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Original Article

Strategy for Cardiovascular Surgery in Patients with Antithrombin III Deficiency

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Antithrombin III (ATIII) deficiency is a rare disorder in which thrombosis can be induced by stimuli that do not usually lead to thrombus formation, including minor injuries and surgery. Therefore, patients with ATIII deficiency undergoing cardiovascular surgery that involves heparinization require careful perioperative management. We experienced five patients with ATIII deficiency who underwent cardiovascular surgery and were managed with ATIII replacement. By administration of ATIII concentrate, preoperative ATIII activity was maintained at ≥120% and postoperative ATIII activity at ≥80%. All five patients were treated successfully without postoperative complications such as hemorrhage or thrombosis. In patients with ATIII deficiency undergoing cardiac surgery, it is important to perform ATIII replacement to achieve preoperative ATIII activity ≥120% and postoperative ATIII activity ≥80%, while the activated clotting time (ACT) is maintained at >400 seconds during cardiopulmonary bypass. In addition, long-term postoperative anticoagulant therapy is necessary in hereditary ATIII deficiency patients with a history of thrombosis.

Keywords: antithrombin III deficiency, cardiovascular surgery

Introduction

Hereditary antithrombin III (ATIII) deficiency is a rare autosomal dominant disorder that was first reported by Egeberg in 1965.[1)] Its prevalence in the general population has been reported as 0.02%–0.17%. From the age of 15 years onwards, about 65% of patients with hereditary ATIII deficiency develop thrombosis, which is predominantly venous thrombosis such as deep vein thrombosis. In these patients, thrombosis can be induced by factors that do not usually cause thrombus formation, such as minor injury, surgery, pregnancy, or use of oral contraceptives. Hereditary ATIII deficiency can be divided into two types. Individuals with the type I (classical) disorder have a low blood level of ATIII level (about 50%) and approximately 50% reduction of ATIII activity. In persons with the type II disorder, the ATIII level is normal and only ATIII activity is reduced because a specific mutation of the AT gene leads to production of abnormal ATIII protein. It should be noted that there are also various causes of acquired ATIII deficiency, including hepatic dysfunction and extensive thrombosis. Before cardiovascular surgery that involves heparinization, patients with ATIII deficiency require replacement of ATIII. Careful perioperative management is also necessary to prevent thrombosis, which can be triggered by surgery. There have been several case reports about cardiovascular surgery in patients with ATIII deficiency.[2–7)] However, the risk of thrombosis or hemorrhage is especially high in patients undergoing thoracic aortic surgery, and there have not been any previous reports of success.

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Table 1 Preoperative characteristics

Case	Age/ gender	Pre-AT III (%)	Thrombotic history	Deficiency type	Anamnesis	Diagnosis	Hemoglobin (g/dl)	Platelet ($\times 10^5$)	PT(s)	APTT(s)
1	64 M	74	Aortic dissection	Congenital (Type II)	Aortic dissection	TAA	14.7	20.5	12.1	37.3
2	71 M	64	Deep vein thrombosis	Congenital (Type II)	HD	AS, AF	14.9	15.9	11.2	31.4
3	55 M	76	(–)	Acquired	MI	AAA, AF	16.0	21.6	11.0	31.8
4	82 F	50	(–)	Acquired	HD, CHF	AS	11.0	4.8	11.6	36.5
5	78 M	74	(–)	Acquired	Prostate carcinoma	AS	13.5	16.9	11.1	31.4

HD: hemodialysis; MI: myocardial infarction; TAA: thoracic aortic aneurysm; AS: aortic stenosis; AF: atrial fibrillation; CHF: chronic heart failure; APTT: activated partial thromboplastin time; PT: prothrombin time

Fig. 1 Strategy for cardiovascular surgery in patients with antithrombin III deficiency.

Here, we report five patients with ATIII deficiency who underwent cardiovascular surgery and discuss the validity of our management plan.

Patients and Methods

Among 207 patients treated for cardiovascular disease from September 2013 to November 2017, five patients (2.4%) had ATIII deficiency. Two patients had hereditary ATIII deficiency, and the remaining three patients (with an aneurysm, dialysis, and prostate cancer) were considered to have acquired ATIII deficiency secondary to consumption of ATIII (**Table 1**).

All five patients received ATIII concentrate before surgery to achieve a target ATIII activity ≥120%, considering intraoperative ATIII consumption due to the use of heparin. The amount of ATIII concentrate needed to achieve an ATIII activity ≥120% was calculated by measuring ATIII activity on the day of surgery and assuming a 1% increase in ATIII activity after administration of the concentrate at 1 IU/kg.

Each patient received 1500 or 3000U of ATIII concentrate (Kenketu Nonthron, Takeda) immediately to achieve an ATIII activity ≥120% before transfer to the operating room. At induction of anesthesia, each patient's ATIII activity was confirmed to be ≥120% and the heparin sensitivity test gave a normal result. Heparin was

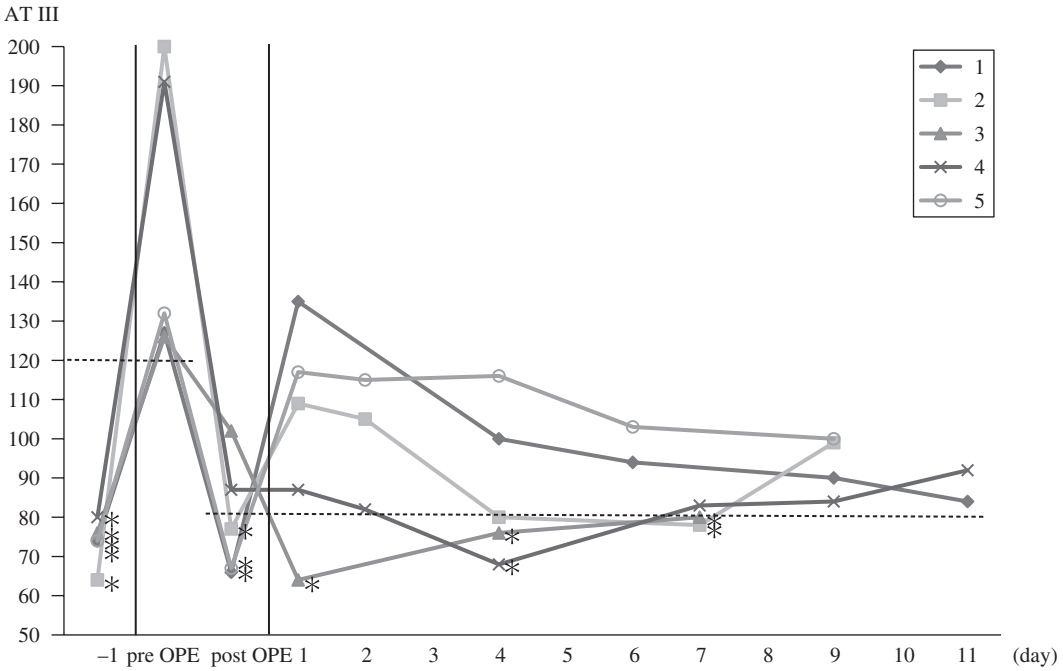

Fig. 2 Changes of antithrombin III activity. *: administration of AT III concentrate

administered intravenously before surgery, which was initiated after confirmation that the activated clotting time (ACT) was ≥ 400 seconds. The ACT was maintained at ≥400 seconds during cardiopulmonary bypass. ATIII activity was measured again at the end of surgery, and further ATIII concentrate was administered to achieve postoperative ATIII activity ≥80%. ATIII activity was monitored for about 1 week postoperatively and ATIII concentrate was administered as required to maintain ATIII activity ≥80% (**Fig. 1**).

Results

In all five patients, ATIII activity was confirmed to be ≥120% before surgery, and the result of the heparin sensitivity test was normal. We minimized administration of heparin while maintaining the ACT at >400 seconds during cardiopulmonary bypass. ATIII activity decreased after surgery in all patients, so ATIII concentrate was administered to maintain their ATIII activity at ≥80% (**Fig. 2**). The perioperative course was unremarkable in all five patients and they were discharged without postoperative complications. Thus, the perioperative outcome of these patients was satisfactory (**Table 2**).

Regarding the long-term outcome, aortic valve replacement was repeated in Case 2 (a dialysis patient with hereditary ATIII deficiency and aortic valve stenosis) about 9 months after initial replacement with a 21-mm Medtronic Mosaic bioprosthetic valve. Macroscopic examination of the removed bioprosthetic valve showed apparent calcification on the tips of the valve leaflets. However, histologic examination revealed deterioration of the valve due to numerous thrombi on the aortic face of each leaflet. Thus, the changes of the leaflets were not due to ectopic calcification caused by dialysis and it seems likely that ATIII deficiency led to multiple thrombi forming on the valve, resulting in its deterioration (**Fig. 3**).

Discussion

Two of the present five patients had hereditary ATIII deficiency (type II), and the remaining three (with an aneurysm, dialysis, or prostate cancer) were presumed to have secondary ATIII deficiency due to increased ATIII consumption. Yamagishi et al. reported that ATIII activity was reduced (≤80%) in about 20% of patients undergoing open heart surgery with cardiopulmonary bypass, but an appropriate coagulation balance was achieved promptly when ATIII concentrate was administered.[8] In addition to the rare hereditary disease, acquired factors presumably led to reduced ATIII activity in three of our patients, suggesting that it is important to measure ATIII activity before cardiovascular surgery. Therefore, we routinely measurement ATIII activity for

Table 2 Postoperative characteristics

Case	Procedure	Operative time (sec.)	CPB (min.)	ACC (min.)	DHCA (min.)	Min. ACT (sec.)	Max. ACT (sec.)	Postoperative AT III administration	Early outcome	Long-term outcome
1	TAR	446	301	193	100	587	980	0POD	No complications	3.8 years in survival
2	AVR + Maze	405	166	132		492	898	0, 7POD	No complications	Bioprosthetic valve thrombosis
3	AAAR	194				420	439	0, 1, 4, 7POD	No complications	0.5 year in survival
4	AVR	382	115	75		727	910	0, 4POD	No complications	1.5 years in survival
5	AVR	283	136	90		465	640	0POD	No complications	3.9 years in survival

CPB: cardiopulmonary bypass; ACC: aortic cross clamp; DHCA: deep hypothermic cardiac arrest; TAR: total arch replacement; AAA: abdominal aortic aneurysm; AAAR: abdominal aortic aneurysm replacement; HD: hemodialysis

all patients treated for cardiovascular disease and all patients with ATIII deficiency require replacement of ATIII, regardless of whether an use of cardiopulmonary bypass or not. Careful perioperative management is necessary to prevent thrombosis that can be triggered by cardiovascular surgery.

Before surgery, it is recommended that ATIII activity should be ≥120% due to consumption of ATIII after administration of heparin. Because 1 IU/kg of ATIII concentrate is generally expected to increase ATIII activity by 1%, the dose of the ATIII concentrate required for each patient can be determined by preoperative measurement of ATIII activity.[9] Our patients received the appropriate dose of ATIII concentrate immediately before transfer to the operating room. At induction of anesthesia, ATIII activity was confirmed to be ≥120%, and the result of the heparin sensitivity test was normal. In all patients, intravenous infusion of heparin was commenced before surgery and incision was initiated after confirming that the ACT was ≥400 seconds. It seems acceptable to start the operation if the heparin sensitivity test is normal.

Low ATIII activity in the postoperative period, especially within one week of surgery, is associated with a risk of thromboembolism causing complications such as cerebral infarction. Therefore, it is necessary to administer doses of ATIII concentrate to maintain ATIII activity at ≥80% or higher after surgery.[9,10] It is also possible for enhanced coagulation after an invasive procedure to result in formation of microthrombi, which can then cause a secondary bleeding tendency due to consumption coagulopathy and activation of the fibrinolytic system.[11] In patients with hereditary ATIII deficiency undergoing thoracic aortic surgery, the risk of both thrombosis and hemorrhage is especially high, and there have been no previous reports of success. However, Case 1 had hereditary ATIII deficiency and required arch replacement surgery, which was performed successfully according to our protocol. The patient was discharged without postoperative complications and the outcome was satisfactory.

It has been reported that there is no significant difference of the lifespan between patients with ATIII deficiency and healthy individuals. However, a high incidence of recurrent thrombosis and occasional fatal thromboembolism are possible,[12] suggesting that patients with a history of thrombosis should be maintained on anticoagulant therapy. Case 2 was a dialysis patient with ATIII deficiency who underwent aortic valve replacement. The bioprosthetic valve showed deterioration due to multiple thrombi on the leaflets and repeat valve replacement was

Fig. 3 Bioprosthetic valve thrombosis.

required 9 months after the initial operation (**Fig. 3**). The likely causes were that the patient received heparin during dialysis at another hospital despite having ATIII deficiency, and that warfarin therapy was discontinued due to bleeding at the vascular access site. This case emphasizes that anticoagulant therapy is necessary for patients with hereditary ATIII deficiency, even after implantation of a bioprosthetic valve. When repeat aortic valve replacement was performed, a mechanical valve was implanted while the patient was on warfarin and the anticoagulant for use during dialysis was switched from heparin to argatroban. Over about 2 years since repeat surgery, the course has been satisfactory with no thromboembolism. In conclusion, long-term postoperative anticoagulant therapy is necessary in patients with hereditary ATIII deficiency and a history of thrombosis. However, the risk of bleeding may exceed the risk of fatal thromboembolic complications in asymptomatic individuals, so long-term anticoagulant therapy is not recommended.[13,14)]

Conclusion

We experienced five patients with ATIII deficiency who underwent cardiovascular surgery. All patients were managed with ATIII concentrate to achieve preoperative ATIII activity ≥120% and postoperative activity ≥80%. As a result, surgery was successful with no postoperative complications. Long-term postoperative anticoagulant therapy is required in these patients if they have a history of thrombosis.

Disclosure Statement

The authors have no funding, no financial relationships, and no conflicts of interests.

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