COMPARISON OF EMPIRICAL PROTAMINE DOSE STRATEGY WITH CALCULATED DOSE BASED ON HEPARIN DOSE RESPONSE CURVE POST CARDIOPULMONARY BYPASS IN CABG PATIENTS

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ABSTRACT

Objective: To investigate whether calculated Protamine dose can obtain satisfactory post Heparin reversal ACT results and reduce protamine usage compared with traditional empirical full protamine dosage.

Study Design: Randomized controlled trial.

Place and Duration of Study: Armed Forces Institute of Cardiology/NIHD between Nov 2018 and Feb 2019.

Methodology: Peri-operative ACT results of 240 consecutive patients, undergoing on pump coronary artery bypass graft (CABG) surgery were collected, they were randomly divided into two groups A and B, Heparin was reversed by administering a calculated protamine dose based on Heparin dose response curve in group A and full dose Protamine (1mg per 100 IU) in group B. Baseline ACT, total Heparin dose administered, Protamine dose, post Protamine ACT were recorded for all patients.

Results: Post Heparin reversal ACT is returned to near baseline values 107.80 ± 14.471 compared with control ACT 106.90 ± 16.843 (*p*-value 0.006) in group A patients, and satisfactory ACT 124.10 ± 20.415 levels in patients of group B, but accompanied with significant additional doses of protamine (*p*-valve 0.02).

Conclusion: Both doses of Protamine whether empirical full dose or based on Heparin Dose response curve provides optimal heparin reversal, while full dose protamine is associated with unnecessary protamine additional doses.

Keywords: ACT, Heparin, On pump CABG, Protamine.

INTRODUCTION

Heparin Sodium (unfractionated heparin) is the most widely used anticoagulant during CPB; its anticoagulation is achieved by administering bolus dose based upon weight and assessed by the most widely used perioperative coagulation monitor test the ACT[1,2]. Heparin average half-life is 1.5 h (1-4 h range) and the elimination time increases by incremental dosage[3,4].

Heparin dose response curve is a technique used to calculate subsequent heparin dose and protamine reversal. It depends on the concentration of heparin in the blood at the time of neutralization

Point A: control ACT, Point D: desired ACT after the 1st Heparin dose E: measured ACT before reversal C: theoretical requirement of an

additional heparin dose. Arrow D: additional heparin dose to achieve an ACT of 480s.

Normal ACT ranges from approximately 107 ± 13 sec (mean ± Standard deviation). Heparin clearly prolongs the ACT, because this test measures the clotting potential of the intrinsic and common pathways of coagulation. It is important test for safe initiation and continuation of CPB, apart from Heparin level in the blood ACT is also affected by hemodilution, hypothermia, low platelet count, coagulation deficiencies and warfarin[5,6]. ICU staff considering Heparin as an accused of high ACT levels and tends to manage bleeding with additional doses of protamine[7].

Protamine is a small, Arginine-rich, nuclear proteins formulated as sterile, isotonic solution in water, it is strongly basic combines with acidic heparin forming a stable neutral 1:1 protamine-heparin complex[8,9]. This is then removed and broken down by the reticuloendothelial system,

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the effect is almost immediate and persists for approximately 2 hours. However studies have shown that unbound form has intrinsic antico-agulant properties and impair hemostasis[9]. Niel-sen and Malayaman, have shown that protamine decreases thrombin activity, reduces factor VII and V activation, enhances fibrinolysis, and imp-airs platelet function[8,11].

There are currently several techniques descr-ibed in literature for anticoagulation with heparin and its reversal with protamine in cardiac sur-gery[11]. The most commonly method is to give 1mg of Protamine for each 100 IU of Heparin. The drawback of this method is that it does takes into account neither the interpatient variability nor the physiological elimination of the heparin and it can result in overdose the drug[13].

Another approach is to adjust the dose of protamine (mg) to neutralize 100 units of heparin depends on the time elapsed since heparin dose is given, <1/2 h: 1-1.5 mg/100 units of heparin, 30-120 min: 0.5-0.75 mg/100 units of heparin, >2 h: 0.25-0.75 mg/100 units of heparin[4].

These mentioned approaches indicating that there is large variability regarding the use of hep-arin dosing, monitoring and reversal[14].

As above there is no clear consensus to the dosage of protamine required to reverse a given dose of heparin and Protamine is having a bipolar effects; neutralizes heparin and exerts an anticoagulant effect making appropriate heparin reversal after CPB is still represent a challenge in the field of postoperative coagulation control.

METHODOLOGY

This study was a double blinded randomi-zed controlled trial conducted at Armed Forces Institute of Cardiology/NIHD between Novem-ber 2018 and February 2019. After approval of the hospital ethics committee, consecutive 240 patients scheduled for elective CABG surgery and who fulfilling our study inclusion criteria (age group 40-70 years, both genders, elective on pump CABG surgery and cessation of antiplatelet at least 5-7 days before surgery) and exclusion criteria (Congenital or acquired disorders of he-mostasis, renal insufficiency, liver insufficiency, patient on anticoagulants, Acute coronary synd-rome and history of Protamine allergy), were randomly allocated in two groups A and B using computer generated random number tables. After taking informed consent from the patient and a day before surgery, when the patients were listed up for surgery, the in-charge nurse of the pre-operative ward was informed by the investigator to allocate the patient in either of the two groups. Pre-anesthetic checkup history and all routine investigations of blood elements, bleeding profile, LFTs and RFTs were carried out as per protocol. All patients received same premedication as per our department's protocol prior to surgery. Anti-platelets and/or other anti-coagulants were stop-ped at least 5 days before the surgery. After indu-ction all patients were managed through stan-dard sequence for anti-coagulation management of CPB. Venous blood sample for baseline ACT
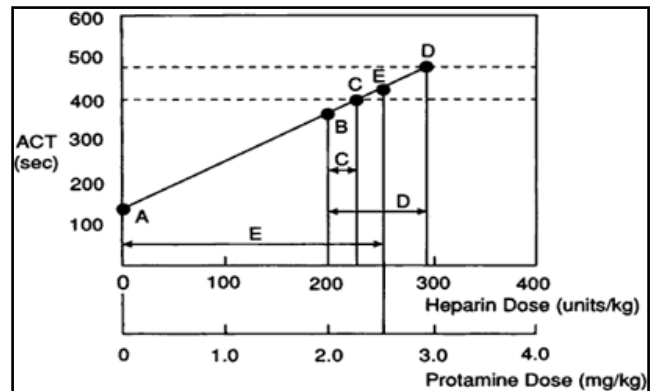

Figure-1: Graph of a heparin and protamine dosing algorithm, from practical approach to cardiac anesthesia.

was taken immediately after patient induction from internal jugular vein cannulation before placement of central line catheter.

All patients were anticoagulated with 300 IU/kg of unfractionated heparin, given via central venous catheter, followed by an arterial blood sample for ACT after 3-5, aiming at an ACT above 3-4 times of baseline ACT (>450s) before initiating CPB.

Further doses of heparin 5000 IU were administered to priming fluid to maintain an

ACT value as required during CPB period by the perfusionist, ACT was monitored at least every 30 min during CPB and additional doses may be added accordingly to achieve and maintain (ACT) of greater than 480s.

After separation from CPB patients were randomly categorized into two groups. Study

Table-I: Demography of patients.

Parameters	Group A Mean ± SD	Group B Mean ± SD
Mean Age (years)	74.46 ± 12.170	73.61 ± 12.421
Mean Weight (kg)	59.86 ± 8.091	59.40 ± 7.786
No. of Male Patients	112 (93%)	114 (95%)
No. of Female Patients	8 (7%)	6 (5%)

Table-II: Coagulation parameters.

Parameters	Group A Mean ± SD	Group B Mean ± SD	*p*-value
Base line ACT	106.90 ± 16.843	109.90 ± 16.498	0. 165
Total heparin dose (unit)	3235.83 ± 364.8	3214.00 ± 371.557	0.658
Protamine dose (mg)	113.25 ± 12.378	202.00 ± 55.444	0.000
ACT after Heparin reversal (sec)	107.80 ± 14.471	124.10 ± 20.415	0.006
Additional protamine mg	25.00 ± 000	33.33 ± 14.852	0.02

group (A) of 120 patients received a calculated dose of protamine obtained by individualized residual Heparin at the moment of protamine dosing, using Heparin dose response curve as following:

Initial ACT ploted on the X-axis as A point, after heparinization B line represent increase in ACT.

Line from T point, intersect with X axis represented ACT after heparin. In case additional Heparin was needed, the desired ACT was present on B line; the amount of additional Heparin needed was the difference on the Y-axis between the present ACT and the desired ACT. ACT

was measure point D and accordingly residual Heparin level was determined on the y axis, then protamine dose calculated.

X axis: ACT (sec), Y axis: heparin (100 IU/kg), Point A: baseline ACT, Point B: increase in ACT after the 1st Heparin dose, T point intersect with X line: is ACT after full dose heparin, point D: is measured ACT before reversal.

RESULTS

Two Hundred forty patients included in this study, in the age group of 40-72 years, 226 (94.0%) were males and 14 (6%) were females. There were no significant differences between groups in the
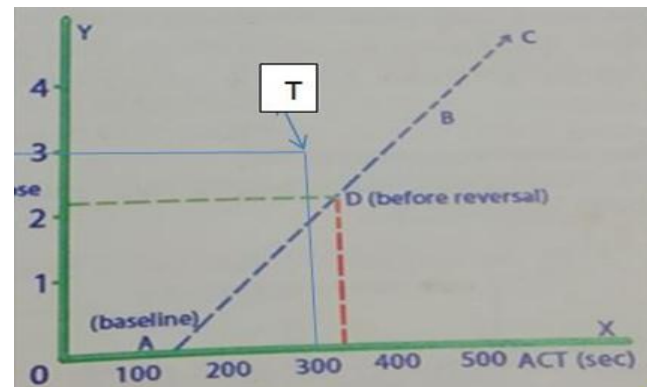

Figure-2: Heparin dose curve.

mean age or weight.

The results are given as Mean ± SD. A *p*-value <0.05 Values is significant with equal variances assumed.

In this study heparin was given to all patients on the bases of weight and there was no significant variation in total heparin given between the study groups *p*-value 0.6.

DISCUSSION

Anticoagulation is part and parcel of open-heart surgery involving CPB. Heparin administration and its reversal always remain a matter of concern in situations where there is more than expected bleeding. Incomplete reversal of heparin is considered number one factor, but that is not always the cause. Most of the time clinicians choose a ratio of 1 mg of protamine to 100 IU of heparin to calculate the protamine dose. However, ideally. Protamine should be administered

in a dose that matches actual heparin levels on blood after the termination of CPB[15]. In our study, the ACT end results gained after using Heparin dose response curve to determine residual Heparin and protamine dose, show satisfactory reversal of heparin indicated by return of ACT to near base line 109.90 ± 16.498 with *p*-value 0.006 with a reduction of protamine dose when compared with the group of patient who were treated with conventional protamine-to-heparin dose strategy (full neutralization), who ended up getting additional protamine doses to manage slightly prolong ACT neglecting other causation.

Taking into account that heparin is broken down, with a half-life of approximately 1.5 to 2 hours and a part of it definitely wasted through blood loss[16,17], protamine dosing based on 1:1 ratio would be in excess for the patients.

In a randomized control trial (RCT), Koster *et al*, demonstrated that protamine dosing based on the initial heparin dose resulted in prolonged ACT and microvascular bleeding compared with Protamine dosing based on the measured heparin concentration following CPB[17]. Another RCT, a protamine-to-heparin dosing ratio of 1.3 over the total heparin dose was associated with significantly more postoperative bleeding compared with a dosing ratio of 0.8.[19] Moreover, Salvatore, *et al* suggested that the commonly applied 1:1 ratio of protamine to heparin could be higher than needed as a complete reversal of heparin could be effectively achieved with 2/3 of protamine dose and additional protamine seems to induce an elongation of the clotting time[11].

Despotis *et al*[20], In a prospective study of 250 patients found that a reduction of post-operative blood, platelet, plasma and cryoprecipitate units administration when protamine dose was calculated considering residual heparin concentration at the end of CPB rather than the initial dose administered before CPB. These same conclusions were also confirmed in the other studies which have been show that a protamine dose reduction led to better outcomes[21-23].

Current guidelines advise a protamine-to-heparin dosing ratio of 1:1 to 1:1.3, with a level IIb recommendation for lower protamine dosing[23-25].

CONCLUSION

Heparin dose response curve provide optimal heparin reversal and guarantee that excess Protamine is not a part of any coagulation derangement if any, Full dose protamine reversal (1:100 ratio) results in additional unwarranted protamine administration.

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CONFLICT OF INTEREST

This study has no conflict of interest to be declare by any author.

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