 IU/kg, which is universally accepted, and this dose can sometimes lead to intraoperative high ACT values.

Heparin, which provides anticoagulation during CPB, is calculated according to the actual body weight (ABW). However, using the lean body weight (LBW) can be a better predictor of drug dose adjustment than total body weight or body surface area, and that LBW can be used to accurately calculate the loading dose required for some drugs to reach the target peak plasma concentration.[3]

In the present study, we aimed to investigate the feasibility of adequate anticoagulation with heparin dose calculated according to the LBW and also to evaluate the possibility of postoperative bleeding, transfusion requirement, and bleeding reoperations related to heparin overdose.

PATIENTS AND METHODS

Between June 2016 and January 2017, this prospective, single-blind, randomized study included a total of 100 adult patients (42 males, 58 females; mean age 52.7 years; range, 22 to 84 years) who were in the American Society of Anesthesiologists (ASA) Class II-III and who underwent elective aortic or mitral valve replacement and combined valvular replacement with CPB. Pediatric patients, coronary and transplant surgeries, vascular surgery, patients with ventricular assist devices, patients operated under emergency conditions, and patients with any hematological disorders were excluded from the study. An informed consent was obtained from each patient. The study protocol was approved by the Türkiye Yüksek İhtisas Training and Research Hospital Ethics Committee (Date 09.06.2016 and No. 55). The study was conducted in accordance with the principles of the Declaration of Helsinki.

In both groups, anesthesia management, surgical procedures, and CPB management were standardized (premedication with the night before oral 5-10 mg diazepam, intraoperative routine cardiovascular monitoring, venous and arterial cannulation, anesthesia induction with fentanyl 10 μgkg^{-1}, midazolam 0.15 $mgkg^{-1}$, and rocuronium 0.6^{-1} $mgkg^{-1}$). Following intubation, the patients were mechanically ventilated with a tidal volume of 6 to 8 mL/kg^{-1} according to their ideal body weight, respiratory frequency was set to keep end-tidal carbon dioxide ($EtCO_2$) level of 35 to 40 mmHg and anesthesia was maintained with sevoflurane 0.8^{-1} minimum alveolar concentration (MAC) with 40% O_2/air mixture. Central venous cannulation was done and nasopharyngeal temperature probe was placed. All patients received tranexamic acid infusion in the form of initial loading dose (10 $mg\text{-}kg^{-1}$ 10 min), resuscitation until the end of the operation (1 $mg\text{-}kg^{-1}$), and addition of 1 $mg\text{-}kg^{-1}$ to the CPB prime solution. The patients were selected by closed envelope method for the study group and control group. The control group (Group ABW) was administered a standard heparin dose regimen calculated at 4 $mg\text{-}kg^{-1}$ according to the ABW before initiating of CPB. In Group LBW, heparin dose was calculated by multiplying the LBW weight by 4 mg. The LBW is part of the body composition that is defined as the difference between total body weight and body fat weight and is between 60 and 90% of the average body weight. There are multiple formulas to calculate the estimated LBW. We used the following James formula in this study:

- eLBW (For males)=1.1*weight(kg)-128*{weight(kg)/height(cm)}^{2}
- eLBW (For females)=1.07*weight(kg)-148*{weight(kg)/height(cm)}^{2}

The lowest target ACT value for the initiation to CPB was accepted as 480 sec. If the desired ACT value was unable to be achieved, 50 mg of heparin was added and, if necessary, added again in the same amount. All additional dose requirements were recorded. Demographic data, comorbidities, postoperative complete blood count values, additional heparin doses, cross-clamp and CPB duration, and intra- and postoperative transfusion requirements were recorded. The baseline ACT values were

measured before the induction of anesthesia and then following heparin administration. Five minute after the initiation of CPB and following protamine application ACT values were obtained and recorded as well. At the exit of CPB, protamine slow infusion was given in a ratio of 1:1 heparin. Blood transfusion during CPB was performed as hematoctrit ≥21%. At the end of surgery, the patients were transferred to the intensive care unit (ICU).

Patients with conscious, communicable, and adequate respiratory whose arterial partial oxygen pressure over 80 mmHg and partial arterial carbon dioxide pressure below 45 mmHg with 40% fraction of inspired oxygen (FiO_2), stable hemodynamic and metabolic parameters, and hourly drainage less than 50 mL were extubated. Mechanical ventilation durations and ICU stay, postoperative drainage volumes, reoperations related to bleeding and mortality rates were recorded.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 15.0 statistical software (SPSS Inc.,

Table 1. Preoperative characteristics

	Lean body weight group (n=50)			Actual body weight group (n=50)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			52.7±13.6			57.5±13.1	0.090
Gender							0.315
Male	22			20			
Female	28			30			
Body Mass Index (kg/m^2)			30.4±15.9			28.1±4.6	0.964
Actual body weight (kg)			74.5±13.4			77.5±14.1	0.419
Lean body weight (kg)			51.7±9.6			54.0±8.9	0.257
Ejection fraction (%)			55.1±8.0			53.1±10.3	0.684
Additional disease							
Diabetes mellitus	10	20		6	12		0.275
Hypertension	20	40		18	36		0.680
Stroke	1	2		4	8		0.362
Chronic obstructive pulmonary disease	11	22		9	18		0.617
Digoxin	6	12		3	6		0.487
Diuretic	16	32		20	40		0.405
Beta-blocker	17	34		18	36		1.000
ACE inhibitor/ARB	18	36		18	36		1.000
Calcium-blocker	10	20		4	8		0.084
Aspirin	10	20		15	30		0.248
Clopidogrel	5	10		0	0		0.056
Warfarin	8	16		14	28		0.148
Low molecular weight heparin	3	6		7	14		0.182
Laboratory data							
Hb (g dL^{-1})			13.6±4.0			13.3±3.0	0.400
Hct (%)			40.5±6.5			39.3±6.1	0.209
Plt (10^9/L^{-1})			217.1±54.2			225.1±62.5	0.667
INR			1.3±0.5			1.6±1.0	0.424
Fibrinogen (mg/dL)			3.7±1.1			3.5±0.7	0.171
BUN (mg/dL)			1.1±1.2			2.8±3.0	0.082
Creatinine (mg/dL)			1.0±0.4			1.0±0.3	0.056
AST (U/L)			22.9±9.7			75.8±25.7	0.154
ALT (U/L)			23.2±21.6			62.3±19.9	0.779

SD: Standard deviation; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; Hb: Hemoglobin; Hct: Hematocrit; Plt: Platelets; INR: International Normalized Ratio, BUN: Blood Urea Nitrogen; AST: Aspartate transaminase; ALT: Alanine transaminase.

Table 2. Intraoperative data

	Lean body weight group (n=50)			Actual body weight group (n=50)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Type of surgery							
MVR	10	20		8	16		0.035
AVR	9	18		5	10		0.057
MVR + AVR	8	16		10	20		0.148
MVR + aortic surgery	12	24		13	26		0.069
AVR + aortic surgery	11	22		14	28		0.114
Cardiopulmonary bypass			139.8±54.1			143.9±51.4	
Cardiopulmonary bypass time (min)			96.3±34.8			97.8±37.0	0.500
Aortic cross-clamp (min)							0.839
Transfusions							
Whole blood (unit)			0.1±0.3			0.0±0.0	0.317
Erythrocyte suspension (unit)			1.2±1.4			1.4±1.8	0.507
Fresh frozen plasma (unit)			0.5±1.1			0.9±2.6	0.433
Platelets (unit)			0.0±0.0			0.0±0.0	1.000

SD: Standard deviation; MVR: Mitral valve replacement; AVR: Aortic valve replacement.

Chicago, IL, USA). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed in mean ± standard deviation (SD) or median values with the interquartile range, if not normally distributed. Categorical variables were expressed in number and frequency. Demographic characteristics, operative and postoperative variables, laboratory data, hemostatic data, and the amount of blood utilization were compared using the independent samples t-test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. A p value of <0.05 was considered statistically significant.

RESULTS

The preoperative characteristics of the patients are summarized in Table 1. There was no statistically significant difference in the age, gender, Body Mass Index (BMI), ABW and LBW, comorbidities,

Table 3. Hemostatic data

	Lean body weight group (n=50)			Actual body weight group (n=50)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Heparin therapy (10^2/IU)							
Initial dose			200.1±39.5			295.6±51.1	<0.001*
Additional dose for target ACT	15	30		13	0		0.656
During cardiopulmonary bypass	13	26		26	0		<0.001*
Total dose			267.9±43.1			354.5±62.1	<0.001*
ACT (sec)							
Baseline			131.9±18.5			126.7±17.6	0.140
After initial dose heparin			473.5±113.8			540.2±164.9	0.011*
Cardiopulmonary bypass login			568.8±144.7			611.6±140.0	0.067
After protamine			133.0±18.9			129.6±28.6	0.676
ICU			145.8±23.4			161.9±34.4	0.403
Protamine (10^2/IU)			276.7±10.1			328.8±24.2	<0.001*
Additional protamine dose in ICU	3	6		8	16		0.110

SD: Standard deviation; ACT: Activated clotting time; ICU: Intensive care unit; * p<0.05.

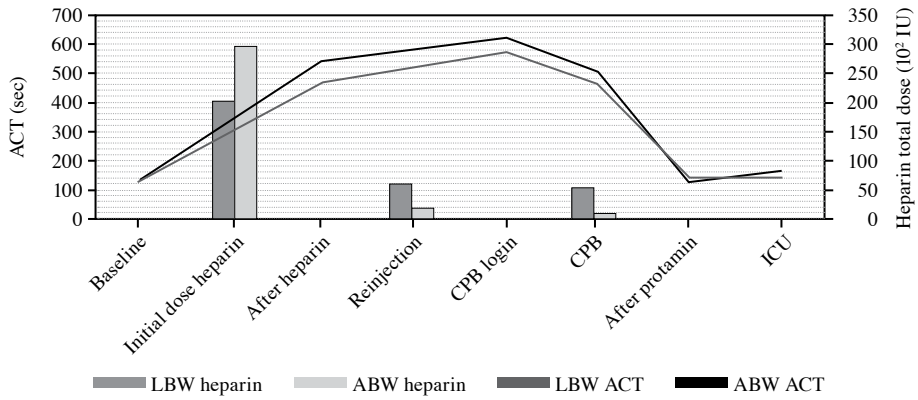

Figure 1. The characteristics of heparin regimen and activated clotting time values.

ACT: Activated clotting time; CPB: Cardiopulmonary bypass; ICU: Intensive care unit; LBW: Lean body weight; ABW: Actual body weight.

medications and preoperative laboratory data of the patients. Type of surgery, duration of CPB or aortic clamping, and intraoperative blood transfusion amounts were also similar (Table 2).

The characteristics of heparin regimen and ACT values during surgery are shown in Table 3 and Figure 1. The groups had comparable ACT at baseline (131.9 vs. 126.7 sec, p=0.140). The initial and total doses of heparin, as well as the total dose of protamine, were significantly higher in the ABW group (p<0.001). The initial dose of heparin administered in the LBW group was 200.1±39.5 IU, while it was 295.6±51.1 IU in the ABW group. The ABW group had significantly higher ACT values after initial dose heparin, as expected (473.5±113.8 vs. 540.2±164.9 sec, p=0.011). Before CPB, the additional heparin administration required to achieve target ACT was similar between the groups (p=0.656). The first ACT value measured after CPB entry was similar between the two groups (568.8±144.7 vs. 611.6±140.0 sec, p=0.067). The number of additional boluses of heparin required during CPB to maintain the target ACT was higher in the Group LBW (26% vs. 0%, p<0.001). However, after reversal with protamine, ACT levels were similar

Table 4. Postoperative events

	Lean body weight group (n=50)			Actual body weight group (n=50)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Hemoglobin (g/dL^{-1})			9.4±1.0			9.0±1.3	0.072
Hematocrit (%)			28.6±2.9			27.6±3.6	0.222
Platelets (10^9/L^{-1})			137.9±47.0			120.9±43.2	0.448
Blood loss (mL)							
At postoperative six hour			302.3±212.1			371.7±339.4	0.312
At postoperative 24 hour			508.2±435.7			638.0±446.1	0.742
Transfusions							
Whole blood (units)			0.2±0.5			0.2±0.7	0.230
Erythrocyte suspension (units)			0.8±1.0			1.8±1.4	<0.001*
Fresh frozen plasma (units)			1.1±1.2			2.8±3.0	<0.001*
Ventilation (hours)			9.4±4.6			11.7±7.5	0.102
Intensive care unit stay (days)			1.4±0.6			1.4±0.8	0.753
Hospital stay (days)			6.4±2.4			8.5±4.2	0.006*
Reoperation	0	0		3	6		0.242
Mortality	1	2		4	8		0.436

SD: Standard deviation; * p<0.05.

between the groups (p=0.676). The number of patients with requiring additional protamine in the ICU was higher in the ABW group (p=0.110) (Table 3).

Postoperative hemoglobin, hematocrit, and platelet values were similar between the groups (Table 4). Postoperative blood loss at six and 24 h was higher in the ABW group, although not statistically significant (p=0.312, p=0.742). The need for blood products using was higher in the ABW group postoperatively (p<0.001, Table 4). Mechanical ventilation and the duration of stay in the ICU were longer in the ABW group, although not statistically significant (p=0.102, p=0.753). The length of stay in the hospital was significantly longer in the ABW group (p=0.006, Table 4). Reoperation for bleeding was required in three patients in the ABW group, while none of the patients required reoperation for bleeding in the LBW group (p=0.242, Table 4). Mortality was observed in one patient in the LBW group and in four patients in the ABW group (p=0.436, Table 4).

DISCUSSION

In the present study, we observed that, heparin dose calculated according to the LBW reached adequate anticoagulation in 70% of the patients. We also found that the total dose of heparin calculated with additional doses and the dose of protamine were lower in the LBW group. In addition, the amount of postoperative drainage, postoperative transfusion requirement, and number of patients requiring protamine in the ICU were lower in the LBW group.

High dose systemic heparin administered in CPB leads to bleeding in the postoperative period and causes non-surgical hemorrhages such as intracranial, gastrointestinal or urinary system, and also increases the need for postoperative blood transfusion and reoperations.[4,5] Reoperation is associated with increased mortality and morbidity, such as renal failure, sepsis, arrhythmia, prolonged mechanical ventilation, and prolonged hospital stay. The half-life of heparin is about 1 to 2 h in human plasma, depending on the dose.[6] The half-life of protamine is shorter than the half-life of heparin. When high doses are used, heparin binds to receptors on endothelial cells and macrophages and to plasma proteins, which leads to slower elimination through the kidneys, longer half-life.[7] Heparin pharmacokinetics include a peripheral process by which the heparin is converted from the free to the bound state. In the postoperative period, heparin binds to peripheral tissues and redistributes to the central compartment, and this phenomenon known as heparin rebound which may increase the amount of bleeding after CPB.[8] The probability of heparin redistribution increases, as the peripheral tissue mass distributed heparin increases. Although attention is paid to drug doses for patients with obesity, drug dose adjustment according to the optimal weight is not often performed in patients with overweight, such as the Turkish population. Therefore, the use of BMI calculation has certain disadvantages, such as not giving ideal results in elderly or athletes.[9] In overweight and obese patients undergoing cardiac surgery, it has been shown that 25% less heparin than previously thought is needed and, then, less protamine is required.[9] However, there is no study using LBW calculations in normal weight patients. In this study, we showed that the heparin dose could be reduced using LBW, whether normal, overweight or obese, without discriminating patients according to their BMI. In our study, the mean BMI values in the LBW and ABW groups were high as expected in the Turkish population (mean 30 and 28 kg/m^2). It has also been observed that the use of LBW without obesity or overweight distinction in patients, or heparin dose adjustment according to LBW may yield better results, if the vast majority of our population is considered to be in this class.

Another method for reducing the amount of heparin is to use lower dosing regimens instead of 4 mg/kg^{-1}. In a study comparing doses of 1-2-2,5-3 mg/kg^{-1} of heparin regimens, target ACT was achieved in 81.5% of patients.[10] Postoperative blood loss in the aforementioned study was also found to be directly proportional to preoperative heparin dose, and postoperative blood loss was found to be lower in patients receiving heparin at 2 mg-kg^{-1} dose. In another study in which heparin doses were administered at 300 IU/kg and 145 IU/kg without calculating the body weight, a lower rate of blood transfusions was required and less postoperative drainage volumes were found in the low-dose heparin group.[11] Although the positive results of heparin reduction were demonstrated in these studies, it is not true that the individual doses of the patients should be administered without taking the standard dose. In a study examining heparin pharmacokinetics during CPB, it was shown that there were wide individual differences in plasma heparin levels, and peripheral compartment distribution contributed to these differences and was responsible for heparin rebound.[12] Therefore, we believe that individualized heparin dose adjustment according to the LBW is a more correct approach than standard low-dose heparin administration.

It has been suggested that ACT has a non-linear relationship with heparin concentration and that ACT tends to plateau in high-dose heparin concentrations. Moreover, the excess of heparin in that plateau phase, which is responsible for the increased perioperative bleeding, cannot be accurately assessed by ACT.[13] It is stated in the EACTA/EACTS 2017 guidelines that the most optimal follow-up would be achieved with heparin blood level, not with ACT.[14] Protamine administration is another important issue and dependent on heparin dose. It is recommended not to exceed a 1:1 dose of the protamine corresponding to the initial heparin dose, as protamine may be associated with overdose perioperative bleeding and increased transfusion.[9] Therefore, it is desirable to reduce the dose of protamine to prevent serious dose-dependent side effects. Coagulation disorders and protamine reactions are the common reported cases in large-scale studies on CPB.[15] In our study, reducing the dose of heparin resulted in reduced dose of protamine, which may have contributed to the reduction of postoperative bleeding and additional protamine requirement in the postoperative ICU. Failure to achieve adequate anticoagulation with heparin in CPB may lead to intraoperative thromboembolic events. There are also reports in the literature describing cases of thrombosis following low-dose heparin administration.[16] In our study, intra- and postoperative thrombosis was not observed in both groups of patients. Conversely, in the ABW group, three patients were re-operated due to bleeding.

Postoperative hemorrhage leading to mediastinal re-exploration significantly affects in-hospital mortality and the length of stay, particularly in valve procedures. Some authors considered that patients undergoing valve procedures were more likely to undergo resternotomy (40.1%) for bleeding than patients undergoing coronary grafting (35.5%).[17] In recent years, patient blood management (PBM) guidelines have been on the agenda to reduce perioperative bleeding and related blood/blood product transfusions. These guidelines provide practical recommendations for all clinicians working in the field of PBM in cardiac surgery, with emphasis on preoperative patient optimization and risk reduction, intraoperative maintenance of hemostasis and postoperative treatment for bleeding complications.[18] According to the guidelines, variation in the efficacy of different heparins may need individual anticoagulation strategies. From heparin's point of view, the use of whole-body LBW approach, even in normal weight, may be a suitable solution for individualized heparin administration. It may be also reasonable to use LBW in areas where the overweight and obese patient populations are particularly large, such as in Turkey.

The main limitation of this study is that blood heparin levels were unable to be detected and evaluated according to the ACT values. Therefore, we believe that further large-scale, prospective, randomized studies would be a guide for the future.

In conclusion, patients undergoing valve surgery underwent heparin administration according to the LBW without regard to normal weight, overweight or obesity, and adequate anticoagulation was obtained in most patients. Also, total heparin and protamine doses decreased, postoperative bleeding, and blood product transfusion and hospital stays decreased. These results are consistent with the desired results in terms of modern cardiac surgery approaches.

Declaration of conflicting interests

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