

Orthopedic surgery and its complication in systemic lupus erythematosus

Anselm Mak

Anselm Mak, Division of Rheumatology, Department of Medicine, University Medicine Cluster, Singapore 119228, Singapore
Anselm Mak, Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119228, Singapore

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Correspondence to: Anselm Mak, MMedSc, MBBS, MD, FRCP Edin, Division of Rheumatology, Department of Medicine, University Medicine Cluster, 1E Kent Ridge Road, Level 10, NUHS Tower Block, Singapore 119228,

Singapore. mcam@nus.edu.sg

Telephone: +65-67-795555 Fax: +65-67-724119

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Abstract

Systemic lupus erythematosus (SLE) is a multi-systemic immune-complex mediated autoimmune condition which chiefly affects women during their prime year. While the management of the condition falls into the specialty of internal medicine, patients with SLE often present with signs and symptoms pertaining to the territory of orthopedic surgery such as tendon rupture, carpal tunnel syndrome, osteonecrosis, osteoporotic fracture and infection including septic arthritis, osteomyelitis and spondylodiscitis. While these orthopedic-related conditions are often debilitating in patients with SLE which necessitate management by orthopedic specialists, a high index of suspicion is necessary in diagnosing these conditions early because lupus patients with potentially severe orthopedic conditions such as osteomyelitis frequently present with mild symptoms and subtle signs such as low grade fever, mild hip pain and back tenderness. Additionally, even if these orthopedic conditions can be recognized, complications as a result of surgical procedures are indeed not uncommon. SLE *per se* and its various associated pharmacological treatments may pose lupus patients to certain surgical risks if they are not properly attended to and

managed prior to, during and after surgery. Concerted effort of management and effective communication among orthopedic specialists and rheumatologists play an integral part in enhancing favorable outcome and reduction in postoperative complications for patients with SLE through thorough pre-operative evaluation, careful peri-operative monitoring and treatment, as well as judicious postoperative care.

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Key words: Orthopedics; Complications; Surgery; Systemic lupus erythematosus; Operation

Core tip: Systemic lupus erythematosus (SLE) is a complex autoimmune condition. Orthopedic specialists often encounter patients with SLE presenting with various orthopedic conditions which require surgical intervention but due to the complexity of SLE and its associated treatment, pre-operative preparation and post-operative care for these patients are often challenging. Concerted effort of management and effective communication between orthopedic specialists and rheumatologists play an integral part in enhancing favorable outcome and reduction in postoperative complications for patients with SLE through thorough pre-operative evaluation, careful peri-operative monitoring and treatment, as well as judicious postoperative care.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an immune-complex mediated autoimmune disease characterized

by protean clinical manifestation and fluctuating disease course^[1]. The exact patho-aetiology of SLE is not fully understood but is believed to be multi-factorial, with environmental, neuroendocrine, genetic, hormonal and infectious factors participating in playing a role^[2]. On the molecular level, failure in clearance of apoptotic bodies which contain a wide array of genetic materials exposes lupus-susceptible individuals to the formation of autoantibodies against these genetic materials. The pathogenic autoantibodies induce inflammatory reactions through complement deposition, leucocyte ingressions and tissue damage due to the consequent formation of immune complexes^[3]. The reason why SLE preferentially affects young females is not fully understood although high estrogen levels and increase in CD40L expression in lymphocytes have been postulated^[4]. Thus far, SLE is an incurable and unpreventable disease. Treatment largely aims at suppressing inflammation and reducing the occurrence of chronic tissue and organ damage^[5]. In general, patients with major organ involvement such as diffuse proliferative glomerulonephritis, severe systemic vasculitis and neuropsychiatric involvement including myelitis will require heavier immunosuppression such as high dose glucocorticoids and cytotoxic agents. In contrast, symptomatic therapy may be the sole treatment in those who present with mild symptoms such as arthralgia, photosensitive rash and mild depression.

While rheumatologists are amongst the chief health-care providers for patients with SLE, these patients often present with common and potentially debilitating conditions which require attention by orthopedic specialists. These conditions include tendon rupture, carpal tunnel syndrome (CTS), osteonecrosis or avascular necrosis (AVN), osteoporotic fracture and infections such as osteomyelitis, septic arthritis and spondylodiscitis. While many of these conditions require surgical treatment, SLE *per se* and its medications may predispose patients to surgical risks^[6]. Currently, strong literature and guideline with respect to pre-operative evaluation and post-operative care for patients with SLE are scarce. In this short review, individual diseases which are more commonly associated with the area of orthopedic surgery will be briefly discussed, followed by discussing how patients should be assessed pre-operatively and monitored peri-operatively and managed post-operatively with an aim to reduce the chance of post-operative complications.

COMMON ORTHOPEDIC CONDITIONS IN PATIENTS WITH SLE

CTS

CTS (or median entrapment neuropathy) is common, especially amongst middle-aged women. If severe, CTS can cause disturbing symptoms such as paresthesia, pain and numbness which can lead to sleep disturbance and poor quality of life especially if they occur nocturnally^[7]. In a study of 436 patients reported in the 1990s, the prevalence of CTS was found to be around 11%^[8]. In severe and prolonged cases, wasting of the thenar muscles

and weakness of palmar adduction would be observed and hand function may be impaired. Since most patients experience satisfactory outcome with night splints and carpal tunnel release as day surgical procedures, most patients will not require specific pre-operative assessment unless patients have bleeding tendency which may need to be corrected before the procedure.

Fragility fracture

Observational studies have unanimously demonstrated a higher risk of osteoporotic fracture in patients with SLE^[9]. One of the largest observational studies found that there was a five-fold increase in fragility fracture occurrence in women with SLE when compared with the general population^[10]. Bone loss in patients with SLE is a result of a number of well-established factors such as glucocorticoid use, renal dysfunction, vitamin D deficiency, immobility, inflammation and premature menopause^[11]. A recent case-control study has found that by using the FRAX[®] risk calculation model, the 10-year major fracture risk was estimated to be increased as a result of post-menopausal state and the use of glucocorticoids^[11]. In fact, other medications which patients with SLE are taking may induce bone loss, such as anti-coagulants and cyclosporin. Apart from treatment, it appears that high SLE disease activity may predispose lupus patients to fracture^[11]. Hip fractures are the most serious consequences of osteoporosis due to the associated disability and high mortality. It has been estimated that the mortality rate in the first year after fracture is up to 20%-30%^[12]. Osteoporotic vertebral fractures, which are clinically silent in two thirds of cases, are also common, with reported prevalence between 9% and 20%^[13,14]. An important point of note is, back pain *per se* is not a manifestation of lupus and uncomplicated osteoporosis. Lupus patients with back pain must be thoroughly investigated for pathological processes such as nerve entrapment, fragility fracture, infection and metastases in the vertebra and their associated structures. To date, the gold standard to diagnose osteoporosis is dual energy X-ray absorptiometry (DXA) of the hips and spine. According to the definition by the World Health Organization, a T-score (the number of standard deviation above or below the peak bone mass of young adult of the general population) of or below -2.5 is considered to be osteoporosis^[15]. However, those who have history of fragility fracture are considered to have established osteoporosis even though their T-scores do not fall into the osteoporotic range. Indeed, many patients do fracture above the osteoporotic range of T-score, suggesting that DXA and the T-score are not perfect predictors for fractures^[11]. Inferior bone quality due to damage of bone micro-architecture is detrimental to bone strength and cannot be assessed by routine DXA^[16]. As for the treatment of osteoporotic fracture, hip fractures are largely managed by hip replacement or arthroplasty, while vertebral fractures are chiefly conservatively managed unless the fractures lead to neurological involvement, which is rare. Medical treatment of osteoporosis includes the use of anti-resorptive agents such as

bisphosphonates and RANKL inhibitor (Denosumab)^[17], or anabolic agents including strontium ranelate and intermittent subcutaneous parathyroid hormone injection (Teriparatide)^[18,19]. While the risks and benefits regarding the use of these agents are beyond the scope of discussion of this review, the benefits of regular weight-bearing exercise and adequate intake of elementary calcium and vitamin D are paramount, in terms of prevention and reduction of the severity of osteoporosis^[20].

AVN

AVN or osteonecrosis is not an uncommon phenomenon in SLE patients. Amongst all rheumatic diseases, the prevalence of AVN is the highest in patients with SLE, as compared with patients with other rheumatological conditions such as autoimmune myositis, vasculitides, rheumatoid arthritis (RA) and systemic sclerosis^[21]. In one of the oldest studies, 4.6% of patients with SLE were found to develop AVN^[22]. One of the main factors of predisposition to AVN is the presence of anti-phospholipid antibodies (APA) and/or anti-phospholipid syndrome. In a one-year prospective magnetic resonance imaging (MRI) study of 687 joints in patients with SLE, the risk factors for the increase in the incidence of AVN in comparison to patients with other autoimmune diseases such as myositis, medium- and large-vessel vasculitides, pemphigoid, RA, scleroderma and Behcet's disease were adult and adolescent patients (OR = 13.2), high glucocorticoid dose of more than 40 mg/d of prednisolone equivalent (OR = 4.2), patients with SLE (OR = 2.6) and the male sex (OR = 1.6)^[21]. Treatment of AVN depends on the stage of the disease, the severity of the involvement of AVN, pain severity and the presence of co-morbidities which may pose patients to higher risks for major operation and anesthesia^[23]. Patients with stage 0 and stage 1 AVN associated with mild symptoms warrant conservative treatment with rest and reduction in weight bearing. However, a randomized controlled trial of 36 patients demonstrated superiority of treatment success with surgical approach compared with conservative therapy (70% vs 20%)^[24]. Free vascularized grafting for AVN of the femoral head appears to be promising in lupus patients although the concern of the health of the graft which might be compromised by SLE-related vasculitis will need to be addressed by further investigation^[25]. Nevertheless, the best approach to manage AVN is prevention and early recognition so as to slow down disease progression and delay the need for hip replacement^[26]. Judicious use of glucocorticoids, especially in patients who are positive for APA, is an important strategy to reduce the incidence of AVN.

Infection

Osteomyelitis and spondylodiscitis: Besides osteoporotic fracture, clinicians taking care of lupus patients with back pain should always carry a high index of suspicion of osteomyelitis of the vertebra and their associated structures. Patients with SLE are more prone to bacterial infection due to a number of reasons, for example,

quantitative and qualitative deficiencies of complement proteins and immunoglobulins, renal dysfunction, impaired phagocytosis and chemotaxis, and obviously, the use of immunosuppressants^[27]. Threshold of suspicion of infection should even be lower if these patients experience fever, night sweating, night pain without promising relieving factors and suboptimal response to painkillers. Apart from appropriate imaging studies such as computed tomography or MRI of the spine, patients suspicious of osteomyelitis should always have complete sepsis workup including blood, urine and stool cultures because aside from common bacterial infections such as those caused by *Staphylococcus aureus*, opportunistic infections such as those due to *Salmonella* should not be overlooked. In regions where tuberculosis (TB) is prevalent, a chest radiograph and sputum smear and culture, as well as TB molecular tests should be performed.

Septic arthritis and tenosynovitis: Only 1% to 2% of patients with SLE satisfy the American College of Rheumatology criteria for classical RA and have erosive arthropathy^[28]. Most patients with SLE do not present with inflammatory arthritis with effusion although up to 90% of lupus patients experience arthralgia during the course of the disease. The "swan-neck" deformities and ulnar deviation observed in lupus patients are more likely due to tenosynovitis, or Jaccoud's deformities. Thus, a high index of suspicion of septic arthritis should always be exercised in lupus patients with joint inflammation and effusion. In sexually-active patients who present with polyarthritis, tenosynovitis and dermatitis, disseminated gonococcal infection (DGI) must be considered. In these patients, blood and extra-articular cultures of urethral, cervical, rectal and pharyngeal sites for *Neisseria gonorrhoeae* with a special medium (chocolate or Thayer-Martin medium) will be helpful. Similar to vertebral infections, TB needs to be excluded in patients with tenosynovitis which is highly suspicious of an infective process^[29]. For the management of non-gonococcal septic arthritis, the prompt use of intravenous antibiotics should be accompanied by drainage of the affected joint, with continuation of antibiotics for at least 6 wk. DGI responds very well to intravenous or intramuscular third-generation cephalosporin, or intramuscular spectinomycin. Open drainage for joints affected by DGI is often unnecessary^[30]. Importantly, patients who are confirmed to have DGI should undergo comprehensive screening for other potentially concomitant sexually transmitted diseases such as hepatitis B, hepatitis C, chlamydial infection and HIV.

Tendon rupture

Spontaneous rupture of tendons which has been reported in patients with chronic renal failure, RA, local glucocorticoid injection and hyperparathyroidism^[31], occurs rarely in patients with SLE but it can be disabling^[32,33]. While no large-scale study has been performed, high dose, prolonged and pulse glucocorticoid therapies, hypercoagulability state and APA positivity tend to be

reported more frequently in lupus patients who experienced tendon rupture^[34]. Most reported sites of tendon rupture are weight-bearing areas such as Achilles' tendon, patellar tendon and extensor tendons of the hands^[33,34]. While tendon rupture can be diagnosed based on physical examination, a definite diagnosis can be made with MRI. Tendon biopsy is not required in most cases unless infection is suspected, since biopsy specimens may yield non-specific findings such as mononuclear infiltration and neovascularization^[35]. Most of the patients require tendon transfer and full recovery is often achieved.

IMPORTANT PRE-OPERATIVE ASSESSMENT FOR PATIENTS WITH SLE

Cardiovascular condition

Data from a number of observational studies of large cohorts invariably revealed a higher prevalence of cardiovascular disease in patients with SLE when compared with the age- and gender-matched general population^[36]. While traditional cardiovascular risk factors such as hypertension, hyperlipidaemia and the use of glucocorticoids are more prevalent in patients with SLE, non-traditional risk factors such as inflammation are also operant in these patients. In fact, a recent study has found that inflammation exerts its impact very early on atherosclerosis by inducing endothelial dysfunction, which is the very first step of the atherogenic process^[37]. Thus, based on the higher cardiovascular risk amongst patients with lupus, pre-operative assessment of the cardiovascular system is essential. Detailed personal and family history of cardiovascular disease and its risk factors should be obtained. A thorough cardiovascular examination including blood pressure, peripheral pulses, carotid bruit, position and character of the apex beat, added heart sounds and cardiac murmur, as well as signs of cardiac failure should be noted. Investigation should include a 12-lead electrocardiogram and chest radiograph at baseline. If possible, a cardiologist should always be consulted for further investigation such as an echocardiogram, Treadmill test or even corangiogram in any suspected cases of heart disease before surgery.

Thrombophilia and thrombocytopenia

Patients with SLE are prone to thrombosis especially if they have history of vascular thrombosis, heart failure, pulmonary hypertension, or if they are positive for APA and/or lupus anticoagulant (LAC). On the other hand, lupus patients with positive APA and/or LAC, hyper-splenism, anti-platelet antibodies and blood marrow suppression due to SLE *per se* or immunosuppressant may present with severe thrombocytopenia which may complicate invasive procedures due to an excessive bleeding risk. Management of patients with thrombotic risk will be discussed in subsequent section. Patients with thrombocytopenia may need to have their platelet count corrected before emergency surgery, an exception is thrombotic thrombocytopenic purpura (TTP) or microangiopathic

hemolytic anemia (MAHA) which is associated with active SLE in some cases. In these cases, thrombocytopenia is often associated with hemolytic anemia with fragmentation of red cells in combination with any of the following including fever, acute renal impairment and altered conscious level. Surgery will need to be postponed in case of TTP or MAHA unless the procedure is an important option to remove the cause of TTP or MAHA, such as severe infection or disseminated malignancy. In elective surgery, thrombocytopenia is preferred to be corrected prior to the procedures, such as the use of intravenous immunoglobulins (IVIg) in patients with autoimmune thrombocytopenia. Prior exclusion of immunoglobulin A (IgA) deficiency which is present in between 2.6% and 5.2% of patients with SLE^[38,39], is beneficial before IVIg infusion in order to avoid anaphylactic transfusion reaction upon subsequent encounter of IgA protein, although no guidance has been established at the time of writing. While there is no universal cut-off value for a safe level of platelet count, a platelet count of at least $80 \times 10^9/L$ is usually advised in major operation such as hip replacement and vertebral instrumentation. Table 1 summarizes the major tests that patients may require before operation, appended with associated main points.

POSTOPERATIVE CARE IN PATIENTS WITH SLE

Deep vein thrombosis and pulmonary embolism

Due to immobilization after operation, screening for deep vein thrombosis (DVT) between day 3 and 5 after operation are routinely carried out in patients with hip and knee surgery in our centre, even in lupus patients without obvious thrombotic risk and whose APA and LAC are negative. Prophylactic low molecular weight heparin and early mobilization are beneficial in preventing DVT until sonographic absence of DVT is proven^[40].

SPECIAL ISSUES ON MEDICATIONS IN PATIENTS WITH SLE

Glucocorticoids

Glucocorticoids are the main immunosuppressants in patients with SLE. However, chronic glucocorticoid administration (*e.g.*, prednisolone 5 mg or equivalent and above for more than 2 wk) suppresses adrenal function. Adrenal suppression is detrimental in patients who are exposed to surgical stress, especially during the first 48 h peri-operatively when patients would develop circulatory shock and renal shutdown if adrenal suppression is not corrected before operation. To assess adrenal function, a physician should be consulted for performing a simple short synacthan test whereby 250 µg of intravenous synthetic adrenocorticotropic hormone is injected and after 60 min a plasma level of cortisol of at least 550 nmol/L or a rise of 200 nmol/L is expected in individuals with normal adrenal response. However, since chronic glucocorticoid administration would affect the central component of

Table 1 Pre-operative workup for patients with systemic lupus erythematosus planned for orthopaedic surgery

Workup and test	Description
Baseline kidney and liver function tests, fasting glucose and lipid profile	Anaesthetists should be alerted to abnormalities of the renal and liver functions as they may have implications on anaesthetics use. Patients need to fast for at least 8 h for fasting glucose and lipid tests. Endocrinologists should ideally be referred to assess diabetic patients in order to maintain stable glucose levels before and after operation by adjusting existing or starting new hypoglycaemic agents and/or insulin.
Full blood count, peripheral blood smear (if hemolysis is suspected or proven) and clotting profile. Type and match if transfusion is contemplated or expected. Thrombophilic screen if there is history or suspicion of vascular thrombosis: Blood protein C and protein S levels, lupus anticoagulant, serum anti-cardiolipin antibodies and serum IgA level if IVIg infusion is required	Poor glycaemic control is associated with poor wound healing Haematology or rheumatology consultation is necessary in case of anaemia, hemolysis, thrombocytopenia and evidence of thrombophilia, especially if patients have history of severe bleeding and/or vascular thrombosis, and if patients are on anti-platelet agents and/or anticoagulants
Resting 12-lead ECG	Patient should be referred for formal CVS assessment if ECG abnormalities such as ST segment changes, heart block or arrhythmia is evident
Chest radiograph	A plain chest radiograph is considered baseline pre-operative assessment in case general anaesthesia is required. In patients with SLE, a chest radiograph allows a crude assessment for pulmonary lesions such as interstitial lung disease and serositis. Assessment by pulmonologists may be required if lung pathology is suspected
Radiograph of the cervical spine (flexion and extension views)	Rarely required unless lupus patients have features of bone erosion in the peripheral joints which might heighten the chance C1-C2 disease
Treadmill test and coroangiogram	Patients with suspected or confirmed ischaemic heart disease may require these tests after assessment by cardiologists on a case-by-case basis. These tests allow diagnosis of coronary artery disease and risk stratification

CVS: Cardiovascular; ECG: Electrocardiogram; SLE: Systemic lupus erythematosus; IgA: Immunoglobulin A; IVIg: Intravenous immunoglobulins.

the hypothalamic-pituitary-adrenal axis and tests for these central components are complex, most authorities recommend empirical glucocorticoid cover pre-operatively. While no strong data are available, in our centre, patients preparing for surgery who are on chronic glucocorticoid administration will be given hydrocortisone 100 mg intravenously on call to operation theatre. Then, hydrocortisone will be given 100 mg intravenously every 8 h on the first day after operation, followed by every 12 hourly and daily on the second and third day after operation. If patient is awake and stable, oral glucocorticoids of the usual dose will be re-commenced.

Methotrexate

A few lupus patients are on methotrexate (MTX) to control lupus arthritis. While traditionally MTX would be held off several weeks before surgery, there is indeed no evidence suggesting that stopping MTX is beneficial unless patients have clinically overt postoperative wound infection^[41]. While wound healing might be affected by MTX, the risk of arthritis flare which may delay postoperative rehabilitation progress outweighs the benefit of continuation of the medication.

Aspirin and warfarin

Aspirin is mainly used in patients with ischaemic heart disease and history of cerebrovascular disease. However, aspirin inhibits cyclooxygenase-1 (COX-1) and impairs platelet aggregation, rendering an excessive risk of peri-operative bleeding. If there is no major contraindication, aspirin can be stopped for 5 to 7 d prior to surgery, and

should be restarted 3 to 4 d postoperatively. For patients who are on warfarin due to conditions such as anti-phospholipid antibody syndrome, the medication should be held off at least 5 d prior to surgery, and replaced by low molecular weight heparin, which should be held off in the morning of surgical procedure^[42]. Anticoagulation should be re-commenced as soon as patients are haemodynamically stable with minimal bleeding risk.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in patients with SLE who present with joint pain, muscle aches and pleuritis. NSAIDs also inhibit COX-1 and they have been shown to be associated with a higher risk of gastrointestinal bleeding when given peri-operatively. Thus, it is encouraged to withhold NSAIDs preoperatively for a period equivalent to five half-lives of the drugs in order to restore normal platelet function while they can be re-started 2-3 d postoperatively. COX-2 NSAIDs do not affect platelet function and hence they are safe to be given peri-operatively. However, an important point of note is, COX-2 may be associated with cardiovascular disease and shall be discouraged in lupus patients who have high cardiovascular risk such as hypertension, diabetes and hyperlipidaemia, and in those patients who are thrombophilic, or those who have a history of vascular thrombosis^[43].

CONCLUSION

The link between SLE and orthopedic surgery is increas-

ingly recognized. Based on the literature, the link is largely facilitated by the use of glucocorticoids and immunosuppressants, infection, bleeding and hypercoagulability states, leading to a number of conditions such as AVN, tendon rupture, vascular thrombosis and postoperative bleeding. Heightened awareness, meticulous pre-operative assessment and judicious monitoring peri-operatively and post-operatively will likely increase the successful outcome of surgery and reduce the post-operative risk in patients with SLE.

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