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Comparison between the Effect of Low and Standard doses of Protamine in Reversing Heparin in Coronary Artery Bypass Graft

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Abstract:

Background: *Cardiac surgery like CABG which is done for revascularization of coronary arteries in advanced CAD needs the use of protamine to reverse the heparin at the end of surgery. Usually the use of protamine associated with many adverse reactions mainly decrease in arterial blood pressure, increase in airway resistance and increase in pulmonary artery pressure. There is much debate about the optimum protamine dose that completely reverse the anticoagulant effect of heparin with less or minimum side effect.*

Objective: *To compare between low and standard doses of protamine sulfate in reversing unfractionated heparin in coronary artery bypass graft surgery with CPB.*

Patient and Method*: A prospective randomized clinical trial conducted on 60 patients divided into 2 groups each group 30 patients. For reversing of heparin after completion of surgery ,first group received standard dose of protamine 1mg:1mg(100U) of heparin administered , second group received low dose of protamine 0.75 mg:1mg(100U) heparin administered. We measured the ACT,SBP,DBP,MAP and Peak airway pressure(Ppeak) for each group before protamine and 5 min. after protamine administration.*

Results: *For patients administered low dose of Protamine, there was a highly significant reduction in the incidence of hypotension(SBP,DBP,MAP) 5 minutes after protamine administration in comparison to patients administered standard dose ($p<0.001$). Patients administered with low dose of Protamine had significantly lower peak airway pressure mean than patients administered with standard dose 5 min. after Protamine administration ($p<0.001$).*

Conclusion: *Use of low dose of protamine in reversing heparin in CABG seems to be clinically safe and effective with highly significant reduction in incidence of hypotension and highly significant low peak airway pressure in comparison with traditional dose.*

Keywords*: Protamine, Heparin, Activated Clotting Time, Peak Airway Pressure, Coronary Artery Bypass Graft, Coronary Artery Disease*

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1. INTRODUCTION

Protamine is widely use in cardiac surgery to reverse the action of heparin specially in coronary artery bypass graft (CABG) with cardiopulmonary bypass machine which is the definitive treatment for advanced sever coronary artery diseases (CAD).

CORONARY ARTERY DISEASES (CAD) :

The prevalence of vascular disease and ischemic heart disease in the United States increases significantly with age. By some estimates 30% of patients who undergo surgery annually in the United States have ischemic heart disease. Angina pectoris, acute MI, and sudden death are often the first manifestations of ischemic heart disease, and cardiac dysrhythmias are probably the major cause of sudden death in these patients. The two most important risk factors for the development of atherosclerosis involving the coronary arteries are male gender and increasing age. Additional risk factors include hypercholesterolemia, systemic hypertension, cigarette smoking, diabetes mellitus, obesity, a sedentary lifestyle, and a family history of premature development of ischemic heart disease. Psychologic factors such as type A personality and stress have also been implicated. Patients with ischemic heart disease can have chronic stable angina or acute coronary syndrome at presentation. The latter includes ST elevation myocardial infarction (STEMI) and unstable angina/non–ST elevation myocardial infarction (UA/NSTEMI). (1)

Revascularization by coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with or without placement of intracoronary stents is indicated when optimal medical therapy fails to control the CAD. (2)

CORONARY ARTERY BYPASS GRAFT (CABG):

It is a procedure in which one or more blocked coronary arteries are bypassed by a blood vessel graft to restore normal blood flow to the heart. These grafts usually come from the patient's own arteries and veins located in the leg (saphenous vein), arm (radial artery), or chest (internal mammary artery) . Coronary artery bypass graft surgery (CABG) can be performed with or without cardiopulmonary bypass. (3) CABG surgery with cardiopulmonary bypass (CPB) remains the standard technique by which the other techniques (ie, PCI, off-pump CABG) are measured. It is expected that it will continue to be a cornerstone in the management of CAD in the foreseeable future. (4, 5)

HISTORY OF CORONARY ARTERY BYPASS GRAFTING

The modern era of myocardial revascularization with cardiopulmonary bypass began in 1954 when Dr. John Gibbon reported the development of the cardiopulmonary bypass machine. An additional advance occurred with the development of coronary angiography by Mason Sones at the Cleveland Clinic in 1957, which opened the door to the elective treatment of coronary atherosclerosis by means of direct revascularization. The success of these techniques was soon demonstrated in larger series initiating the modern era of coronary artery surgery. (6)

BASIC CIRCUIT

The typical CPB machine has six basic components (figure 1) a venous reservoir, an oxygenator, a heat exchanger, a main pump, an arterial filter, tubing that conducts venous blood to the venous reservoir, and tubing that conducts oxygenated blood back to the patient. Most machines also have separate accessory pumps that can be used for blood salvage (cardiotomy suction), venting (draining) the left ventricle, and administration of cardioplegia solutions. A number of other filters, alarms, and inline pressure, oxygen-saturation, and temperature monitors are also typically used. (7-9)

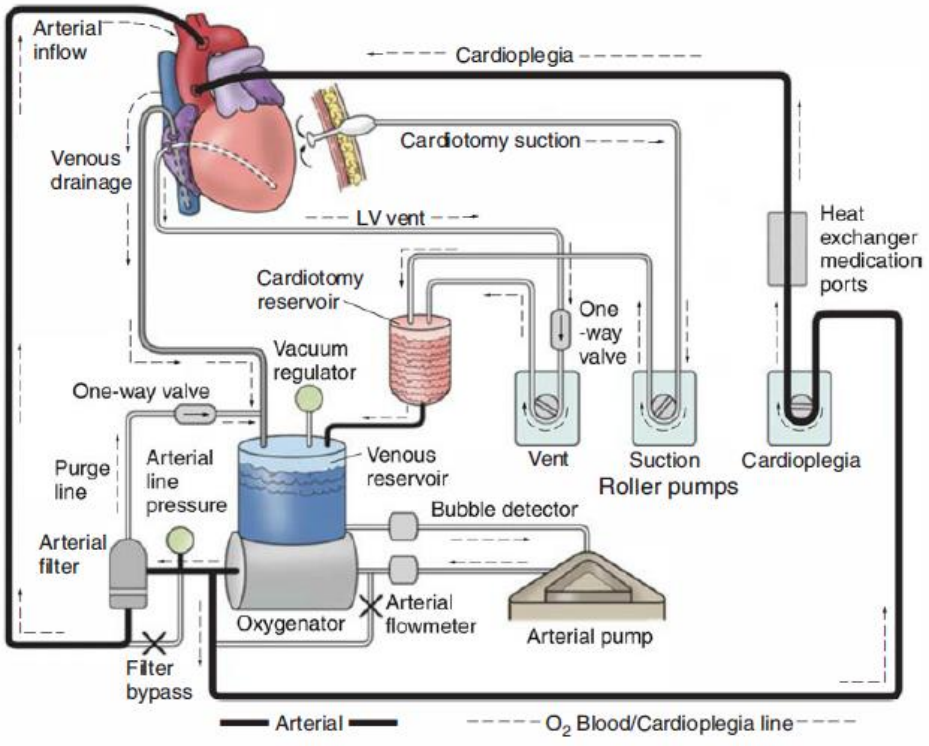

Figure 1: Cardiopulmonary Bypass Machine

SEQUENCE OF EVENTS:

Although the approach to surgical procedures that require CPB varies among institutions, all procedures loosely follow a predictable sequence of events. At any institution, CPB requires circuit selection and priming, anticoagulation, usually heparin or alternates, cannulation, initiation and maintenance of CPB, myocardial protection, and finally, weaning and termination from CPB. (10)

Prior to use, the CPB circuit must be primed with fluid (typically 1200–1800 mL for adults) that is devoid of bubbles. A balanced salt solution, such as lactated Ringer's solution, is generally used, but other components are frequently added, including colloid (albumin or starch), mannitol (to promote diuresis), heparin (500–5000 units), and bicarbonate. At the onset of bypass, hemodilution decreases the hematocrit to about 22–27% in most patients. Blood is included in priming solutions for smaller children and severely anemic adults to prevent severe hemodilution. (9)

PROBLEMS OF CBP:

1.Problems associated with venous cannulation e.g arrhythmias ,atrial or caval tears, bleeding, air embolization & unexpected decanulation,

Improperly placed purestring sutures may obstruct cava when tied

2. Problems associated with arterial cannulation e.g: Difficult insertion, bleeding, tear in aortic wall, intramural or malposition of cannula tip, air emboli, plaque emboli & aortic dissection.

3. Inflammatory Response to Cardiopulmonary Bypass :

The contact of blood with the extracorporeal circuit results in the activation of numerous cascades, including the kallikrein, coagulation, and complement systems. Among the consequences of this contact are thrombin generation, the release of proinflammatory cytokines, and a systemic inflammatory response. Endothelial-based reactions, including platelet adhesion, aggregation, and activation, as well as leukocyte adhesion and activation have been implicated in myocardial reperfusion damage, pulmonary and renal dysfunction, neurocognitive changes, and a generalized capillary leak. Fortunately, adverse effects of this inflammatory response are not clinically significant in most patients. However, in patients requiring long pump runs or in those with significant hemodynamic compromise following surgery, this systemic inflammatory response may persist for days, leading to multiple organ system compromise. (11-15)

4. Despite adequate heparinization, the bypass circuit is a potent activator of the coagulation system with generation of factor Xa and thrombin that contribute to the inflammatory response and potentially to ischemia/reperfusion injury. A coagulopathy may develop from activation of platelets and the fibrinolytic system, as well as from dilution of clotting factors and platelets during bypass. (16)

5. Interstitial edema:

Interstitial fluid loss results from the development of intercellular gap formation and vascular permeability.

6. Pulmonary dysfunction :

Acute postoperative pulmonary dysfunction is one of the most noticeable common effects of CPB. Acute lung injury after CPB can be documented by measuring the alveolar-arterial oxygenation gradient, intrapulmonary shunt, degree of pulmonary edema, pulmonary compliance, and pulmonary vascular resistance.

7. Renal dysfunction : In addition to the generalized inflammatory changes that result from CPB, and that may affect the kidneys, the generation of free hemoglobin during CPB can result in increased delivery of toxic-free iron to the renal endothelium and tubular epithelium, providing a major pathway for the induction of post-CPB renal failure.

8. Neurological injury :

In addition to clearly defined cerebrovascular events or strokes,

some patients who have had heart surgery experience a cognitive

impairment or delirium. Another common finding is depression.

The mechanisms for brain injury with CPB include reduced cerebral blood flow, embolic events, and the systemic inflammatory response to CPB.

9. Bleeding complications :

The complexity of the coagulation dysfunction after CPB results from the technical variations in the operative procedures and the many uncontrolled variables that are associated with CPB, including the effects of anesthetic or pharmacological agents, the nature of the priming solution, hemodilution, hypothermia, the type of oxygenator, and the use of transfused blood products. (17) .Other problems listed below

Heparin :

Historical Considerations :

Heparin, one of the oldest anticoagulant drugs currently still in widespread clinical use, was discovered in 1916 by a second year

medical student, Jay McLean, and Professor Howell at Johns Hopkins University.

Research on heparin continued into the 1930s. Jorpes described the structure of heparin in 1935, which made it possible for the Swedish company Vitrum AB to launch the first heparin product for intravenous use in 1936.

Heparins are available as unfractionated heparin (UFH) and

low molecular weight heparins (LMWHs), which are chemical

modifications of unfractionated heparin.

UNFRACTIONATED HEPARIN :

UFH is a naturally occurring glycosaminoglycan. It is a negatively charged sulfated polysaccharide formed from alternating residues of D- glucosamine and L-iduronic acid.

Heparin is mostly located in lung, intestine, and liver in mammals. Standard preparations are derived from either porcine intestine or bovine lung and prepared as calcium or sodium salts. Molecular weights range from 3000 to 30,000 Da, with a mean of 15,000 Da representing 40 to 50 saccharides in length. (18)

Heparin is also present endogenously in basophils, mast cells, and the liver and the biologic activities of commercial preparations of heparin parallel endogenous heparin.

Standardization of heparin potency is based on in vitro comparison with a known standard. A unit of heparin is defined as the volume of heparin-containing solution that will prevent 1 mL of citrated sheep blood from clotting for 1 hour after the addition of 0.2 mL of 1: 100 calcium chloride.

Heparin must contain at least 120 United States Pharmacopeia (USP) units per mL. Because the potency of different commercial preparations of heparin may vary greatly, the heparin dose should always be prescribed in units. (19)

Mechanism of action:

Heparin acts by accelerating the rate of reaction of an endogenous antithrombin in plasma (formerly known as antithrombin III or heparin cofactor) with many activated clotting factors. Antithrombin is a serpin (a serine protease inhibitor) which normally combines with

many activated proteolytic factors in plasma and neutralizes their coagulant activity by forming a stable complex. Heparin significantly increases the rate of binding of antithrombin to thrombin (1ooo fold), thus producing immediate anticoagulant effects (both in vivo and in vitro). Heparin also inhibits factor Xa, but in a rather different manner. Its reaction with antithrombin produces a conformational change that facilitates its binding with factor Xa, and its action does not depend on the simultaneous binding of antithrombin and factor Xa by heparin.

Other actions

Heparin affects blood coagulation in several other ways. In high doses, it inhibits platelet aggregation and prolongs the bleeding time. Heparin also activates lipoprotein lipase in vascular endothelium, hydrolyzing plasma triglycerides to glycerol and free fatty acids and reducing plasma turbidity. The resultant increase in free fatty acid levels may interfere with the plasma protein binding of certain drugs (e.g. propranolol, phenytoin) in blood sampled from cannula which are intermittently flushed with heparin. (20)

Pharmacokinetics :

Heparin is a poorly lipid-soluble, high-molecular-weight substance that cannot cross lipid barriers in significant amounts. As a result, heparin is poorly absorbed from the gastrointestinal tract and is usually administered by intravenous (IV) or subcutaneous (SC) injection. Intramuscular (IM) administration of heparin is avoided due to the
risk of hematoma formation. Heparin does not cross the placenta and can be administered to the mother without producing anticoagulation in the fetus.

The onset of action: It is immediate after iv injection but can be delayed 20 to 60 minutes following s.c injection.

Duration of action 6-12 hr

Volume of distribution: 40-70 mL/min (approximately the same as blood volume)

Although heparin does not distribute into adipose tissues, clinicians should use actual body weight in obese patients to account for extra vasculature.

Protein binding: Very high, mostly to low-density lipoproteins. It is also extensively bound by globulins and fibrinogens.

Half-life:1.5 hours. The plasma half-life of heparin increases from about 60 minutes with a 100 unit/kg dose to about 150 minutes with a 400 unit/kg dose.

Toxicity: In mouse, the median lethal dose is greater than 5000 mg/kg. Symptoms of overdose may show excessive prolongation of aPTT or by bleeding,

R*eversal of heparin* : protamine sulfate

After injection, heparin circulates bound to many plasma proteins. It is removed from the circulation by the reticuloendothelial system,& It is metabolized by hepatic heparinase.

It is eliminated from the body by renal and hepatic mechanisms. (21)

The main limitation of heparin results from its propensity to bind to positively charged proteins and surfaces. Pharmacokinetic limitations are caused by AT-independent binding of heparin to plasma proteins, proteins released from platelets, and endothelial cells, resulting in a variable anticoagulant response

Decreases in body temperature below 37°C greatly prolong the elimination half-time for heparin. Hepatic and renal dysfunction may also increase the elimination half-time of heparin. (19)

Clinical use—Common uses include treatment of DVT, pulmonary embolism, and acute myocardial infarction. Heparin is used in combination with thrombolytics for revascularization(to prevent clot formation in CPB) and in combination with glycoprotein IIb/IIIa inhibitors during angioplasty and placement of coronary stents. Because it does not cross the placental barrier, heparin is the drug of choice when an anticoagulant must be used in pregnancy. (22)

Dosage: Lower heparin doses (e.g., 5000–7500 U every 12 hours) are administered subcutaneously to prevent DVT, whereas higher subcutaneous doses (e.g., 17 000 U every 12 hours) can be used for long-term anticoagulation when warfarin is contraindicated.

Generally, monitoring is not used in these two scenarios.

An initial intravenous bolus dose (5000 U or 80 U kg–1) followed by a continuous intravenous infusion (1200–1600U/h) is used when immediate anticoagulation is required. Greater initial intravenous doses are administered for interventional cardiology procedures (100–200 U/ kg) and during cardiac surgery (300–400 U/kg) subsequent doses of 5000–10 000 units are administered to maintain sufficient anticoagulation. (23)

contraindications: Heparin is usually contraindicated in haemorrhagic states, after recent ophthalmic or neurosurgery, in patients with peptic ulceration or oesophageal varices, in hypertensive patients with a diastolic pressure greater than 110mmHg and in cases of known hypersensitivity to heparin. (23)

Side effects: 1. Hemorrhage – this is the most common side effect and is due to a relative overdose.

2.Thrombocytopenia- a non-immune based thrombocytopenia (type I)

occurs within 4 days of anticoagulant doses of heparin. this rarely has clinical significance and the platelet count recovers without stopping heparin, this contrasts with the more severe (type II) immune-mediated thrombocytopenia, which occurs within 4–14 days of starting intravenous or subcutaneous heparin (fractionated and unfractionated). Heparin complexes with platelet factor 4, which is bound by IgG causing platelet aggregation and thrombosis

3. Cardiovascular – hypotension may follow rapid iv administration of a large dose.

4. Miscellaneous – osteoporosis, due to complexing of mineral substance from bone, and alopecia have been reported.

Heparin (including LMWH) can cause hyperkaliemia, which may be due to inhibition of aldosterone secretion. (24)

5. Problems with heparin as an anticoagulant for cardiopulmonary Bypass A. Heparin resistance (due to decreased levels of AT III),

B. Heparin rebound (Several hours after protamine neutralization for cardiac surgery, some patients experience development of clinical bleeding associated with prolongation of coagulation times. This phenomenon is often attributed to reappearance of circulating heparin. Theories accounting for “heparin rebound” include late release of heparin sequestered in tissues, delayed return of heparin to the circulation from the extracellular space via lymphatics, clearance of an unrecognized endogenous heparin antagonist, and more rapid clearance of protamine in relation to heparin. (25)

PROTAMINE SULFATE:

A low-molecular-weight polycationic protein, is a chemical antagonist of heparin. This agent rapidly forms a stable complex devoid of anticoagulant effect with the negatively charged heparin molecule through multiple electrostatic interactions.

Protamine is most active against the large heparin molecules in unfractionated heparin and it can partially reverse the anticoagulant

effects of low-molecular-weight heparins, but it is inactive against fondaparinux. (26).

Protamine is a mixture of basic polypeptides isolated from salmon sperm. (27).It is high in arginine content, which explains its basicity.(28)

Protamine is available as sulfate and chloride salts. Protamine chloride may have a more rapid onset compared with protamine sulfate. Nevertheless, clinical study reveals no superiority of one preparation over the other. (29)

Uses and Actions:

Two long-acting insulin preparations contain protamine. Protamine-zinc
insulin and NPH (neutral protamine Hagedorn) insulin.

Neutralization of heparin-induced anticoagulation remains the primary use of protamine. Formation of complexes with the sulfate groups
of heparin forms the basis for this "antidote" effect. Protamine neutralizes the AT effect of heparin far better than its anti–factor Xa effect. This distinction may arise from the need for thrombin, but not factor Xa, to remain complexed to heparin for AT to exert its inhibitory effect. Because porcine mucosal heparin has more potent anti–factor Xa activity than bovine lung heparin,porcine heparin may prove to be more difficult to neutralize with protamine. Protamine's poor efficacy in neutralizing anti–factor Xa activity limits the utility of LMWH compounds as anticoagulants for CPB.Protamine exhibits antihemostatic properties by affecting platelets and by releasing t-PA from endothelial cells. Thrombocytopenia follows protamine administration in dogs and in humans.Heparin-protamine complexes inhibit thrombin-induced platelet aggregation. In addition, protamine appears to bind to thrombin,
inhibiting its ability to convert fibrinogen to fibrin. (25)

Pharmacokinetics :

Half-life elimination: 7 min ,Onset of action: 5 min ,Duration: 2 hr

Vd: 5.4 L ,Metabolism: Unknown ,Clearance: 1.4 L/min

IV Preparation Reconstitute with 5 mL sterile water. Resulting solution equals 10 mg/ml.

IV Administration: Inject without further dilution over 10-15 min;

Storage: Refrigerate, avoid freezing

Administration, Distribution, and Fate :

Neutralization of heparin occurs by intravenous injection of protamine.Subcutaneous administration is limited to prolongation of insulin absorption. Presumably, these highly charged polycations distribute only to the extracellular space. In the presence of circulating heparin, protamine forms large complexes with heparin.(30)

Excess protamine creates larger complexes.The reticuloendothelial system may then dispose of these particles by endocytosis. Although this action has not been proved, macrophages in the lung may constitute the site for elimination of these complexes because intravenous administration of protamine permits formation of heparin-protamine complexes in the pulmonary circulation first.(31)

Proteolytic degradation of the protamine complexed to heparin conceivably results in free heparin. Protamine degradation in vivo proceeds by the action of circulating proteases, among them carboxypeptidase N, an enzyme that also clears anaphylatoxins and kinin pathway products.(32)

Adverse Reactions:

Protamine is associated with several hemodynamic effects that can be categorized by their presentation and mechanism. Adverse reactions to protamine range from moderate hypotension to more profound and hemodynamically significant reactions that can increase in-hospital mortality risk. Commonly, these reactions are classified as type I, type II, or type III. (33)

2. PATIENTS AND METHODS

This is a prospective randomized clinical trial had been conducted in Medical city complex / Iraqi center for heart disease from 24/8/2015 - 24/8/2016 included 60 patients scheduled for elective coronary artery bypass grafting surgery (CABG) in which we used cardiopulmonary bypass machine (CPB) i.e on pump. The study is approved by the scientific council of anesthesia and intensive care .Written consent taken from all the patients.

Inclusion criteria:

- Patient with ASAIII and ASA IV
- Age 40 – 80 years
- CABG on CPB
- Elective cases

Exclusion criteria:

- Fish allergy
- Anemia
- Pulmonary hypertension
- COPD and asthma

- Vasectomy

-Prior exposure to protamine

- Diabetic patients on Protamine-zinc insulin and NPH (neutral protamine Hagedorn) insulin.

-patient on anticoagulant

-hepatic and renal impairment

patient needed further doses of heparin.-

For all patients we take a detailed history , physical examination, vital signs and investigations The data taken and recorded in data collecting form sheet already constructed.(figure 3).

The study included 60 patients divided in to 2 groups according to the dose of protamine, first group received standard dose 1mg:1mg heparin and second group received low dose of protamine 0.75mg :1mg heparin

Early morning at the day of operation ,the anesthesia team ,surgical team, CPB machine team, lab. team with collaboration of ICU team prepare the OR ,equipment and medications. Then let the patient sit on the OR table to put ECG discs for monitoring on his back, then 2 large bore i.v lines ,pulse oximetry probe ,NIBP cuff, all placed and secured, establish base line measurement of the patient vital signs.

Induction of anesthesia started by 3 min. preoxygenation .With i.v ringer solution in the i.v line ,GA started by midazolam 0.1 mg/kg ,ondansetron 4mg i.v ,dexamethasone 0.1mg/kg, ketamine 1-2 mg/kg ,patient is advised to breath regularly & deeply.

Invasive arterial B.P line & monitoring started.

Propofol 1-2mg/kg ,fentanyl 5-7 mic/kg given ,rocuronium 0.6-0.8mg/kg ,lidocain 1-1.5 mg/kg ,with gentle bag ventilation of 100% O2 via face mask ,ETT done ,examined & secured well,Ventilator started ,with continuous monitoring of the patient parameters ,blood gas analysis (ABG) performed.

Central venous catheter (CVC) is performed usually the internal jugular vein or subclavian vein or femoral vein & secured by suturing .

CVP is monitored now via one of the 4 or 3 lines in the CV line ,other line for inotropic drugs also the ringer solution flow through one of the lines .

Remifentanil via syringe pump start to flow to the patient in a dose ranging from 0.1 up to 0.6 mic/kg/min. for continuous analgesia through out the operation time.

We obtain a basal ACT reading at the end of the induction.

When the surgeons start working for opening the sternum and pericardium,heparin is given i.v in a dose of 3−4 mg/kg , ACT performed after 5 min. if it is 3 folds or more of the normal value so the surgeons proceed in cannulation of the aorta for the arterial line & cannulation of the right atrium for the venous line of the CPM.

Then cardiopulmonary bypass start, anesthesia machine ventilator is stopped, lungs will be deflated so the field is ready for the operation.

Aortic cross clamp is secured so that the heart is almost free from any blood flow.

Cardioplegia solution which contains high concentration of K+, Mg2+& procaine is flushed through a cannula to the coronary circulation & cardiac arrest is obtained.

With the aortic cross clamping hypothermia(280- 300 c) started and the surgery proceed for grafting surgery with continuous monitoring through out the the surgery & maintaining the anesthesia with remifentanil, muscle relaxant.

After completion of surgery ,we start infusing inotrops with or without vasoactive agents , rewarming started & when the temperature reach 370 &the heart start beating either spontaneously or by internal D.C. shock ,then the blood gradually shifted back to the patient by CPM team & if all hemodynamics of the patient are stable and within normal values ,the CPM stopped .

We record the SBP,DBP,MAP &Ppeak readings (pre protamine reading),hydrocortisone given i.v in a dose of 2-3 mg/kg .

After that protamine infusion started in a dose of 1mg:1mg heparin in the standard dose group and 0.75mg :1mg heparin in the low dose group within 10-15 min.

After 5 min. we record ACT with SBP,DBP,MAP and Ppeak readings.

After completing the surgery , the patient is admitted to the I.C.U.

Statistical Analysis :

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 21 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables and fishers' exact test was used when 20% of expected variables was less than 5. Independent sample t-test was used to compare between two means and one way ANOVA analysis was used to compare between more than two means. In all statistical analysis, level of significance (p value) set at

≤ 0.05 and the result presented as tables and/or graphs. Statistical analysis of the study was done by the community medicine specialist.

3. RESULTS

A total of 60 patients scheduled for CABG were included in the present study.

No significant difference was observed between patients administered standard and low Protamine doses regarding their age and BMI. All these findings were shown in (Table 1).

No significant difference was observed between patients administered standard and low Protamine doses regarding all measured parameters before Protamine administration. All these findings were shown in (Table 2).

No significant difference was observed between patients administered standard and low Protamine doses regarding activated clotting time after Protamine administration. For patients administered low dose of Protamine, there was a highly significant reduction in incidence of hypotension in systolic blood pressure, diastolic blood pressure and mean arterial pressure means 5 minutes after Protamine administration in comparison to patients administered standard dose ($p<0.001$). Patients administered with low dose of Protamine had significantly lower peak airway pressure mean than patients administered with standard dose 5 minutes after Protamine administration ($p<0.001$). All these findings were shown in (Table 3 & Figure 2).

No significant differences were observed in systolic blood pressure, diastolic blood pressure and peak airway pressure means after low dose of Protamine according to patients age groups. There was a significant decline in activated clotting time after low dose of Protamine associated with increased age of patients ($p=0.04$). A significant decrease in mean arterial pressure mean was observed after low dose of Protamine among patients with increased age ($p=0.004$). All these findings were shown in (Table 4 & Figure 3).

No significant differences were observed in systolic blood pressure, diastolic blood pressure and mean arterial pressure means after low dose of Protamine according to patients BMI groups. There was a significant decrease in activated clotting time after low dose of Protamine associated with obese patients ($p=0.007$). A significant increase in peak airway pressure mean was observed after low dose of Protamine among obese patients ($p=0.04$). All these findings were shown in (Table 5 & Figure 4).

Table 1. Distribution of patients' age and BMI according to Protamine dose.							
Variable		Standard		Low		χ^2	P. value
		No.	%	No.	%		
Age (year)	<50	1	3.3	5	16.7	4.3*	0.200
	50-59	12	40	7	23.3		
	60-69	14	46.7	16	53.3		
	>70	3	10	2	6.7		
BMI category	Normal	8	26.7	6	20	0.4	0.700
	Overweight	19	63.3	20	66.7		
	Obese	3	10	4	13.3		
**Fishers exact test*.							

Table 2. Distribution parameters before Protamine administration according to Protamine dose.				
Variable	Standard	Low	t-test	P. value
	Mean± SD	Mean± SD		
Bypass time (min.)	106.1±14.5	106.3±14.7	0.06	0.9
Activated clotting time(sec)	113.5±9.5	117.7±9.4	1.7	0.09
Systolic blood pressure (mmHg)	108.6±16.3	112.7±14.1	1.03	0.3
Diastolic blood pressure (mmHg)	70.2±10.5	72.8±9.6	0.9	0.3
Mean arterial pressure (mmHg)	83±12.3	86.1±10.6	1.02	0.3
Peak airway pressure (cmH_2O)	22.6±1.5	22.5±1.6	0.1	0.8

Table 3. Distribution parameters 5 minutes after Protamine administration according to Protamine dose.				
Variable	Standard	Low	t-test	P. value
	Mean± SD	Mean± SD		
Activated clotting time(sec)	113.5±9.5	117.7±9.4	1.7	0.090
Systolic blood pressure (mmHg)	96.5±12.4	114±13.6	5.1	**<0.001***
Diastolic blood pressure (mmHg)	57.4±7.1	72.1±9.5	6.7	**<0.001***
Mean arterial pressure (mmHg)	70.4±8.1	86.3±9.4	6.9	**<0.001***
Peak airway pressure (cmH_2O)	26.3±2.3	22.8±1.7	6.4	**<0.001***
*Highly significant				

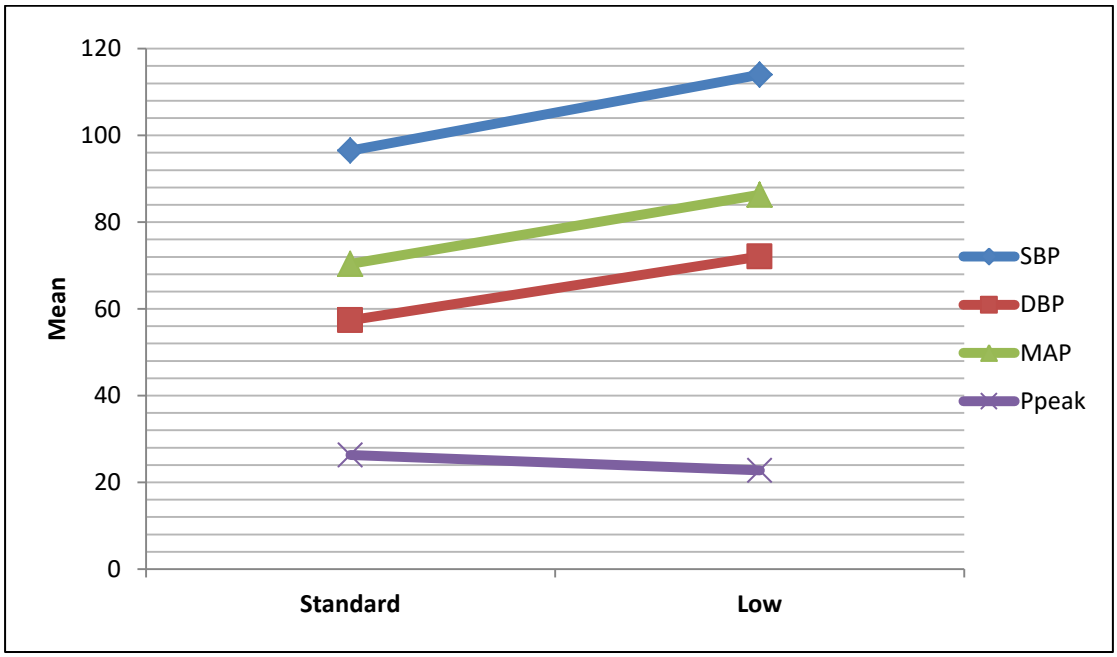

Figure 2. Distribution of some parameters according to Protamine dose.

Table 4: Distribution of parameters after low dose of Protamine according to patients' age groups.

Age (year)	ACT	Systolic BP	Diastolic BP	MAP	Ppeak
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD
<50	124±5.9	125.4±13.5	70.6±16.1	88.8±11.1	24.6±1.5
50-59	114.8±8.7	119.7±11.8	75.4±8.9	90.1±8.8	22.8±2.1
60-69	119.5±7.7	109±12.6	71.6±8.1	84.6±9.5	22.3±1.4
>70	98.5±7.7	106±8.4	68±5.7	80.7±2.8	22±1.4
*P value**	0.04	0.7	0.4	0.004	0.07

**ANOVA test used in comparison*
SD: standard deviation of mean

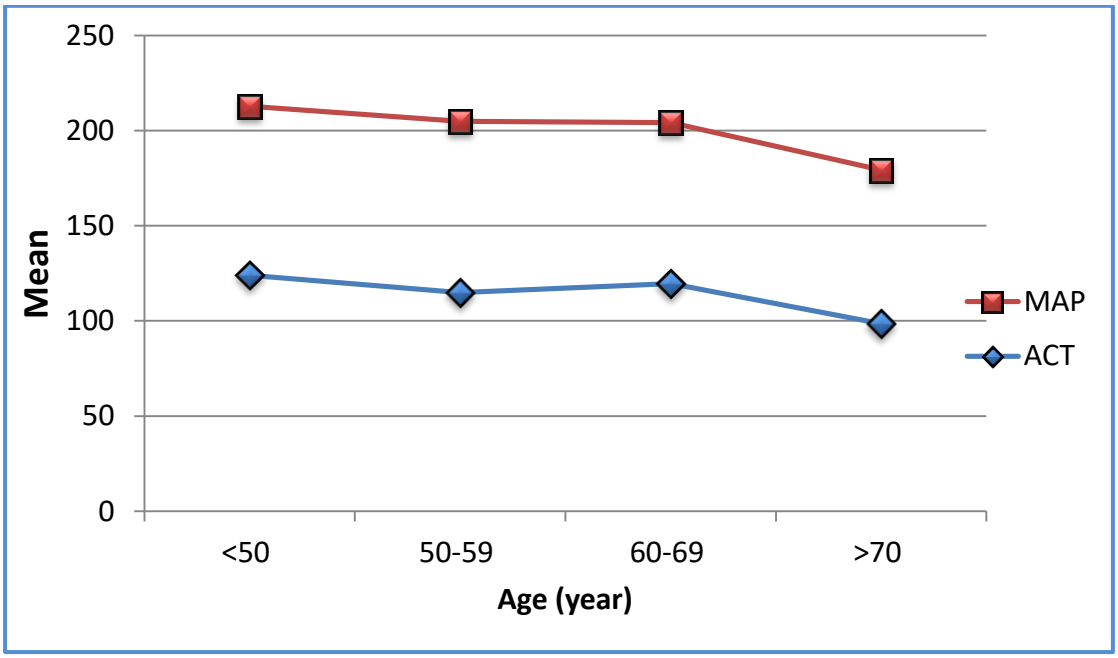

Figure 3. Distribution of ACT & MAP according to patients' age groups.

Table 5. Distribution of parameters after low dose of Protamine according to patients' BMI groups.

Age groups	ACT	Systolic BP	Diastolic BP	MAP	Ppeak
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD
Normal	120±13.6	99.8±3.1	69.3±4.6	81±7.2	21.5±1.3
Overweight	117.3±8.4	116.4±12.2	71.8±10.3	86.7±8.9	22.9±1.7
Obese	116.7±9.7	123.2±17.1	77.5±10.6	92.7±12.7	24.2±1.5
*P value**	0.007	0.400	0.100	0.800	0.040

**ANOVA test used in comparison*
SD: standard deviation of mean

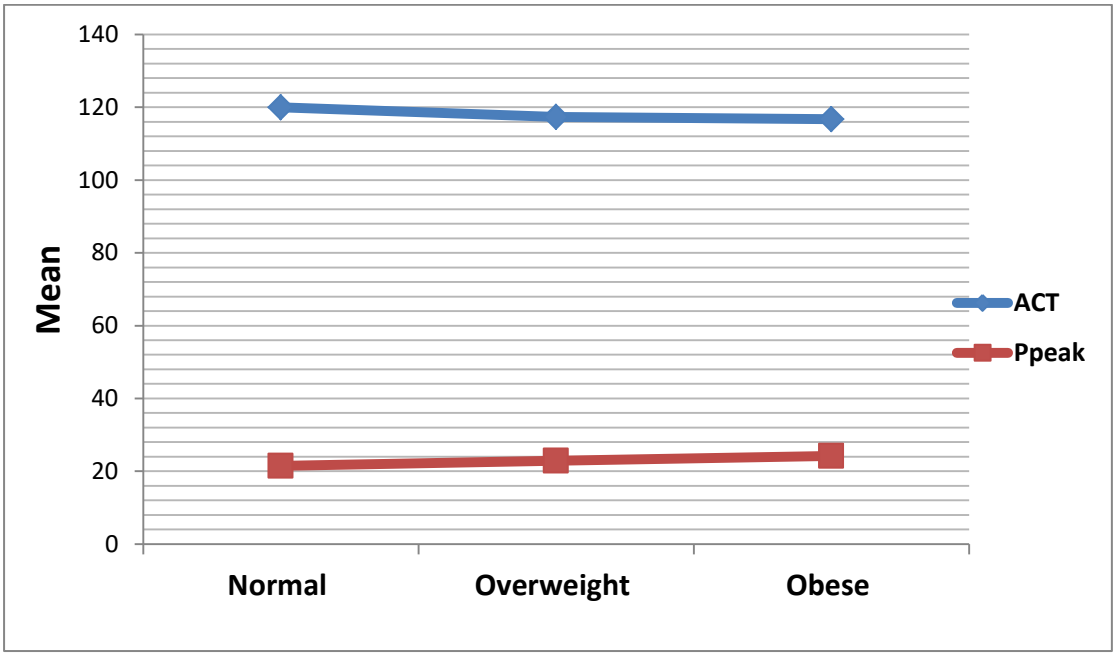

Figure 4: Distribution of ACT & Ppeak according to patients' BMI groups.

4. DISCUSSION

Protamine, which has been in clinical use for as long as heparin has, remains the heparin reversal drug of choice in cardiac surgery. The protamine dose required to reverse heparin is somewhat controversial and usually the use of protamine associated with many side effects mainly hypotension , increase in peak airway pressure due to increase airway resistance and increase in pulmonary artery pressure.(10). From our study there was a highly significant reduction in the incidence of hypotension (SBP,DBP,MAP) 5 min. after protamine in low dose group(p value<o.oo1) in compare with standard dose group which shows high incidence of hypotension (SBP,DBP,MAP).Also the low dose group shows highly significant lower peak airway pressure after 5 min after protamine in comparison with standard dose group. Also there was a significant decline in activated clotting time after low dose of Protamine associated with increased age of patients (p=0.04). A significant decrease in mean arterial pressure mean was observed after low dose of Protamine among patients with increased age (p=0.004). Another finding in our study was a significant decrease in activated clotting time after low dose of Protamine associated with obese patients (p=0.007). A significant increase in peak airway pressure mean was observed after low dose of Protamine among obese patients (p=0.04).

After searching in MEDLINE, PubMed, Anesthesia& Analgesia, BJA and other famous anesthesia websites there is no theses or papers studied the effects of using low dose of protamine in reversing heparin in CABG

The study conducted by Welsby IJ et al, the authors retrospectively studied 6,921 CABG patients. Degree/duration integrals of systemic hypotension (< 100 mmHg) and pulmonary hypertension (> 30 mmHg) for the 30-min after traditional dose protamine administration were assessed for linear associations with mortality using multiple logistic regression models adjusting for risk factors. Strong associations of both systemic hypotension and pulmonary artery hypertension related to protamine administration with mortality are present in the data. (34) This study was agree with our study regarding systemic hypotension.

Limitations of this study:

We couldn't directly measure pulmonary artery pressure because we don't have the facility to do it.

5. CONCLUSION

The use of low dose of protamine in reversing heparin in CABG seems to be clinically safe and effective with highly significant reduction in incidence of hypotension and highly significant low peak airway pressure in comparison with traditional dose.

From the findings of our study, it's recommended to:

1. Use low dose of protamine in reversing heparin in CABG.
2. Study larger sample of patients & measure the pulmonary artery pressure.
3. Study the effects of low dose in other cardiac surgeries.

Ethical Issues: All ethical issues were approved by the authors from the Iraqi Ministry of Health. Verbal and signed informed consents were obtained from all patients who included in the study during their first visit.

Conflict of interest: None

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