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ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2019;8(1):123-8

Does heparin dosage calculated with ideal body weight reduce blood product use in open heart surgery?

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Received 31 July 2018; Accepted 12 September2018
Available online 13.11.2018 with doi:10.5455/medscience.2018.07.8926

Abstract

The heparin regimen providing anticoagulation during cardiopulmonary bypass (CPB) is usually adapted to total body weight (TBW). However, this may cause redundant anticoagulation and increase perioperative bleeding, transfusion requirements and reoperation. We compared a heparin regimen based on ideal body weight (IBW) with the traditional regimen. After ethical approval, 100 adults undergoing elective cardiac surgery with CPB were recruited for the prospective, observational study in a tertiary hospital. Prior to CBP an unfractioned heparin dose was adjusted to 300 IU/kg based on TBW (Group TBW, n=50), or IBW (Group IBW, n=50). IBW was calculated using the Lorentz formula. The minimal Activated Coagulation Time (ACT) target value is 400 sec for CPB. Demographic data, cross-clamp and CPB durations, and Hb, Htc, platelet, PT, Aptt and fibrinogen values were similar between the groups ($p>0.05$). Heparin and total protamine doses were significantly higher in Group IBW ($p<0.001$). Differences were also determined in ACT-1, ACT-2, and ACT-3 ($p<0.05$). Group TBW had significantly higher ACT values after initial heparin doses ($p=0.02$) and Group IBW after reversal with protamine ($p=0.001$). Amounts of blood and blood products used differed significantly ($p<0.001$). In terms of drainage at 6 and 24 h, blood loss was significantly higher in Group TBW ($p<0.001$). Postoperative erythrocyte suspension and fresh frozen plasma use were higher in Group TBW ($p<0.001$), and length of ICU stay was significantly longer ($p<0.006$). Heparin doses based on IBW provided sufficient anticoagulation. Heparin and protamine doses decreased, while postoperative bleeding, transfusion requirements and hospitalization decreased.

Keywords: Ideal body weight, total body weight, heparin, protamine, cardiopulmonary bypass, blood transfusion

Introduction

Contact between blood components and the cardiopulmonary bypass (CPB) circuit during cardiac surgery induces coagulation activation. Potent anticoagulation by means of unfractionated heparin (UFH) injection is therefore required to avoid thrombosis in the circuit. There is currently no consensus concerning the modalities of UFH in cardiac surgery and the optimal anticoagulation target assessed intraoperatively on the basis of activated clotting time (ACT). In a recent review, Finley et al. [1] considered an ACT target of at least 350 sec as necessary and sufficient to perform CPB under safe conditions. All situations, including heparin resistance, can be managed with a plasma heparin concentration of at least 4 IU/ml [1]. The initial heparin dose is usually calculated based on the patient's total body weight (TBW). In the standard regimen, a dose of 300 IUUFH/kg of TBW is injected before the start of CPB. Inappropriate doses of heparin may result in intraoperative and postoperative bleeding. Heparin administration is required to prevent thromboembolism caused by blood contact with the CPB machine during cardiac surgery. However, excess heparin doses may cause bleeding, tamponade and bleeding-related reoperation in the postoperative period [2]. There are no specific standards for the clinical management of heparin administration during CPB [3]. Anticoagulation and the heparin response may be complicated in clinical practice, due to heparin insensitivity, antithrombin III deficiency, heparin binding proteins and the use of different heparin formulations [4]. No universal consensus has been achieved regarding the quantitative value of heparin and anticoagulation in CPB, in other words, the ideal ACT value for CPB. Most cardiac centers have specified a target ACT value for CPB of 400-480 sec [5,6]. and also most of the centers where CPB and open heart surgery are performed,

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heparin is usually administered at a dose of 300 IU / kg, which has been determined by observations and is universally agreed, although this dosage may sometimes lead to high perioperative ACT values [7]. Protamine is used for heparin neutralization at the end of CPB. Similarly to heparin, protamine also has its own particular side-effects. These include hypersensitivity, systemic hypotension, pulmonary hypertension, right ventricular failure, angioedema, bronchospasm and anticoagulation with overdoses [8]. The risk of heparin-induced bleeding and the need for protamine increases in a dose-dependent manner, and the risk of developing both complications also rises [8].

The purpose of this study was to investigate the feasibility of adequate anticoagulation with heparin doses calculated based on ideal body weight (IBW), and also to evaluate the risk of postoperative bleeding, transfusion requirements and bleeding reoperations associated with heparin overdose.

Material and Methods

Following ethical committee approval (No. 55, 09.06.2016), 100 ASA II-III patients scheduled for elective cardiac surgery with CPB were recruited for the study. Written informed consent was obtained from all patients before surgery. The primary objective of the study was to compare the effects of a standard heparin injection based on TBW during cardiac surgery on ACT in elective cardiac surgery patients. The secondary objectives were to evaluate the ACT in each group of patients and, at different time points during CPB, and to compare the incidence of bleeding, intraoperative blood transfusion and complications in the two patient groups. An additional objective was to calculate the optimal heparin regimen for all patients depending on their IBW, which can be easily assessed using the Lorentz formulae [9]. The patients included in the study were at least 18 years of age and were scheduled for cardiac surgery (coronary artery bypass graft or valve surgery) under CPB. Exclusion criteria included receipt of preoperative heparin therapy (UFH or low molecular weight heparin), emergency surgery, redo surgery, heart transplantation, surgery for circulatory assistance, and heparin allergy. Routine monitoring with electrocardiography, pulse oximetry and non-invasive arterial blood pressure measurement were performed in the operating room. Following the insertion of two peripheral large bore venous cannulas (18 and 16 gauge), arterial cannulation was performed via the right/left radial artery. After preoxygenation, anesthesia was induced with fentanyl 10 µg/kg and midazolam 0.15 mg/kg. Muscle relaxation was achieved with rocuronium 0.6-1 mg/kg. Patients were generally intubated with 7.5 internal diameter (ID) endotracheal tubes (ETTs) for women and 8.5 ID ETTs for men according to the physical characteristics of the patients. Following intubation, patients were mechanically ventilated with a tidal volume of 4-6 ml kg-1 depending on their IBW. Respiratory frequency was set such as to maintain an EtCO2 level of 35-40 mmHg, and anesthesia was maintained with sevoflurane 0.8-1 MAC with a 40% O2/air mixture. Central venous cannulation was performed via the internal jugular vein. Nasopharyngeal probes were used to monitor body temperature. All patients received tranexamic acid infusion in the form of an initial loading dose (10 mg/kg 30 min), resuscitation until the end of the operation (1 mg/kg per hour), and the addition of 1 mg/kg to the CPB prime solution. Patients were selected in the light of demographic similarities using the closed envelope method for the study and control groups. The control group (Total body weight group, TBW) was administered a standard heparin dose regimen calculated 300 IUUFH/kg according to total body weight before initiating of CPB. In group IBW (Ideal body weight group, IBW), the ideal body weight was calculated according to the Lorentz formulae [9]. and the heparin dose was calculated by multiplying the IBW weight by 300 IUUFH/kg with a target ACT value of at least 400 s. Additional boluses of UFH (50 to 100 IUUFH /kg TBW) were injected if ACT, measured every 30 min during CPB, was insufficient. Surgery was performed under normothermia or mild hypothermia. The body temperature of the patients were kept at the same standard value at different time points. At the end of CPB, the residual effects of heparin were reversed by injection of protamine, based on the total heparin dose (1:1.3). The cut-off point for transfusion was defined as a postoperative hemoglobin concentration of 10 g/dl or less. Blood samples were collected intraoperatively at the following times: T0, at the start of the operation, measurement of baseline ACT (Hemochron Signature Elite, Gamida, Paris, France); T1, 3 min after injection of UFH, measurement of ACT; and T2, at the end of cardioplegia, measurement of ACT, heparin and antithrombin concentrations. ACT measurements were then performed every 30 min during CPB, with maintenance of the target value of at least 400 sec; T3, ACT was measured 10 min after the injection of protamine. All patients were transferred to the ICU postoperatively. Multimodal analgesia was provided and adapted to each patient. The data collected for each patient included the characteristics, use, or discontinuation of antiplatelet agents; type of surgery; CPB and aortic clamping times; data concerning the heparin protocol and its monitoring; intraoperative transfusions; blood loss from chest drains at 6 h (H6) and 24 h (H24); postoperative transfusions of blood products or factor concentrates; total number of days spent in the ICU; postoperative complications; and reoperation requirements. IBW was calculated for each patient using the Lorentz formulae:

IBW women= (height - 100) - ((height - 150)/2.5)
IBW men= (height -100) - ((height - 150)/4)

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables were expressed as mean± standard deviation (SD) or median values with the relevant interquartile range if not normally distributed. Categorical variables were expressed as numbers and percentages. Demographic characteristics, operative and postoperative variables, laboratory data, hemostatic data and amount of blood utilization were compared using the independent samples t-test or the Mann-Whitney-U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. A p value < 0.05 was considered statistically significant. All statistical analyses were performed on SPSS statistical software (SPSS for Windows 15.0, Inc., Chicago, IL, USA).

Results

One hundred patients were recruited into the study. The preoperative characteristics of the two groups of patients were similar (Table 1). Comparison of groups TBW and IBW revealed no significant differences in terms of Hb, Htc, platelet, PT, Aptt or fibrinogen

values (p>0.05) (Table 2). Type of surgery, CPB and aortic clamping times were also similar. Mean CPB time in Group TBW was 77.0±20.2 min, and mean cross-clamp time was 53.4±18.4 min, while in Group IBW, mean CPB time was 83.4±31.5 min and mean cross-clamp time was 54.6±38.7 mean. The differences between the two groups were not statistically significant (Table 3).

Table 1. Preoperative characteristics of the study population

	Group TBW	Group IBW	p value
Age (years) (mean±SD)	59.3±11.36	59.78±10.34	0.72
Gender			
Female, n(%)	24 (%48)	12 (%24)	0.07
Male, n(%)	26 (%52)	38 (%76)	
Height (cm)	165.8±7.4	163.6±9.7	0.35
Total body weight (kg) (mean ±SD)	74.0±11.0	73.0±15.7	0.53
Ideal body weight (kg) (mean ±SD)	-	59.8±8.0	-
Diabetes n(%)	18 (%36)	18 (%36)	1.00
Dyslipidaemia n(%)	12 (%24)	12 (%24)	1.00
Hypertension n(%)	26 (%52)	28 (%54)	0.77
Smoker n(%)	10 (%20)	12 (%24)	0.73
COPD n(%)	10 (%20)	14 (%28)	0.50
OSAS	0 (%0)	0 (%0)	-
Stroke	0 (%0)	0 (%0)	-
Renal failure	0 (%0)	0 (%0)	-
Heart Disease			0.64
Ischaemic	38 (%76)	40 (%80)	
Valvular	8 (%16)	4 (%8)	
Ischaemic,valvular	4 (%8)	6 (%12)	
Antiplatelet agents			
None	38 (%76)	34 (%68)	
Acetylsalycyclic acit	4 (%8)	14 (%28)	
Warfarin	2 (%4)	0 (%0)	
Clopidogrel	6 (%12)	2 (%4)	

SD: standart deviation, COPD: chronic obstructive pulmonary disease, OSAS: obstructive sleep apnoea syndrome

The characteristics of heparin therapy and ACT values during surgery are shown in Table 3. The initial and total doses of heparin, as well as the total dose of protamine, were significantly higher in Group TBW (p<0.001). The initial dose of heparin administered in Group IBW was 17,964.0±2400.5, compared to 21,856.0±3505.6 in Group TBW. Patients in Group TBW with ACT<400 during pump received no additional heparin dose, while six patients in Group IBW received an additional dose of heparin, and the difference was statistically significant (p=0.02). Patients in Group TBW received a total heparin dose of 21,856.0±3505.6 IU during CPB, while those in Group IBW received 18,824.0±3527.9 IU, and the difference was again significant (p=0.004). Patients in Group TBW received 33,500.0±5199.9 IU protamine for heparin neutralization after conclusion of CPB, while those in Group IBW were administered 26,618.0±4066.7 IU, and the difference was significant (p<0.001). Significant differences were also determined between the two groups in terms of ACT-1, ACT-2, and ACT-3 values (p<0.05). ACT values in the two groups were comparable at baseline (Group IBW 142.6±20.8 sec, Group TBW 124.3±20.5 sec, p=0.005). However, as expected, Group TBW had significantly higher ACT values after the initial dose of heparin (Group IBW 526.7±74.1 sec ±113.79, Group TBW 605.2±20.5 sec, p=0.02). The number of additional boluses of heparin required during CPB to maintain the target ACT was higher in the Group IBW (Group IBW 12%, Group TBW 0%0, p=0.02). Group IBW had significantly higher ACT values after reversal with protamine (p=0.001) (Table 3). A mean 3.96±2.23 units of blood and 2.12±1.01 units of fresh frozen plasma were used in the operative period in Group TBW patients. In Group IBW, a mean 1.48±0.51 units of blood and 1.12±0.67 units of fresh frozen plasma were used. The differences between the blood and blood products used in the two groups were statistically significant (p<0.001) (Table 3). When the two groups were compared in terms of amounts of drainage at 6 and 24 h, blood loss was significantly higher in Group TBW than in Group IBW (p<0.001). When the two groups were compared in terms of use of blood and blood products, the amounts of erythrocyte suspension and fresh frozen plasma given in the postoperative period were higher in the Group TBW patients than in those in Group IBW, and the difference was statistically significant (p<0.001). No patient in either group required bleeding control (Table 3). Length of stay in the ICU was significantly longer in Group TBW (p<0.006, Table 3). No significant difference was observed in the patients

included in the study in terms of development of postoperative complications. However, length of stay in the ICU was statistically significantly shorter in Group IBW (p= 0.005) (Table 3). Mortality was observed in 4 patients in Group IBW and in 10 patients in Group TBW (p=0.41, Table 3).

Table 2. Laboratory data of the study population

	Group TBW	Group IBW	p value
Haemoglobin (gr/dL) (mean±SD)	14.2±1.6	14.9±1.3	0.07
Haematocrit (%)(mean ±SD)	42.2±6.0	45.1±4.1	0.10
Platelets (109 L-1) (mean ±SD)	239,760±67,020	265,375±63,963	0.18
Phrothrombin time (10.5-14.9 sn)(mean ±SD)	13.2±1.58	12.7±0.8	0.28
Aptt (21-35sn) (mean ±SD)	25.8±5.0	25.0±2.3	0.79
Fibrinogen (180-350 mg/dL) (mean ±SD)	353.0±48.4	326.1±73.8	0.11

SD: standart deviation, aPTT: activated partial thromboplastin time

Table 3. Intra- and postoperative data of the study population

	Group TBW	Group IBW	p value
Surgery type n(%)			0.34
CABG	38 (%76)	40 (%80)	
AVR	2 (%4)	0 (%0)	
MVR	6 (%12)	2 (%4)	
CABG, MVR	4 (%8)	2 (%4)	
CABG, AVR	0 (%0)	2 (%4)	
AVR, MVR	0 (%0)	4 (%8)	
CPB time (sn) (mean±SD)	77.0±20.2	83.4±31.5	0.48
Aortic clamp time (sn) (mean±SD)	53.4±18.4	54.6±38.7	0.08
RBC (units) (mean±SD)	3,96±2.23	1.48±0.51	**<0.001***
Platelets (units) (mean ±SD)	0	0	-
FFP (units) (mean ±SD)	2.12±1.01	1.12±0.67	**<0.001***
Fibrinogen (180350 mg/dL) (mean±SD)	0	0	-
Heparin initial dose (IU) (mean ±SD)	21856.0±3505.6	17964.0±2400.5	**<0.001***
Reinjection dose n (%)	0 (%0)	6 (%12)	**0.02***
Total heparin dose (IU) (mean ±SD)	21856.0±3505.6	18824.0±3527.9	**0.004***
Protamin dose (IU) (mean ±SD)	33500.0±5199.9	26618.0±4066.7	**<0.001***
ACT-1 (sn) (mean ±SD)	124.3±20.5	142.6±20.8	**0.005***
ACT-2 (sn) (mean ±SD)	605.2±20.5	526.7±74.1	**0.002***
ACT-3 (sn) (mean ±SD)	117.5±14.8	127.8±12.4	**0.001***
Blood loss – H6 (mL) (mean ±SD)	548.0±108.4	403.2±101.2	**<0.001***
Blood loss– H24 (mL) (mean ±SD)	770.0±170.7	596.4±149.6	**<0.001***
Post-op RBC (units) (mean ±SD)	2.3±0.9	1.56±0.5	**0.001***
Post-op platelet (units) (mean ±SD)	0	0	-
Post-op FFP (units) (mean ±SD)	2.3±0.6	1.0±0.7	**<0.001***
Reoperation n(%)	6 (%12)	4 (%8)	**1.00**
Complication			0.35
None	38 (%76)	42 (%84)	
Stroke	4 (%8)	0 (0)	
Sepsis	4 (%8)	2 (%4)	
Acute renal failure	2 (%4)	0 (%0)	
Respiratuar depression	2 (%4)	6 (%12)	
Length of ICU stay (days) (mean±SD)	3.8±1.2	3.0±0.9	**0.005***
Mortality n(%)	10 (%20)	4 (%8)	0.41

*: statistically significant, SD: standart deviation, Values are expressed as mean_SEM, or n (%). FFPr6, fresh frozen plasma; H24, 24th hour postoperation; H6, sixth hour postoperation;

Discussion

In this study we observed that heparin doses calculated based on ideal body mass provided adequate anticoagulation in cardiac surgery patients. The total dose of heparin calculated including additional doses and the protamine dosage were lower in the IBW group. Postoperative drainage, postoperative blood and blood product transfusion requirements, and number of patients requiring protamine in the ICU were also higher in the TBW group. High-dose systemic heparin administered in CPB leads to bleeding in the postoperative period and causes non-surgical intracranial, gastrointestinal or urinary system hemorrhage, and also increases the need for postoperative blood transfusion and reoperations [5, 6]. The half-life of heparin is approximately 1-2 h in human plasma, depending on dose [10]. The half-life of protamine is shorter than that 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, and a longer half-life [11]. Heparin rebound may be caused by high-dose heparin that is bound to the protein and does not form a complex with protamine sulfate, and these complexes may slowly dissociate and produce anticoagulant effects [12]. Several authors have reported a higher risk of postoperative bleeding when high heparin doses are used during CPB [13-16]. Dercksen et al. [17] showed that the use of high doses of heparin and protamine was responsible for defective postoperative coagulation. In a study comparing 1, 2, 2.5, and 3 mg/ kg heparin regimens, target ACT was achieved in 81.5% of patients. Postoperative blood loss in that study was found to be directly proportional to preoperative heparin doses, and postoperative blood loss was lower in patients receiving heparin at 2 mg/ kg [8]. In a study in which heparin doses were administered at 300 IU/kg and 145 IU/kg irrespective of body weight, less blood transfusion was required and less postoperative drainage volumes were observed in the low-dose heparin group [18]. Haas et al. [19] reported that when heparin was administered to obese patients based on IBW, both the amount of heparin used and potential complications associated with heparin use decreased. Evidence suggests that as body mass index increases, the percentage of body fat receiving less blood flow per gram increases [20,21]. In our opinion, dosages based on IBW can be used not only for obese, but also for non-obese patients. One study examining heparin pharmacokinetics during CPB reported wide individual differences in plasma heparin levels, and that peripheral compartment distribution contributed to these differences and was responsible for heparin rebound [22]. We therefore think that individualized heparin dose adjustment based on IBW represents a more correct approach than standard low dose heparin administration.

It has been suggested that ACT has a nonlinear 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 increased perioperative bleeding, cannot be accurately assessed using ACT [19]. The EACTA/EACTS 2017 guideline states that the best follow-up can be achieved with heparin blood levels, not with ACT [23]. Protamine administration is another important issue and is heparin dose-dependent. Since protamine may be associated with perioperative bleeding and increased transfusion requirements, a 1:1 dosage, equivalent to the initial heparin dose, should not be exceeded [23]. It has also been suggested that high-dose heparin and protamine may result in postoperative clotting problems [17]. The protamine dosage should therefore be reduced in order to prevent serious dose-dependent side-effects, including arterial hypotension, pulmonary vasoconstriction, reduced cardiac output, platelet inhibition, and allergy [24,25]. The most common side-effects in large-scale CPB studies are coagulation disorders and protamine reactions [26,27]. Low-dose heparin has been shown to result in a significant decrease in postoperative blood loss and lower protamine requirements [28]. In our study, reducing the heparin dosage resulted in a decrease in that of protamine, which contributed to decreased postoperative bleeding and additional protamine requirements in the postoperative intensive care unit.

However, studies have also reported that low-dose heparin administration in patients undergoing off-pump CABG does not result in any difference in terms of intraoperative and postoperative bleeding, transfusion requirements, or complication rates [29,30]. However, these studies involved off-pump cases without CPB. Conditions used for on-pump CABG, such as CPB, high heparinization requirement, and hypothermia, lead to very complex and deleterious effects on the coagulation system. Off-pump and on-pump surgery may therefore produce inconsistent results.

Our study has a number of limitations. First, blood heparin levels according to ACT values were not determined. Second, other factors such as the surgical technique employed and the surgeon's experience may influence postoperative bleeding rates, however, the operations performed by senior surgeons with extensive experience of cardiac surgery. Investigation of such factors would elicit a better understanding of the pharmacokinetics and volume of heparin in cardiac surgery patients.

Conclusion

In conclusion, sufficient anticoagulation was achieved with titration of heparin doses calculated based on IBW in cases of cardiac surgery using CPB, and total heparin and protamine dosages decreased, postoperative bleeding, blood and blood product transfusion, and hospital stays all decreased.

Competing interests
The authors declare that they have no competing interest

Financial Disclosure
The financial support for this study was provided by the investigators themselves.

Ethical approval
Our study was approved by the local ethics review board.

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