

Plasma Antithrombin III Levels in Postoperative Patients

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ABSTRACT

Aim: To determine preoperative and postoperative plasma concentration of antithrombin III in three different disciplines of surgery as well as to carry out an inter-comparison of antithrombin III levels after major surgical procedures in orthopedic, gynecologic and general surgery.

Settings: Study was carried out in department of pathology, at postgraduate medical institute Lahore, Pakistan during a period extending from January 1995 to December 1995.

Design of study: An observational study.

Methodology: Forty-five patients admitted in services hospital of Lahore, were selected from three different disciplines of surgery. All these patients underwent major surgical procedure. Out of forty-five patients, fifteen patients each were selected from orthopedic, gynecologic and general surgery ward. Fifteen normal healthy subjects, who were age and sex matched with patients were also selected as controls. Two citrated blood samples were drawn from each patient, preoperative sample was drawn one day prior to surgery and postoperative sample on third postoperative day. A single citrated blood sample was taken from each control subject.

Results: Plasma antithrombin III concentration decreased significantly during postoperative period in all three disciplines of surgery. In our study percentage decrease in antithrombin III concentration was highest in orthopedic surgery (29.3%), followed by (25.1%) and (25.0%) in gynecologic and general surgery respectively.

Conclusion: In all three surgical disciplines after major surgical procedures, there was highly significant decrease in concentration of antithrombin III. This postoperative decrease in concentration of antithrombin III was more pronounced in orthopedic surgery and less in gynecologic and general surgery.

Keywords: Antithrombin III, Gynecologic surgery, Major orthopedic surgery.

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two well recognized serious and potentially fatal complications of hospitalized patients after major surgery^{1,2}. Whereas major surgery is defined as any surgical procedure which require general anesthesia, operation duration of more than an hour and postoperative hospital stay of 4-7 days³. Silent pulmonary embolism is a serious and fatal postoperative complication of DVT, usually seen when patient is about to be discharged from hospital after a complication free postoperative stay⁴. In ambulatory outdoor patients both thrombosis and pulmonary embolism are less frequently diagnosed¹. Risk of thrombosis and embolism after major surgery depends upon type of surgery, its duration, underlying pathology for which surgery is being carried out, venous stasis accompanying bed rest after operation and induction of hypercoagulable state during and after surgery^{5,6}. Patients presenting with advance age, cardiac disease, malignant disorders, obesity, pregnancy and females using contraceptives are more prone to deep vein thrombosis after surgery.

Antithrombin III (AT III), a small protein molecule consisting of 432 amino acids which are arranged in a single chain to constitute a glycoprotein. It contains three disulfide bonds and 04 glycosylation sites. Alpha and beta antithrombin III are its two types found in human plasma. Alpha AT III is dominant variety whereas beta is a minor form. It is a natural vitamin K independent anticoagulant being synthesized by hepatocytes and having biological half-life of 2-3 days⁷. It is an important family member of

serine protease inhibitors. Antithrombin III is a major inhibitor of thrombin and factor Xa. Almost all serine proteases like IXa, XIa, XIIa, plasmin and kallikrein which are activated during coagulation activation are inhibited by it through formation of a equimolar, irreversible complexes with active enzymes^{8,9}. Its normal plasma concentration is 110-140 mg/dL¹⁰. Its plasma activity varies with age of the individual, being 60-90% in newborns and 80-120% in children and adults. Antithrombin III contributes about 70% of total antithrombotic activity of plasma¹¹. Heparin increases its functional activity many folds by increasing its ability to bind with thrombin and factor XIa¹². Risk of thrombosis in patients is moderate when concentrations of AT III is between 50-75% of normal and marked when concentration of antithrombin III is less than 50% of normal¹³.

Plasma antithrombin III deficiency may be hereditary or acquired. Whatever the etiology of AT III deficiency may be, these individuals are at increased risk of thrombosis, may be up to 50-folds^{10,14}. In general AT III deficient individuals are more prone to develop venous thrombosis and pulmonary embolism than individuals with protein C or protein S deficiency¹⁵. Hereditary AT III deficiency individuals are more commonly affected by venous thrombosis, pulmonary embolism and arterial embolism as they typically exhibit AT III activity levels between 40-60%.

Major surgical procedures, severe trauma and parturition are acquired etiologies, where there are chances of 12-40% decrease in concentration of AT III and any individual is at high risk of developing venous thrombosis. Preoperative AT III concentration of less than 80% of

normal is strong risk factor for almost 100% postoperative venous thrombosis. Utilization of AT III is considered to be an important factor ultimately leading to decreased plasma level postoperatively. Antithrombin III may be utilized in maintaining hemostasis at operative site, during healing of traumatized tissues, in suppurative infection of wound or in venous thrombosis. It is also seen that a fall of more than thirty percent in AT III concentration is critical and predisposes an individual to thrombosis. Thromboembolism and death are frequently encountered complications of total hip and knee replacement. Similar postoperative complications are also seen after major gynecologic and major general surgery, but much less frequently.

MATERIAL AND METHODS

Sixty subjects were included in this observational study, irrespective of age, sex and occupation. These sixty individuals were placed in four groups.

Group A: Included fifteen healthy subjects who were age and sex matched with three patient groups.

Group B: Included fifteen patients from the list of major orthopedic surgery.

Group C: Included fifteen patients from major gynecological surgery.

Group D: Included fifteen patients from major general surgery.

Exclusion criteria: Two groups of patients were not included in this study.

- Subjects already having disorders in which plasma AT III level is markedly reduced like, chronic renal disease, chronic liver disease, recent myocardial infarction and inflammatory bowel disease.
- Subjects with history of bleeding tendency, thromboembolism, intake of drugs like estrogen and anticoagulants.

Sample collection: Two blood samples were drawn from each patient. First sample was taken a day before surgery and second on third postoperative day. Only one sample was drawn from each control subject. 1.8 ml of blood was drawn and delivered into a tube containing 0.2 ml of tri-sodium citrate solution. Supernatant was collected after centrifugation of blood sample for AT III estimation by using radial immunodiffusion plates containing monospecific sheep polyclonal antibodies.

RESULTS

This study included sixty subjects in total, 15 healthy individuals constituted a control group which was age and sex matched with patient group. Patient group comprised 45 subjects, fifteen patients from each three disciplines of surgery were selected who underwent major orthopedic, gynecological and general surgery procedures. The comparison of patient and control group was carried out by using student “t” test.

The normal controls were 38.9 ± 10.66 years of age with a range, 20-58 years. Patients of orthopedic surgery (group B) were 39.3 ± 19.49 years, of gynecological surgery (group C) were 41.0 ± 7.45 and of general surgery (group D) 41.06 ± 12.62 years of age. (Table I).

Table I: Age distribution in patients and controls (The values are expressed as mean ± SD years)

Group	Age
A (n=15)	38.9 ± 10.66 (20-58)
B (n=15)	39.3 ± 19.49 (15-62)
C (n=15)	41.0 ± 07.45 (20-50)
D (n=15)	41.1 ± 12.62 (22-60)

There were 19 (42.2%) male and 36 (57.8%) female gender in patient group. Among orthopedic surgery patients 06 (40%), were male and 09 (60%) females, in gynecological surgery patients 15 (100%), were females and in general surgery group 05 (33.3%), were male and 10 (66.7%) females. Control group comprised 08 (53.3%) male and 07 (46.7%) female gender. (Table II).

Table II: Gender distribution in patients and controls

Group	Male	Female
A (n=15)	08 (53.3%)	07 (46.7%)
B (n=15)	06 (40.0%)	09 (60.0%)
C (n=15)	NIL	15 (100.0%)
D (n=15)	05 (33.3%)	10 (66.7%)

In our study the control subjects group plasma antithrombin III concentration was 261.7 ± 22.41 mg/L (240-295). In orthopedic surgery group (group-B), concentration of AT III was 291.0 ± 37.33 mg/L, with a range as 225-355mg/L, a value statistically highly significant when compared to control subjects (P < 0.01). On third postoperative day AT III concentration was 202.7 ± 44.03 mg/L with a range from 150-325 mg/L. This postoperative value was very highly significant statistically (P < 0.001), when compared to control subjects as well as to preoperative AT III levels (Table III). In gynecological surgery group (group-C), concentration of AT III before operation was 273.7 ± 62.09 mg/L with a range from 225-475 mg/L, a value statistically non-significant when compared to controls (P>0.05). On third postoperative day in the same group AT III level was 205.1 ± 41.81 mg/L, values range was from 110-275 mg/L, a value very highly significant when compared to control subjects and to preoperative AT III levels of patients in group C. In general surgery group (group D), concentration of AT III before operation was 174.7 ± 41.9 mg/L, with a range from 190-380 mg/L. This value was statistically non-significant when compared to control subjects, (P>0.05). On third postoperative day antithrombin III levels in the same group was 206 ± 30.31 mg/L with a range of 150-265 mg/L and this value was very highly significant when compared to control and preoperative concentration, (P< 0.001) (Table III).

Table III. Comparison of plasma AT III levels in group B, group C and group D patients before and after operation.

Group	Preoperative Value	Postoperative Value	Difference	Percentage Fall (%)
B	291.0 ± 37.33 (225- 355)	202.7 ± 44.03 (150-325)	85.3	29.3
C	273.7 ± 62.09 (225-475)	205.1 ± 41.81 (110-275)	68.6	25.1
D	174.7 ± 41.90 (190-380)	206.0 ± 30.31 (150-265)	68.7	25.0

B Orthopedic surgery patient group.
D General surgery patient group.

C Gynecological surgery patient group.

DISCUSSION

It is generally accepted that antithrombin III is a principal natural physiological inhibitor of almost all activated coagulation factors. It is synthesized by hepatocytes and endothelial cells. Whenever there is decrease in its plasma concentration, whether inherited or acquired, is associated with high risk of thromboembolic disorder^{16,17,18,19}. Thromboembolic events during early postoperative period of major surgery in the disciplines of orthopedic, gynecology and general surgery are a real threat to patients as well as to surgeon. During early postoperative period, a fall of AT III concentration between 12-40% increases the chances of thromboembolic disease by many folds and decrease in plasma AT III levels of more than 30% is critical for thrombus formation^{20,21,22}. In our study decrease in plasma concentration of AT III in all three groups was significant. In orthopedic surgery group (group B), decrease in AT III concentration after operation was significant and when compared with preoperative levels, it was very highly significant. Results similar to our study were published by Winter et al¹⁷, Francis et al⁶, Kim²³ and Ofose et al²⁴. It is generally accepted that venous thrombi are mostly formed during operation or in immediate postoperative period. The lowest antithrombin III activity at this stage may be due to increased consumption of AT III in achieving hemostasis at surgical site, during healing activity and by formation of complexes with thrombin.

In gynecological surgery group (group C), there was observed a very highly significant decrease in AT III levels when pre and postoperative AT III levels were compared. This finding was in accordance with findings of Gallus et al²⁵ and Breddin and Kirchmaier²⁶. Another study carried out by Donati et al²⁷ did not find results in accordance with this study as their results did not show statistically significant fall in AT III levels postoperatively. Factor responsible for variance in Donati et al study may be multifactorial like relatively younger patients, short duration of surgery, small group of 17 patients, relatively uncomplicated surgery and better postoperative management.

In general surgery group (group D), postoperative fall in AT III level was very highly significant when compared with preoperative level. This finding was in conformity with findings of few other international studies^{3,6,26,28,29}. In this study it was concluded that hypercoagulability and local intravascular coagulation during postoperative period may ultimately lead to increased consumption of antithrombin III. In present study it was concluded that percentage fall of antithrombin III was the highest in orthopedic surgery group and lowest in general surgery. It was also concluded that during orthopedic surgery there is a marked systemic activation of coagulation pathways as a result of more severe tissue trauma, release of larger quantities of tissue thromboplastin, extensive vessels injury and local stasis in femoral vein, an event usually not found in general surgery operations. During and after hip or knee arthroplasty, the fall in antithrombin III concentration is more than in gynecological or general surgery.

CONCLUSION

In our study plasma antithrombin III level decreased significantly in all three groups of surgeries after operation. It was finally concluded that postoperative fall in AT III level was maximum in orthopedic surgery patients (29.3%), followed by gynecologic surgery group (25.1%) and general surgery (25.0%). In patients undergoing surgical procedure hemostatic balance is achieved by a balance by coagulation promoting and inhibiting factors. A fall of more than 30% in AT III concentration during postoperative period is declared significant for the development of thrombosis, as this much of reduction in AT III is unable to inactivate activated procoagulant factors. It is already declared that without prophylactic treatment after total hip or knee arthroplasty, incidence of venous thrombosis is 45-70% and that of fatal pulmonary embolism 1-3 percent. It can be concluded from this study that AT III levels must be ordered in all patients before and after major surgery to help the surgeon in deciding whether and when to anticoagulate patient. Secondly antithrombotic modalities should be started few hours before surgery and continued for few days after surgery as 50% of DVT are detected on first postoperative day and approximately 30% on second day. Thirdly for high risk patients and patients presenting with inherited AT III deficiency, antithrombin III concentrates should be used to overcome thromboembolic complications. As oral contraceptives intake is associated with increased risk of DVT, their usage must be stopped at least one week before planned surgery.

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