

Plasma Antithrombin III Concentration: A Predictor of Thromboembolism in Orthopedic Surgery

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ABSTRACT

Aim: The purpose of this study was To know any alteration in plasma antithrombin III concentration during postoperative period of major orthopedic surgery.

Place and duration of study: In hematology section of pathology department at postgraduate medical institute (PGMI), Lahore from 1stFebruary2014 to31stJanuary 2015.

Study design: It was an observational study.

Methods: After visiting orthopedic ward of Services Institute of Medical Sciences (SIMS) Lahore, forty patients were selected for this study who were planned and enlisted for major orthopedic surgery. Out of forty patients, twenty were of male gender and remaining twenty of female gender, having mean age of 48.6 years. Ten healthy subjects were selected to constitute control group after a proper matching in respect to age and sex of subjects in patient group. Two anticoagulated venous blood samples were drawn from each patient. First sample 24 hours prior to surgery and second 72 hours after surgery. A single blood sample was drawn from control subjects.

Results: It was observed at the completion of this study that almost in all patients there was a remarkable fall in concentration of plasma antithrombin III (AT III) after major orthopedic surgery. This critically noteworthy fall of 29.3% in AT III levels might be the outcome of potent systemic activation of all clotting factors as a result of local vascular trauma inflicted during surgical procedure, local vascular stasis, massive trauma to tissues and release of tissue thromboplastin during surgery.

Conclusion: There was a significant decrease in plasma level of antithrombin III during postoperative period of major orthopedic surgery, an observation usually not appreciated in general surgery patients.

Keywords: Preoperative blood sample, Major Orthopedic surgery, AT III.

INTRODUCTION

Plasma Antithrombin III, a natural anticoagulant not requiring vitamin K for its activity. AT III being a glycoprotein and its molecule is constituted by 432 aminoacids arranged in a single chain and 04 side chains of carbohydrate. Its plasma half-life is 2-3 days whereas normal plasma concentration is 110-140mg/dL¹. It is included in family of serine protease inhibitors². It primarily inhibits thrombin and factor Xa. It also inhibits all activated serine proteases formed during coagulation cascade stimulation including XIIa, XIa, IXa, kallikrein and plasmin^{3,4}. AT III inhibits activated serine proteases after its 1:1 binding with active proteins. ATIII anticoagulant activity is remarkably enhanced after combination with heparin and different heparan sulfates. There occurs a change in AT III molecule after its union with heparin molecule resulting in an increase in its antithrombotic capability by 4000 times. Human heparan sulfate is detected in cells of endothelial lining of blood vessels and thus resulting in limiting AT III antithrombotic activity⁶. When AT III combines with heparan sulfate on surface of lining endothelial cells, there is release of prostacyclin also from endothelial cells, thus resulting in inhibition of adhesion and aggregation of thrombocytes⁷.

The importance of AT III in humans is realized when an individual is experiencing repeated attacks of thromboembolic disorder^{8,9,10,11}. Inherited AT III deficiency is an autosomal dominant disease with multiple presentations. In antithrombin III deficiency states, whether

acquired genetically or acquired after birth, the individual is 50 times more vulnerable to venous thrombosis and thromboembolism^{12, 13}. It is generally accepted that individuals with protein C or protein S deficiency are less prone to thromboembolic complications than deficiency of antithrombin III¹⁴. ATIII is responsible for about 70% of antithrombotic function of circulating plasma¹⁵. Hereditary antithrombin III deficiency individuals are more prone to suffer from recurrent venous thromboembolism and less commonly arterial thrombosis^{16,17}.

Major operations, extensive injury and delivery are conditions of serious concern where 12-40% decrease in plasma AT III concentration is usually noted, a critical percentage fall which can expose these individuals to venous thromboembolism^{18,19}. Postoperative venous thromboembolism is expected in 100% individuals in whom before operation AT III concentration is less than 80% of average normal AT III plasma concentration²⁰. AT III is consumed to a great extent during and after major surgical procedures resulting in its decreased plasma concentration.

AT III decreased plasma concentration after operation may be the result of attempts in maintaining hemostasis at operation site, consumption during healing and repair, usage during abscess formation or in development of venous thrombosis¹⁹. The critical level of decreased plasma AT III concentration required for thrombus formation is more than 30%, at this concentration procoagulant factors inactivation by AT III becomes poor and final control on thrombosis is lost¹⁰. Venous

thromboembolic disease, a frequently encountered unwanted outcome of extensive or complicated orthopedic surgery. Without prophylactic measures, about 45-70 percent patients present with venous thrombosis. Mortality resulting from pulmonary embolism during postoperative period after hip replacement and arthroplasty of knee is 1-3 percent^{21, 22, 23}. The prevalence of deep vein thrombosis (DVT) is thirty two percent (32%) during postoperative period of hip replacement and sixty six percent (66%) after total knee replacement²⁴.

PATIENTS AND METHODS

Site selected for this study was orthopedic ward of Services Institute of Medical Sciences Lahore, and duration was from 1stFebruary2014 to 31stJanuary2015. Two groups were designed, labelled as group 1 and group 2. Group 1 comprised forty patients who were enlisted for major orthopedic surgery. Ten healthy subjects were selected for control group after proper matching with patient group in reference to age and sex. Group 1 and group 2 were comparable regarding demographic data. Written consent received from all individuals after verbally explaining the purpose of sample collection. Two anticoagulated venous blood samples were drawn from all patients, i.e. one sample a day prior to surgery and other on third day after surgery. One anticoagulated blood sample was taken from control subjects. Platelets poor plasma was obtained after proper centrifugation of blood sample.

Estimation of antithrombin III concentration of each sample was carried out by using platelet poor plasma on radial immunodiffusion plates containing monospecific sheep polyclonal antibodies. Following individuals not included in study:

1. Humans with prolonged renal disorder, recent acute infarction of myocardium, chronic hepatic disorder and inflammatory intestinal disease, as these diseases ultimately decrease the plasma AT III concentration.
2. Individuals with recent or past history of hemorrhagic tendency, venous thromboembolism, history of drugs intake like estrogen containing medication, contraceptive pills or intravenous intake of anticoagulants.

RESULTS

In group one, out of forty patients who were enlisted for major orthopedic surgery, 20 (50%) belonged to male and 20 (50%) to female gender. In patient group age ranged from 40 to 72 years, mean was 48.6 years. The control group comprised 05 (50%) male and 05 (50%) female gender. In control group age ranged from 40 to 70 years, mean was 48.0 years. (Table I).

When antithrombin III preoperative and postoperative levels were compared after major orthopedic surgery, it was concluded that there was a significant decrease (29.3%) after operation (Table II). This fall in plasma antithrombin III level after surgery was statistically significant (p-value <001).

Table I: Age, sex and type of operation data of patients and controls.

	Group 1 (n=40)	Controls (n=10)
Mean age ± SD (Years.)	48.6± 14.60	48.0± 10.92
Sex (Male:Female)	20:20 (1:1)	5:5 (1:1)
Surgical procedure		
a. Knee arthroplasty	12	
b. Complete hip replacement	08	
c. Laminectomy or Decompression surgery.	08	
Open reduction and internal fixation	12	

Table II: Antithrombin III levels in Patients and Controls.

Control Group	Pre-operative Levels of Antithrombin III	Post-operative levels of Antithrombin III
n = 10	n = 40	n = 40
262.5 ± 22.40	290.0 ± 37.28	206.6 ± 43.60
(238 – 288)	(223 – 353)	(152 – 327)

DISCUSSION

Thromboembolism is a serious complication during postoperative period of major orthopedic surgery. Major complicated surgery and extensive tissue trauma are real threats to surgeon. These individuals experience a decrease in plasma AT III concentration by 12-40%^{25,16,17}. Decreased concentration of AT III after surgery is at its peak on third day after surgery, an observation which is in accordance with already conducted multiple studies^{17,18,19,20,21,26,27}. In our study average fall in concentration of antithrombin III was 29.3%, whereas it was 13 and 14 percent in some previously conducted studies respectively^{19,28,30}. In these studies less trauma during surgery, less complicated procedures and best possible intraoperative and postoperative management may be responsible for less decrease in AT III concentration.

The postoperative decrease in plasma level of Antithrombin III may result from its utilization to maintain hemostasis at surgical trauma site, during process of healing and repair, thrombin-antithrombin complex formation or in generation of venous thrombosis. Severity and nature of injury are other important factors in predicting extent of decrease in postoperative antithrombin III concentration. Local blood vessels at surgical site exhibit hypercoagulability during postoperative period resulting in increased utilization of AT III²⁹. This study as well as other studies concluded that potent coagulation activation plus local vascular stasis and injury in large femoral vein may be responsible for decreased AT III concentration, an event not seen in general surgery patients^{19,20,30}.

CONCLUSION

Postoperative period is high risk after knee arthroplasty, hip replacement or any other major orthopedic surgery, because during this period occurs highly significant fall in plasma AT III concentration. When preoperative AT III concentration is lower than 80% of normal plasma concentration, there is associated 100% incidence of venous thrombosis after operation. Antithrombin III levels must be carried out before and after major and complicated

orthopedic surgery. By keeping a close eye on noteworthy postoperative decrease in AT III concentration, it is easy for a surgeon to decide when to anticoagulate a patient to prevent thromboembolic complication.

Final message for orthopedic surgeons is that they can limit the risk of thromboembolism, can decrease morbidity and mortality in patients enlisted for major orthopedic surgery by just getting preoperative and postoperative AT III levels done.

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