

## Warfarin dose in Patients with Heart Valve Replacement Undergoing to Cardio Pulmonary Bypass

### By:

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### Abstract

**Objectives:** the aim of the present study was to provide guidelines for optimal Warfarin anticoagulation in Sudanese patients after mechanical heart valve replacement undergoing to Cardio Pulmonary Bypass.

**Methodology:** A Carbomedics valve was implanted in 80 patients between July 2006 and July 2008. The INR calculate direct from the machine using coagulation analyzer model Bio – Bas.1,

**Results:** The mean international normalized ratio (INR) was  $2.8 \pm 0.38$ , however there was a significant variation (p. value  $< 0.05$ ) between the patients and the controls ( $0.88 \pm 0.38$ ). Sudanese patients with mechanical heart valves, bleeding was the major complication rather than thromboembolism. Low-dose anticoagulation international normalized ratio was 1.4–2.0 which could markedly decrease bleeding and effectively prevent thromboembolism.

**Conclusion:** These findings suggest that the INR was most unstable in the first postoperative month, re-examination of patients in this period is critical.

**Key Words:** Anticoagulation, warfarin, dose, Heart, Valve, Replacement, Cardio, Pulmonary, Bypass, INR, PT.

### Introduction

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR  $> 4.0$ ), age  $\geq 65$ , highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR

monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physician's signs and symptoms of bleeding <sup>[1]</sup>.

Cardiopulmonary bypasses (CPB) have placed a great problem in the clotting system mechanism and some of coagulation clotting factors affected. Bleeding associated with cardiac surgery procedures is a one of the big problem take place and blood loss reduces the adaptative of clotting factors capacity of cardio vascular system. Complications following heart valve replacement are not common, but can be

serious. All valves made from animal tissue will develop calcium deposits over time. These deposits interfere with the function of the valve, it must be replaced. Blood clots may form on the surface of the supplying blood to the brain, kidney and legs. These blood clots may cause fainting spells, stroke, kidney failure, or loss of circulation to the legs. These blood clots can be treated with drugs or surgery [2, 3]. The infection of heart muscles affects up to 2% of patient who have heart valve replacement. If the infection persists, the new valve may have to be replaced. The prothrombin time (PT) and International normalized ratio (INR) is useful for identifying coagulation factor deficits after cardiopulmonary bypass (CPB) [4]. However, long processing times and the need for fresh frozen plasma (FFP) to be thawed cause delays in factor replacement. We hypothesized that, by treating with warfarin, blood sampled toward the end of CPB can provide PT results that help to determine the requirement for follow up after CPB. Laboratory delays can be eliminated with point-of-care. Compared with PT measurements done after CPB, the mean bias for laboratory PT and INR measurements taken during CPB seemed to be minimal, suggesting a moderate degree of agreement. Nonetheless, the limits of agreement around PT during CPB exceeded our threshold of -1.0 second, with the largest discrepancy seen with larger PT measurements. In choosing this threshold, we did not find any previously published data to guide us [5-7]. Although it is stringent, a more relaxed threshold such as -2.0 seconds seemed too wide to be clinically meaningful [8].

### Materials and methods

This is an observational comparative case control study done during the period of July 2003 to July 2008 Sudan Heart Center Khartoum state to measure PT and INR to provide guidelines for optimal Warfarin anticoagulation in Sudanese patients after

mechanical heart valve replacement undergoing to Cardio Pulmonary Bypass. Eighty (80) patients with cardiopulmonary bypass disease and twenty (20) healthy individuals control groups.

### Preparation of platelet poor plasma (PPP):

The blood samples were collected from patients and controls in 3.2% tri-sodium citrate (3.2%) anticoagulant (ratio 1:9). PPP samples were prepared by centrifugation at 2000g for 15 min. The samples were being kept at room temperature for PT and INR estimation using coagulation analyzer model Bio-Bas.1 [9].

### Data analysis

All data are presented as mean±SD using statistical package for social science (SPSS), unless otherwise noted. Statistical comparisons were performed using unpaired student's t-test with p<0.05 considered as significant.

### Results and Discussion:

Eighty patients and twenty normal controls were recruited for this study. Patients were those who fulfilled the clinical diagnosis to undergo to Cardiopulmonary bypass of either sex, on or off treatment. The controls were normal individuals of either sex. The age of patients ranged between 20 to above 50 years with mean of 35 years, the controls have the same age range. The results showed that 49% of the patients were in age group of 36-50 years, 26% of the patients were between 20-35 years and 25% were above 50 years as summarized in fig (2).

The cardiopulmonary bypass patient's family history was 98% of patients had not family history while only 2% of patients had family history of disease Fig (1). In this study there were 49% of patients with ages (36-50) years and female affecting more than male Fig. (3).

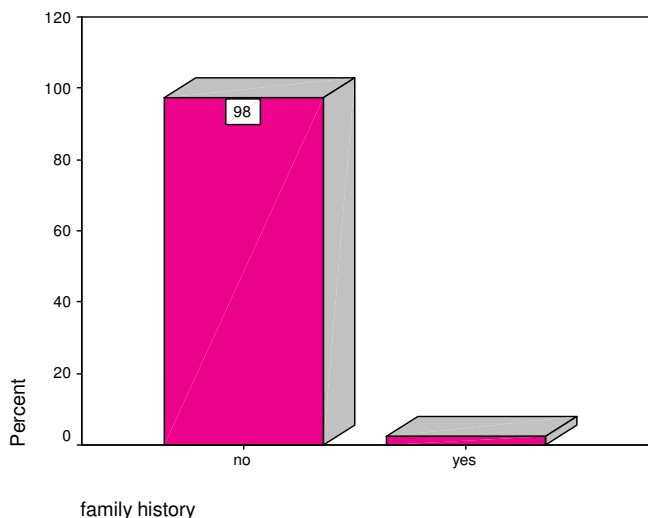
The mean PT was 38.5 seconds, INR was 2.8 in cardiopulmonary bypass patients under warfarin dose which indicated a significantly increased (p<0.05)

compared to the mean control groups (13.9 seconds, 0.88), table (1) and (2) respectively. Therefore, this finding demonstrated that activation of the extrinsic coagulation pathway occurs during clinical CPB and that TF contributes to this process. TF is a cell surface Tran's membrane protein that, in conjunction with factor VII, causes thrombus formation through the extrinsic coagulation pathway. TF is expressed constitutively on sub endothelium and organ capsules and acts as a hemostatic envelope when injury occurs to the physical barrier that normally separates factor VII from TF<sup>[10]</sup>. The present study of extrinsic coagulation pathway activation during clinical CPB would determine the extent PT and INR to elevate at the end of CPB.

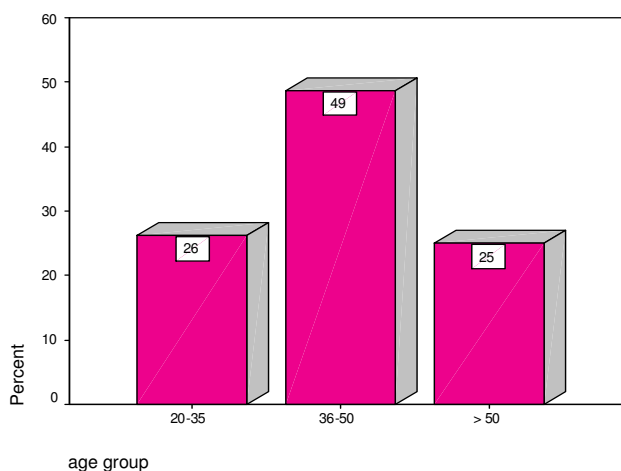
The mean value of International Normalization Ratio in patients uunder warfarin therapy taking different doses as followwed; The mean INR was 2.6 in the patient dose of 1.0 - 3.0 mg., 3.1 in patient dose of 3.1-5.0 mg, 2.9 in patients dose of more than 5.0 mg and 2.7 in patient did not take any warfarin dose. Fig. (4), these data indicated that the extrinsic coagulation pathway was activated and provides an alternative to the intrinsic system for thrombin formation during clinical CPB. The increase in PT indicates that prothrombin has been cleaved by factor Xa to form thrombin and occurs at the same sampling points as increases in TF and factor VIIa. Studies by Boisclair *et al*<sup>[11]</sup> and Burman *et al*<sup>[12]</sup> did not show activation of the contact system during CPB. In the Boisclair *et al*<sup>[11]</sup> study, factor XIIa activity did not correlate with generation of PT during CPB. In the Burman *et al* study, a 12-year-old girl with severe factor XII deficiency who had CPB for the repair of an atrial septal defect generated as much thrombin as normal control subjects; a corresponding rise in activation products of the intrinsic coagulation system was not detected. A comprehensive study of contact, extrinsic and intrinsic system activation with

correlation of factor X and thrombin formation is needed to fully understand the mechanisms of coagulation during clinical CPB<sup>[13, 14]</sup>.

**Fig. (1).** Family history among patient under going to cardiopulmonary bypass:

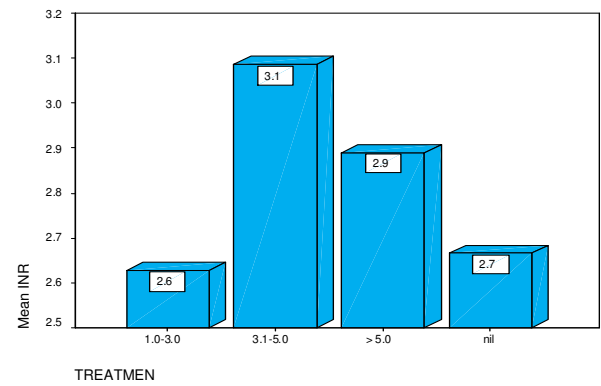


**Fig. (2).** Age related incidence among patient with cardiopulmonary bypass:

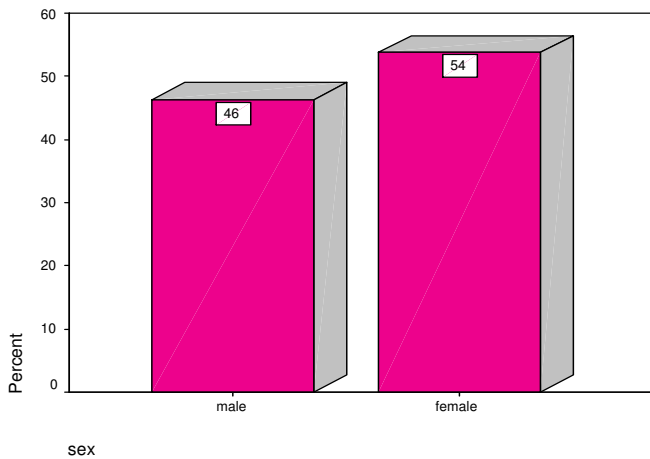


**Fig. (3).**The male and female percentage among patients with cardiopulmonary bypass:

	Count	Mean	STD. Deviation
Patients	80	38.5	10.1
Control	20	13.9	0.31



**Table (1).** The mean of Prothrombin Time in patients and controls



**Fig. (4).** The mean of International Normalized Ratio result according to the warfarin dose therapy in patient with cardiopulmonary bypass

**Table (2).** The mean of International Normalization Ratio in patient and controls

	Count	Mean	STD. Deviation
Patients	80	2.8	0.86
Control	20	0.88	0.05

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