Case Series

Perioperative Medical Management of Antiphospholipid Syndrome: Hospital for Special Surgery Experience, Review of Literature, and Recommendations

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ABSTRACT. Patients with antiphospholipid syndrome (APS), who are predisposed to vascular thrombotic events, are at additional risk for thrombosis when they undergo surgery. Serious perioperative complications (recurrent thrombosis, catastrophic exacerbation, or bleeding) occur despite prophylaxis. We describe our perioperative experience with APS patients who underwent a variety of surgeries, review the literature, and discuss strategies that may guide other physicians in their perioperative evaluation and management of patients with APS. Recommendations: perioperative strategies should be clearly identified before surgical procedure; pharmacological and physical antithrombosis interventions vigorously employed; periods without anticoagulation kept to a minimum; and any deviation from a normal course should be considered a potential disease related event. (J Rheumatol 2002;29:843–9)

Key Indexing Terms:
ANTIPHOSPHOLIPID SYNDROME SURGERY

The antiphospholipid syndrome (APS) is a distinct clinical syndrome consisting of vascular thrombosis and/or pregnancy morbidity in the presence of antiphospholipid antibodies (aPL), most commonly lupus anticoagulant (LAC) or anticardiolipin antibodies (aCL)[1]. In the absence of an underlying connective tissue disorder (CTD), this syndrome is defined as "primary" APS. "Secondary" APS is seen in patients with other CTD, most often systemic lupus erythematosus (SLE). LAC interfere with phospholipid dependent coagulation studies *in vitro* and cause prolongation of activated partial thromboplastin time (aPTT) or dilute Russell's viper venom time. The prothrombin time (PT) is often normal or only slightly prolonged[2]. Thus, aPTT is frequently used as the initial screening test for the presence of LAC.

Patients with LAC may have increased risk of postoperative thrombosis, particularly after vascular surgery[3]. The standard of care in patients with APS who present with vascular thrombosis is longterm high dose anticoagulation, which can be challenging during the surgical period. Perioperative thromboses can occur due to: (1) withdrawal of warfarin[4]; (2) increased hypercoagulability despite ongoing, optimal warfarin or heparin therapy[5]; and (3) catastrophic exacerbation of APS[6]. Thus, patients with APS are classified in the very high risk category for venous thromboembolism during the postoperative period[7].

In addition to thromboses, life threatening bleeding complications can occur during the perioperative period due to: (1) excessive anticoagulation; (2) thrombocytopenia (which occurs in 20–40% of APS patients)[8]; and (3) associated coagulation factor deficiencies such as high affinity anti-prothrombin (factor II) antibodies[9].

In summary, serious perioperative complications (recurrent thrombosis, catastrophic exacerbation, or bleeding) occur despite prophylaxis. We describe our perioperative experience with APS patients who underwent a variety of surgeries, review the literature, and discuss the strategies that may guide physicians in their perioperative evaluation and management of patients with APS.

CASE REPORTS AND REVIEW OF THE LITERATURE

Case 1. Gynecological surgery. A 49-year-old woman with a 9 year history of rheumatoid arthritis and APS was admitted for an elective hysterectomy. Six months before, she had developed left lower extremity deep venous thromboses (DVT) and 3 months before admission, she had recurrent DVT complicated by pulmonary embolism while taking a therapeutic dose of warfarin [international normalized ratio (INR) > 3]. An inferior vena cava filter was inserted and the warfarin was changed to enoxaparin 60 mg subcu-

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taneously (SQ) twice daily (BID). Two months before admission, she developed an early catastrophic occlusion syndrome manifested by myocardial infarction and hepatic infarction. Aspirin 81 mg daily was added and enoxaparin continued. During this period, extreme menometrorrhagia due to multiple fibroids required multiple blood transfusions and could not be controlled with leuprolide or norethindrone. Radiation endometrial ablation and radiation castration were considered but thought to be not appropriate or definitive in this clinical setting.

Enoxaparin was discontinued the night prior to and aspirin one week prior to surgery. The hysterectomy was performed without incident under general anesthesia. In the recovery room, she developed edema, pain, and numbness of her left hand, which appeared dusky, and felt cool. Radial and ulnar pulses were palpable, and capillary refill was normal. A Doppler study was negative for venous thrombosis.

The next day, she noted increasing numbness in her hand and worsening swelling. Compartment pressures were elevated. Urgent fasciotomies were performed and enoxaparin (60 mg SQ BID) was restarted. On postoperative day (POD) 4, she developed violaceous blistering and erythema at the incision site. Enoxaparin was changed to intravenous heparin. Incision and drainage of the fasciotomy was performed; no purulent material was found. On POD 7, her radial and ulnar pulses were present by Doppler examination. One week later, the hand appeared duskier with scattered vesicles. Magnetic resonance angiography of left upper extremity revealed that the radial, ulnar, and interosseus arteries were occluded distal to the elbow, and that the muscle was necrotic distal to the midforearm. On POD 21, she underwent amputation of her hand through the middle forearm, following which she made an uneventful recovery.

Pathology showed diffuse dilation and fibrin clot deposition of the vessels (Figure 1). The dilation of the vasa vasorum, which is not shown in the image, supports the concept that overall dilation of vessels is due to continued perfusion in the face of restriction of outflow (due to thrombosis induced by aPL), rather than to extrinsic compression (compartment syndrome).

This case demonstrates that a surgical procedure can result in serious complications despite the most vigorous prophylaxis. In our patient, there was no break in the perioperative management.

Case 2. Obstetric surgery. A 37-year-old woman with the diagnosis of primary APS (history of 6 miscarriages between 20 and 24 weeks of pregnancy) was admitted for elective cesarean section (C/S) at 35 weeks. She was taking daily 81 mg aspirin, enoxaparin 30 mg SQ BID, and monthly intravenous immunoglobulin (IVIG) infusion (0.3 g/kg for 3 days) throughout the pregnancy. Aspirin and enoxaparin were stopped 3 and 2 days prior to the surgery, respectively. She underwent a successful C/S under spinal anesthesia. Intermittent venous compression devices were used as per protocol. Unfractionated heparin 5000 U SQ q 12 h was started the night of C/S and switched to enoxaparin 30 mg SQ BID on the discharge date (POD 7). Enoxaparin was stopped 3 months after the C/S and aspirin 81 mg daily was continued. There were no complications during the perioperative period.

This case is important because even if APS is diagnosed solely as a result of pregnancy morbidity, there is a high incidence of subsequent non-pregnancy related thrombosis[10]. We believe that this subgroup of patients should be managed very aggressively during the perioperative period to prevent thrombosis. In addition, low dose aspirin, which is likely effective for prophylaxis during non-pregnancy periods, should be continued postoperatively[10].

Case 3 and 4. Cardiovascular surgeries. Two patients with primary APS (case 3: history of recurrent pregnancy losses; case 4: history of recurrent pregnancy losses and catastrophic APS that resulted in endstage renal disease) underwent elective mitral valve replacement (MVR) and MVR/aortic valve replacement, respectively. Both patients were taking aspirin preoperatively, which was discontinued 1 day before surgery. During cardiopulmonary bypass, intravenous heparin was administered to keep the activated

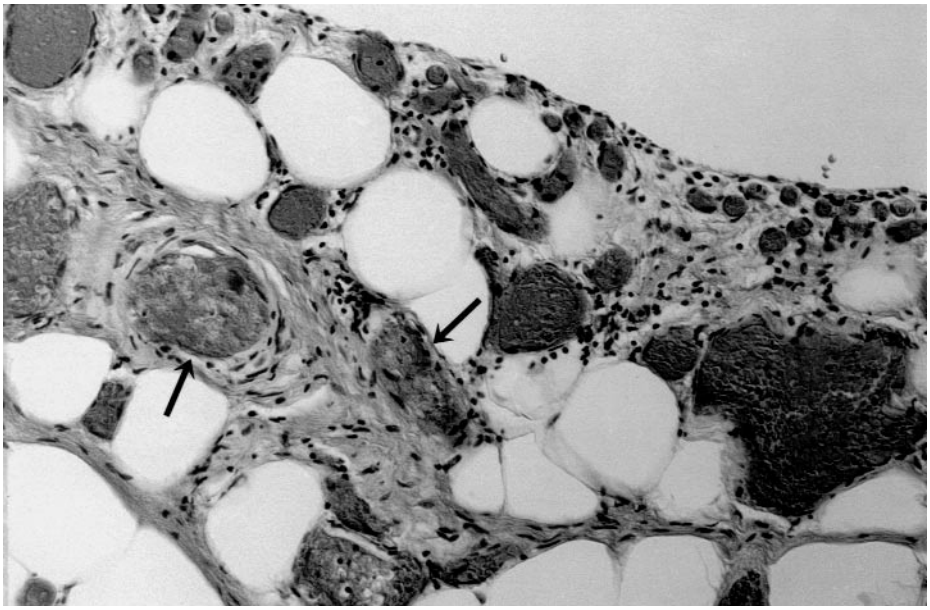

Figure 1. The synovial lining of a tendon sheath after the amputation of left hand through the middle forearm (case 1). This photomicrograph shows dilation and patency of all blood vessels, a finding that was apparent throughout the amputated specimen. A few of the vessels (arrows) contain fibrin clots. Evidence of extrinsic compression, as would be seen in compartment syndrome, is not apparent (hematoxylin and eosin ×25).

coagulation time (ACT) level 2 times the upper limit of normal. Protamine was used to normalize the ACT postoperatively. Unfractionated heparin 5000 U SQ q 12 h was started on the first postoperative day in addition to bilateral lower extremity elastic bandages. Warfarin was added to heparin on postoperative day 3 in the first case and on day 1 in the second case. The course was uneventful for both patients.

APS is associated with cardiac valve involvement. In our experience, 41% of primary APS patients have valvular lesions at 10 years followup[11]. Patients with positive aPL may be prone to excessive postoperative morbidity and mortality after cardiovascular surgical procedures. In one retrospective report, 16 of 19 patients with a positive ELISA for IgG aCL suffered major postoperative complications, and 12 died of complications related to surgical interventions[12].

There are, however, numerous reports of uncomplicated cardiac valve replacements in patients with APS[13-16]. Hogan, *et al* recently reviewed the intraoperative management of cardiac valvular surgeries in APS patients[17]. Intraoperative heparin monitoring during cardiopulmonary bypass surgery can be challenging because APS patients may have elevated baseline ACT level[17,18]. Suggested methods for monitoring include: doubling the baseline ACT level[13]; obtaining heparin concentrations by protamine titration rather than following ACT levels[17,18]; and performing heparin-ACT titration curves preoperatively to determine patient-specific target ACT levels[16]. Heparin, followed by warfarin, is generally used to prevent postoperative thrombotic complications; however, there is no consensus on the timing of anticoagulation, especially warfarin. Both of our patients had uneventful surgeries with rapid reinitiation of anticoagulation. Reported cases of cardiovascular surgeries, anticoagulation regimens, and outcomes are shown in Table 1. From a different vantage point, Taylor, *et al* concluded that vascular surgery patients with positive aPL are more likely to have failure of lower extremity bypass procedures. In this cross sectional study, aPL was present in one-quarter of patients with severe symptomatic peripheral arterial disease and had strong association with premature occlusive failure[20].

Case 5. Orthopedic surgery. A 24-year-old woman with SLE and APS (3 miscarriages followed by hepatic artery thrombosis, which resulted in hepatic necrosis) was admitted for elective left total hip replacement due to avascular necrosis. She also had history of LAC-hypoprothrombinemia syndrome, which resulted in severe gastrointestinal (GI) bleeding while taking warfarin and related to low prothrombin level. Aspirin 81 mg was stopped 3 days prior to surgery. Prothrombin level was 26% (normal 85–140%) on the day of surgery. Two units of fresh frozen plasma were given 6 h prior to surgery as well as stress dose steroids. Surgery was completed without complications and with 300 cc blood loss. Fresh frozen plasma was continued for 24 h (q 6 h). One day after the surgery prothrombin level was 41%. Intermittent venous compression devices were used for additional DVT prophylaxis. Enoxaparin 30 mg SQ BID was started 24 h after surgery (enoxaparin was preferred due to the history of warfarin related GI bleeding), but stopped next day due to epistaxis and worsening thrombocytopenia (70×10^9/l) and anemia. Initial laboratory investigation was negative for other sites of bleeding, platelets stabilized, and epistaxis was thought to be related to traumatic intubation. Enoxaparin was restarted after 24 h and the patient was discharged 5 days after. Despite management as described, she developed left upper quadrant pain 5 days after discharge and was readmitted. Further laboratory investigation revealed new hepatic necrosis with normal hepatic artery and vein blood flow. She was treated with high dose IV heparin and steroids; discharged 5 days later taking enoxaparin.

As in case 1, this case reveals that perioperatively, patients with APS can develop recurrent events despite appropriate prophylactic efforts. Orthopedic procedures, especially total joint replacements, have a high risk of DVT even in the absence of a preoperative hypercoagulable state. Schnitz, *et al* described a patient with APS who underwent 2 sequential total knee replacements. Heparin was not given perioperatively due to history of heparin induced thrombocytopenia. Warfarin was withheld for 5 days prior to surgery and resumed on the day of surgery. Short term withdrawal of warfarin with continuance of aspirin resulted in successful perioperative course[21]. However, despite warfarin treatment, postoperative complications can occur. Bhagia, *et al* reported a patient with LAC (no history of thrombosis) who underwent total left knee replacement. The patient developed DVT and pulmonary embolism on POD 5 despite warfarin treatment (started the night of surgery). Prothrombin time at the time of thrombosis was 15.3 s and intermittent pneumatic compression of the calves was used[22].

Case 6. Neurosurgery. A 44-year-old woman with SLE and APS (history of 3 DVT, complicated by pulmonary embolism) devel-

Table 1. Experience with postoperative thrombosis prophylaxis after cardiovascular surgeries in antiphospholipid antibody positive (aPL) and in patients meeting the Sapporo criteria[1] for antiphospholipid syndrome (APS).

Author	Diagnosis	Surgery	Postoperative Regimen	Timing (Day)	Postoperative Thrombosis
Sheikh [13]	*	CABG	—	—	Yes
Sheikh [13]	APS	MVR	Heparin/warfarin	1/1	No
Matsuyama[14]	APS	AVR	Warfarin	1	No
Yoshida[15]	APS	MVP	Heparin/warfarin	NR	No
Yoshida[15]	APS	CABG/MVP	Heparin/warfarin	NR	No
East[16]	APS	CABG/MVR	Warfarin	NR	No
East[16]	APS	MVR	Warfarin	NR	No
Hogan[17]	aPL	AVR	Aspirin	NR	No
Ducart[18]	aPL	CABG	NR	NR	No
Myers[19]	aPL	AVR/MVR	Warfarin	NR	No
Present study	APS	MVR	Heparin/warfarin	1/3	No
Present study	APS	MVR/AVR	Heparin/warfarin	1/1	No

*APS was diagnosed after surgery. CABG: coronary artery bypass grafting; MVR: mitral valve replacement; AVR: aortic valve replacement; MVP: mitral valve prolapse; NR: not reported.

oped sudden severe occipital headache when her INR was 5. Computed tomography revealed a posterior fossa subdural hematoma. Fresh frozen plasma was given and the hematoma was evacuated by the neurosurgical team. Postoperatively, intermittent venous compression was applied and an inferior vena cava filter was placed. She remained with no anticoagulation for 4 months, and then restarted warfarin, maintaining her INR between 2 and 2.5, without further hemorrhagic or thrombotic complications.

The literature on patients with APS undergoing neurosurgical procedures is very limited. Bocquet, *et al* described an 11-year-old patient with APS who underwent surgery for a cerebrovascular malformation responsible for an intracerebral hematoma. Heparin was administered 16 h after the surgery and the postoperative course was uneventful except for heparin induced thrombocytopenia, which was normalized with switch to low molecular weight (LMW) heparin[23].

Case 7. Kidney transplantation (2nd surgical procedure for case 4). A 47-year-old woman with history of catastrophic APS in 1987 (myocardial infarction, hepatic necrosis, and renal artery thrombosis, which gradually resulted in endstage renal disease) was admitted for kidney transplantation. Warfarin was changed to enoxaparin 60 mg SQ BID 7 days prior to surgery, which was stopped on the day of surgery and resumed 2 days postoperatively. She also started cyclosporine, mycophenolate mofetil, and steroids. On POD 3, her creatinine began to rise to 3.0 mg/dl and platelet count fell. Renal biopsy revealed thrombotic microangiopathy. Cyclosporine was discontinued, plasmapheresis was begun, and IVIG, IV heparin, high dose steroids and FK-506 (tacrolimus) were administered. Two weeks later she was discharged with a falling serum creatinine, and heparin was changed to warfarin. In followup, her creatinine improved to 1.0 mg/dl.

An increased risk of transplant failure in patients with aPL occurs. Wagenknecht, *et al* found aPL were present in 57% of patients with early allograft failure[24]. Stone, *et al* in a retrospective review of 96 consecutive patients with SLE undergoing transplant found that 10 patients (40% of aPL positive patients) either died of APS or had an APS associated event within 3 months of transplant[25]. Marcen, *et al* reported that of 16 transplants done in LAC positive patients, 6 failed, all due to allograft renal vascular thrombosis[26]. Vaidya, *et al* reported 11 endstage renal disease APS patients undergoing renal transplant[27]. Four received concomitant anticoagulation with warfarin while 7 did not. All 7 untreated patients lost their allografts within one week due to renal thrombosis. Thus, aPL positive patients appear to be at high risk of graft failure and APS associated events after renal transplant.

DISCUSSION

Perioperative thrombosis prophylaxis in patients with APS. Stasis, intimal injury, and hypercoagulability are the 3 major factors that contribute to the development of postoperative thromboembolic events[28]. Their presence mandates prophylaxis with heparin or warfarin in patients with APS.

Gastrointestinal, gynecologic, thoracic, and urologic surgery patients with history of a hypercoagulable state and lower extremity orthopedic major surgery patients are at significantly increased risk of thrombotic complications compared to uncomplicated minor surgeries in patients less than 40 years old (calf vein thrombosis, 40–80% vs 2%; proximal vein thrombosis 10–20% vs 0.4%; clinical pulmonary embolism 4–10% vs 0.2%; and fatal pulmonary embolism 1–5% vs 0.002%)[7]. Up to 80% of total hip replacement patients and 60% of total knee replacement patients develop DVT without prophylactic treatment[7]. Pooled data from large trials show significant reduction of DVT and pulmonary embolism with perioperative anticoagulation[7].

In general surgery patients, low dose unfractionated (LDU) heparin and LMW heparin are the most effective in reducing the incidence of DVT. LMW heparin differs in molecular weight and half-life, and does not require monitoring except in patients with renal failure and a creatinine clearance < 30 ml/h, in which case anti-factor Xα activity monitoring is required. Data from metaanalyses and placebo controlled, double blind randomized trials show no significant increase in major bleeding with the use of LDU or LMW heparin[7]. Heparin induced thrombocytopenia occurs in 3% of patients, more commonly with LDU than LMW heparin[7]. In general surgery patients, warfarin therapy may be cumbersome compared to other effective agents. In total hip and knee replacement patients, LMW heparin is more effective than warfarin but causes more surgical site bleeding and wound hematomas, especially if started within 24 h after the surgery.

In 1993, Menon and Allt-Graham reported an SLE patient with APS who underwent laparoscopy for a pelvic mass, and who suffered disseminated intravascular coagulation and adult respiratory distress syndrome, cardiac, respiratory and renal failure and died 10 days after admission. The authors published their anesthetic recommendations, which are nonspecific and do not discuss anticoagulation management[29]. In 1997, Madan, *et al* discussed 2 APS patients: one died of myocardial infarction after warfarin withdrawal and the other developed pulmonary embolism following hepaticojejeunostomy. These authors stated the importance of perioperative high dose thromboprophylaxis in APS patients, LDU heparin 25,000 U SQ in divided doses, as their patient developed pulmonary embolism despite 10,000–15,000 U of daily LDU heparin[30]. Two of our patients received high dose anticoagulation (enoxaparin 60 mg BID), while 4 patients received standard recommended doses (enoxaparin 30 mg BID or LDU heparin 5000 U q 12 h). Standard antithrombotic regimens recommended by Geerts, *et al* for high risk patients are summarized in Table 2, which should be the minimum administered dose in patients with APS. No further studies are available for the most accurate dosing; it is possible that the current recommended doses result in "under-anticoagulation" of APS patients.

Timing of the anticoagulation is also crucial in APS patients to keep periods without anticoagulation to an absolute minimum. Practice patterns can vary based on surgeons' experience. For APS patients already receiving longterm warfarin, the drug is usually restarted on the night of surgery unless there is a surgical contraindication. Short

Table 2. Recommendations[7] of standard antithrombotic regimens to prevent venous thromboembolism in high risk general and orthopedic surgery patients. These dosing schedules may result in "under-anticoagulation" of APS patients and should be the minimum administered dose.

Surgery	LDU Heparin	LMW Heparin*
General surgery	5,000 U q 8–12 h, start 1–2 h before surgery	30 mg q 12 h, start 8–12 h after surgery or 40 mg q 24 h, start 1–2 h before surgery
Orthopedic surgery	5,000 U q 8–12 h, start 12–24 h after surgery	30 mg q 12 h, start 12–24 h after surgery or 40 mg q 24 h, start 10–12 h before surgery

LDU: low dose unfractionated; LMW: low molecular weight.
*Dosing schedule for enoxaparin (other LMW heparin preparations available for perioperative thrombosis prophylaxis are ardeparin, dalteparin, danaparoid, nadroparin, and tinzaparin). These LMW preparations have similar clinical efficacy and the choice of medication depends on physician preference[44,45].

term anticoagulation with heparin should continue until the INR is therapeutic. In general surgery patients, LDU or LMW heparin can begin 2 h before the operation, whereas in orthopedic patients, it is often started 12 to 24 h after surgery because of bleeding concerns[7]. For general surgery patients taking longterm aspirin treatment, LDU or LMW heparin should be continued until the patient is fully ambulatory. For orthopedic surgery patients taking longterm aspirin, longterm prophylaxis with warfarin or LDU or LMW heparin should be considered.

Elective neurosurgical procedures are high risk for postoperative venous thromboembolism. Physical methods of prophylaxis are preferred because of concerns about intracranial or spinal bleeding[31]. However, randomized trials have demonstrated no increased risk of intracranial bleeding in neurosurgical patients who had prophylaxis with LDU or LMW heparin[32]. The combination of LMW heparin and elastic stockings is more effective in risk reduction than elastic stockings alone[33].

Intermittent venous compression devices, which provide rhythmic external compression to the calf/thigh about once a minute, improve venous return and reduce leg DVT in surgical patients with malignancy[34]. Graded compression elastic stockings are also effective[35]. Inferior vena cava filter placement can be used in patients who are at extremely high risk for both postoperative thrombosis and bleeding[7], when other prophylactic regimens are not possible.

Catastrophic antiphospholipid syndrome. A small minority of APS patients develop catastrophic syndrome defined as vascular occlusions involving multiple organs over a short period. This has been described in the setting of major or minor surgical procedures and interventions such as hysterectomy, dental extraction, endoscopic retrograde cholangiopancreatography, and uterine dilatation and curettage[36]. Mortality approaches 50% in patients with catastrophic APS and the best outcomes are achieved with combinations of anticoagulation, corticosteroids, plasmapheresis, IVIG, and cyclophosphamide[36]. Although the factors that may trigger a catastrophic event rather than perioperative thrombosis are unknown, the prophylactic strategy is not different.

Special considerations in renal transplant patients. Patients with APS undergoing renal transplant should be anticoagulated aggressively during the perioperative period. Recommendations for managing asymptomatic aPL positive patients undergoing renal transplant have not been formally addressed to date. It is intuitive that these patients should be maintained on anticoagulation therapy and we recommend prophylactic perioperative heparin for all aPL positive patients undergoing renal transplant.

Our transplant patient with thrombotic microangiopathy raises the additional question of which type of anticoagulation is most protective and what level of anticoagulation is necessary to optimize graft survival in patients with APS. Thrombotic microangiopathy occurred after our patient had been switched from longterm low dose warfarin to enoxaparin and while she was taking cyclosporine. The intraoperative time without anticoagulation may have made her susceptible to thrombosis. Additionally, cyclosporine has been associated with thrombosis[37], a possible factor in our patient's thrombotic microangiopathy. It is unknown whether patients with APS are at higher risk for this complication. Aspirin may be of benefit in preventing cyclosporine induced thrombosis[38].

In those patients who despite anticoagulation develop allograft renal vascular thrombosis, plasmapheresis may be of some benefit, as it was in our patient. Montgomery, *et al* describe this regimen given as a "rescue therapy" in acute humoral rejection in renal transplant recipients[39]. They describe 7 patients in whom donor-specific antibodies developed post-transplant. Plasmapheresis alternating with IVIG in addition to FK-506, mycophenolate mofetil, and bolus corticosteroids reversed the rejection. We used a similar multiregimen protocol for our patient (case 7), which is also the treatment strategy in catastrophic APS.

Management of anticoagulation during urgent or emergency surgery. Patients with APS taking warfarin need

Table 3. Authors' recommendations for perioperative medical management of patients with antiphospholipid syndrome (APS).

Preoperative assessment
• Prolonged activated partial thromboplastin time and/or slightly prolonged prothrombin time when known to be due to APS are *not* contraindications for surgical procedures
• Platelet count > 100×10^9/l due to APS requires no specific therapy; thrombocytopenia does not protect against thrombosis
• Surgical and interventional procedures should be the last option in the management of patients with APS
Perioperative considerations
• Minimize intravascular manipulation for access and monitoring
• Set pneumatic blood pressure cuffs to inflate infrequently to minimize stasis in the distal vascular bed
• Avoid tourniquets
• Maintain high suspicion that any deviation from a normal course may reflect arterial or venous thrombosis
Perioperative anticoagulation
• Keep periods without anticoagulation to an absolute minimum
• Employ pharmacological and physical antithrombosis interventions vigorously and start immediately before the operation, continuing until the patient is fully ambulating
• Be aware that patients with APS can develop recurrent thrombosis despite appropriate prophylaxis
• Be aware that current conventional doses of antithrombotic regimens can result in "under-anticoagulation"; patients with APS may benefit from an aggressive approach with higher than standard doses
• Manage patients with APS whose only clinical manifestation is pregnancy morbidity as if they had vascular thrombosis
Renal transplant patients
• Perioperatively, anticoagulate all APS patients (history of thrombosis) undergoing renal transplant aggressively
• Strongly consider perioperative anticoagulation in antiphospholipid antibody positive asymptomatic patients (no history of thrombosis)

prompt reversal of anticoagulation before an urgent or emergency surgery. Fresh frozen plasma contains all the coagulation factors found in fresh plasma, and warfarin induced deficiency of vitamin K dependent factors may be rapidly reversed with fresh frozen plasma. Overcorrection, i.e., use of high dose vitamin K, should be avoided and anticoagulation restarted as soon as possible postoperatively.

Management of thrombocytopenia or bleeding complications during perioperative period. Corticosteroids and/or IVIG are the first line treatments for platelet counts < 50×10^9/l when patients need urgent or emergency surgery. IVIG works rapidly and has relatively few side effects. Platelet transfusions are usually not helpful in patients with APS as the mechanism of thrombocytopenia is thought to be destructive[40] and may increase the risk of thrombosis. Besides IVIG, danazol or even splenectomy may need to be considered in corticosteroid resistant cases before an elective surgery.

Corticosteroid is also the first line treatment in LAC-hypoprothrombinemia as it decreases the clearance of the prothrombin-antiprothrombin antibody complexes[9].

Special considerations in patients receiving heparin prophylaxis and regional anesthesia. A US Food and Drug Administration Public Health Advisory called attention to 30 patients who developed epidural or spinal hematomas with concurrent LMW heparin prophylaxis and regional (spinal or epidural) anesthesia or spinal puncture[41]. The problem has also been reported with LDU heparin. In 1997, Horlocker, *et al*[42] reviewed the complications associated with concurrent LMW heparin prophylaxis and regional anesthesia and offered recommendations. Insertion of the spinal needle should be delayed for 10–12 h after the initial LMW heparin dose; subsequent doses should be delayed at least 2 h after spinal needle placement or catheter removal. For patients in whom LMW heparin prophylaxis is started post-operatively, the initial dose should also be delayed at least 2 h.

We have presented examples of our patients with APS to discuss major difficulties of perioperative medical management and to illustrate possible complications. The frequency of these outcomes is unknown. Literature on the perioperative medical management of APS is limited. We summarized strategies that may guide physicians in their preoperative, intraoperative, and postoperative management of APS patients in Table 3.

In summary, when a patient with APS undergoes a surgical procedure, the most effective pharmacological methods should be combined with physical methods like intermittent venous compression, and patients should be closely observed for the signs and symptoms of thrombotic clinical events. These recommendations may also apply to patients with inherited thrombophilias, since they have genetic predisposition to venous thrombosis[43].

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