

WJO 5th Anniversary Special Issues (10): Rheumatoid arthritis

Perioperative management of the patient with rheumatoid arthritis

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Received: December 2, 2013 Revised: March 20, 2014

Accepted: May 8, 2014

Published online: July 18, 2014

Abstract

A multidisciplinary approach is required to care for patients with rheumatoid arthritis (RA) in the perioperative period. In preparation for surgery, patients must have a cardiovascular risk assessment performed due to the high risk of heart disease in patients with RA. Treatment of RA is with immunomodulatory medications, which present unique challenges for the perioperative period. Currently, there is no consensus on how to manage disease modifying antirheumatic drug (DMARD) therapy in the perioperative setting. Much of the data to guide therapy is based on retrospective cohort data. Choices regarding DMARDs require an individualized approach with collaboration between surgeons and rheumatologists. Consensus regarding biologic therapy is to hold the therapy in the perioperative period with the length of time dictated by the half-life of the medication. Special attention is required at the time of surgery for potential need for stress dose steroids. Further, there must be close communication with anesthesiologists in terms of airway management particularly in light of the risk for cervical spine disease. There are no consensus guidelines regarding the requirement for cervical spine radiographs prior to surgery. However, history and exam alone cannot be relied upon to

identify cervical spine disease. Patients with RA who undergo joint replacement arthroplasty are at higher risk for infection and dislocation compared to patients with osteoarthritis, necessitating particular vigilance in postoperative follow up. This review summarizes available evidence regarding perioperative management of patients with RA.

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Key words: Rheumatoid arthritis; Perioperative management; Disease modifying antirheumatic drugs; Tumor necrosis factor inhibitors; Postsurgical complications

Core tip: Patients with rheumatoid arthritis (RA) require specialized care in the perioperative setting. Special attention must be given to management of immunomodulatory therapies, temporarily suspending their administration in the perioperative period. Patients on corticosteroids may require stress doses. Anesthesiologists should be aware of the possibility of cervical spine disease and appropriate measures, including obtaining cervical spine radiographs preoperatively. Patient with RA are at heightened infection risk because of their disease and its treatment, requiring particular vigilance in the postoperative period.

Krause ML, Matteson EL. Perioperative management of the patient with rheumatoid arthritis. *World J Orthop* 2014; 5(3): 283-291 Available from: URL: <http://www.wjgnet.com/2218-5836/full/v5/i3/283.htm> DOI: <http://dx.doi.org/10.5312/wjo.v5.i3.283>

INTRODUCTION

Unique factors impact the perioperative care of patients with rheumatoid arthritis (RA). Not only does a patient with RA require routine perioperative management in the

setting of elective surgery, there are also disease specific management issues such as immunosuppressants and care of the cervical spine.

PREOPERATIVE EVALUATION

General preoperative evaluation

RA, both the disease itself as well as the medications used in therapy, can impact multiple organ systems beyond the joints. Prior to elective surgery, patients must be carefully evaluated for organ involvement that may impact their fitness for surgery including cardiovascular, pulmonary, hepatic, and hematologic.

Cardiovascular risk evaluation

Prior to elective surgery, the risk of perioperative cardiovascular events must be assessed. Overall, individuals with rheumatoid arthritis have a higher risk of myocardial infarction which is similar to individuals with diabetes mellitus or a person 10 years older than the age of the patient^[1]. There is an increased risk of cardiovascular related death for patients with RA as compared to the general population^[2]. Traditional risk factors do not completely explain the risk for cardiovascular disease in patients with RA^[3]. To complicate evaluation further, patients with RA often present with fewer symptoms of angina and have higher rates of unrecognized disease^[4]. While RA itself has not been demonstrated to be an independent risk factor for perioperative death or cardiovascular events, cardiovascular risk must be carefully evaluated^[5].

As part of the American College of Cardiology/American Heart Association (ACC/AHA) perioperative guidelines, in the setting of emergent surgery, no additional cardiac evaluation is recommended. However, in the elective setting, first, active cardiac conditions must be identified which would require further cardiovascular evaluation prior to surgery including unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease.

If no active cardiac conditions are present, then the next step is to determine the risk of the procedure. Low risk procedures do not require further evaluation. Most orthopedic surgeries are considered moderate risk. In the setting of moderate risk procedures, identifying the clinical risk factors stratifies the perioperative risk and, therefore, the recommendations for further perioperative evaluation. If a patient is able to complete 4 metabolic equivalents (METs) then the perioperative risk is low enough to not require further evaluation^[6]. Four METs could be equated to the ability to walk up a flight of stairs^[6,7]. Unfortunately, patients with RA are often unable to be readily assessed for their functional capacity as a consequence of pain or disability related to arthritis^[8].

In those with moderate risk procedures and inability or unknown ability to complete 4 METs, then further cardiovascular risk stratification is needed. Different risk calculators have been generated to predict perioperative cardiovascular risk. The Revised Cardiac Risk Index

(RCRI), as incorporated into the ACC/AHA algorithm, includes ischemic heart disease, compensated or prior heart failure, use of insulin, renal insufficiency (creatinine > 2.0 mg/dL), and cerebrovascular disease as important comorbidities^[9]. A more recent cardiac risk calculator has been demonstrated to perform better than the RCRI based on the type of surgery, functional status, abnormal creatinine, American Society of Anesthesiologists class, and age^[10]. If risk is determined to be low, patients can proceed to surgery. If not, further consultations will be required^[6].

Evaluation for cervical spine disease

RA can involve the cervical spine with important implications for perioperative management, particularly positioning for anesthesia. The prevalence of cervical instability based on radiographs differs among cohorts. The rates of cervical instability in patients undergoing elective joint replacement can be as high as 61%^[11]. Anterior atlantoaxial subluxation has been estimated to range from 18%-49% with the majority of cohorts demonstrating approximately 20%^[11-15]. Atlantoaxial impaction ranges from 12%-26%^[11,13,14]. Subaxial subluxation has varying estimates of 9.0%-43.6%^[11-15]. Evaluating the posterior atlanto-odontoid interval can help assess the risk of paralysis in patients with RA. A cut-off of ≤ 14 mm is associated with increased risk of paralysis^[16].

Older age, longer duration of RA, erosions, increased disease activity, and increased disability are associated with higher rates of subluxation^[14]. Despite the advances in RA therapy, between 1983 and 2001 there were no changes in the number of hospitalizations for cervical spine disease related to RA^[17]. Symptoms alone cannot be relied upon to signal the presence of relevant cervical spine disease, as in one cohort only 50% of those with radiographic abnormalities had evidence based on history or physical evaluation such as neck pain, neck stiffness, or radicular symptoms^[11]. Even radicular pain occurred at similar rates between patients with or without subluxation^[14].

In terms of the choice of imaging modality, the majority of studies are based on conventional radiography of the cervical spine. In one study evaluating computed tomography (CT) and plain radiographs, in 1 out of 12 patients, the CT demonstrated information not identified by plain radiograph. In that case, the plain radiographs identified posterior subluxation, but spinal cord impingement was only identified on CT^[18]. Magnetic resonance imaging (MRI) findings including atlantoaxial spinal canal stenosis, atlantoaxial cervical cord compression, and subaxial myelopathy are associated with neurologic dysfunction^[19]. However, MRI underestimates the degree of anterior atlantoaxial subluxation^[20].

There are currently no guidelines regarding radiographic imaging in patients pursuing surgery. In routine clinical practice, there is variability regarding if and what imaging studies should be performed. In a retrospective review, 21% of patients undergoing their first surgery had

no cervical spine plain radiographs performed prior to surgery. Of the patients who did have plain radiographs performed, 36% were inadequate as defined by images of a lateral view of the neck in neutral position and frontal view of entire cervical spine only. Plain radiographs were felt to be complete if there were lateral views of neck in flexion and extension plus frontal view of entire cervical spine plus frontal open-mouth odontoid view. Complete views were only performed in 5% of patients. Adequate views as defined by lateral views of neck in flexion and extension plus frontal view of entire cervical spine were obtained in 59%^[12]. In a more recent retrospective evaluation utilizing the same definitions of adequacy of plain radiographs, half of patients had no cervical spine plain radiographs performed within 2 years while 4% had complete plain radiographs, in contrast to 18% with inadequate studies^[21].

In an attempt to optimize cost effective care, radiology imaging is most important if it impacts management. In an older retrospective cohort, there was a difference in the type of anesthesia in those known to have cervical instability in contrast to those without. In patients with known cervical instability, regional blocks and general anesthesia with flexible fiberoptic bronchoscope under local anesthesia were more commonly used than general anesthesia with spontaneous respiration with laryngeal mask airway or facemask or direct laryngoscopy^[12]. In a more recent evaluation, neither completion of cervical spine plain radiographs nor radiographic abnormalities were associated with the airway management techniques^[21].

While there are no clinical guidelines regarding preoperative imaging of the cervical spine in patients with RA, clinicians must be aware of the risk of cervical instability which may be asymptomatic. If performed, radiology imaging should include at least flexion-extension views of the cervical spine. Close communication between surgeons, anesthesiologists, and rheumatologists is critical to provide the best care for these patients.

Medication management

Patients with RA suffer higher rates of infection at baseline compared to other patients without RA^[22]. This underscores the added importance of optimizing the use of immunosuppressants in the perioperative period. The risk of infection/delayed wound healing must be balanced with the risk of flare which if occurs may require an escalation of immunosuppressants such as corticosteroids.

Traditional, nonbiologic disease modifying antirheumatic drugs

Methotrexate: Methotrexate is widely considered the cornerstone of RA management^[23,24]. The majority of data regarding the perioperative safety of methotrexate are from retrospective cohort studies. Five retrospective cohort studies did not demonstrate any difference in perioperative infection or wound complications between those who continued or discontinued methotrexate in

the perioperative period^[25-29]. In a retrospective evaluation of total joint replacements, 60 patients who had received methotrexate within 4 wk of surgery compared to 61 not receiving methotrexate, there was no difference in postoperative complications including infection or wound healing effects. The group who had received methotrexate within 4 wk of surgery was further divided into those who continued it throughout the perioperative time period and those who stopped; these 2 groups had no difference in postoperative complications. Of note, these patients were on low dose methotrexate, mean weekly dose 8 mg with a range of 5-12.5 mg. Further, it is unclear if the disease severity was similar among the 2 groups; they were similar in terms of duration of disease and concurrent prednisone dose^[25].

Retrospective review of hand surgery in patients who continued on their routine treatment for RA including methotrexate, with median weekly dose of 10 mg, did not demonstrate an increased risk of infection^[26]. Another retrospective review demonstrated no increased risk of infection in 66 patients who received methotrexate. The mean dose or details regarding discontinuation or continuation are not available^[27]. In a retrospective chart review evaluating 42 patients with RA who underwent reconstructive surgery of the hand and wrist, 15 were on methotrexate at the time of surgery with mean dose 10.7 mg per week. None of these patients suffered from infection or delay in wound healing^[28]. A further retrospective review of 122 patients undergoing 201 elective surgeries receiving low dose methotrexate, 2-8 mg/wk, did not demonstrate any difference in postoperative infection or rates of flare between those who continued or discontinued methotrexate perioperatively^[29].

A prospective evaluation of 201 patients (94% of whom had RA) were enrolled to an open label study in which they continued their stable therapy of methotrexate, leflunomide, or anti-tumor necrosis factor- α (TNF- α) therapy during the perioperative time period. There was no increased risk of perioperative infection in those who continued on methotrexate^[30]. A case-control study evaluating patients who underwent foot or ankle surgery did not demonstrate an association with methotrexate, with unclear dosing, and infection or wound healing complications^[31].

Confounders that may have led providers to recommend holding versus continuing methotrexate can complicate interpretation of retrospective cohort and case-control studies. There are differing results from randomized trials regarding methotrexate. One randomized trial demonstrated no difference between those who continued or discontinued methotrexate in the perioperative period. In this randomized unblinded study regarding continuation versus discontinuation of methotrexate with a total of 89 cases, there were no postoperative infections in either group. There was no difference in prolonged wound healing, 6/50 (12%) in those who discontinued and 4/39 (10%) in those who did not discontinue methotrexate^[32].

In contrast, in one randomized trial evaluating methotrexate continuation versus discontinuation, the surgical complications and infection frequency occurred less often in those who remained on methotrexate than those who discontinued. Further, there was an increased risk of rheumatoid arthritis flare, occurring in 8% of patients, in those who discontinued its use. However, it should be noted that the patients were doses of methotrexate (7.5-10 mg weekly) than usually prescribed for RA management^[33].

One study demonstrated an increased risk of continuation of methotrexate in the perioperative period. This was a small prospective trial of 32 patients, in which patients were assigned either to continue methotrexate or hold for a total of 2 wk based on the preference of the patient's rheumatologist/orthopedic surgeon and therefore not randomized. The mean weekly methotrexate dose was 12.5-13.1 mg. No infections occurred in those who held the methotrexate while 4 infections occurred in those who continued methotrexate ($P = 0.03$). No patients suffered a flare of RA in either group^[34].

Due to its frequent use, management of methotrexate in the perioperative period will be an issue commonly faced by clinicians. The majority of studies demonstrate safety of methotrexate in the perioperative period; however much of this data comes from retrospective cohort studies.

Leflunomide: Conflicting data are available regarding perioperative use of leflunomide. In one study, patients with RA treated with leflunomide were randomized to continue versus hold for 2 wk before and after hip, knee, or elbow arthroplasty. There was no difference in the number of infections between the groups. All patients who developed infection were also taking prednisone in addition to their leflunomide. However, corticosteroids were also not found to be associated with higher risk of infection^[35]. In contrast, in another prospective study, patients with predominantly RA were prospectively followed as they continued leflunomide therapy during the perioperative time period. Leflunomide was associated with a higher risk of postoperative wound complication with an odds ratio of 3.48^[30].

Cholestyramine can be utilized to facilitate leflunomide drug elimination if required in the setting of leflunomide associated adverse reactions^[36]. However, advanced planning is required as protocols with cholestyramine require 11 d of therapy^[37].

Hydroxychloroquine: Limited data is available regarding hydroxychloroquine and risk of perioperative infection. In one case-control study evaluating infectious complications, there was no difference in the use of hydroxychloroquine^[31]. Further, an additional retrospective study did not demonstrate any association with risk of infection^[27]. Expert opinion frequently recommends continuation of hydroxychloroquine in the perioperative period^[8,38].

Other nonbiologic traditional DMARDs: There are

only limited data regarding other DMARDs. In one retrospective study, azathioprine, while associated with infection in univariate analysis did not demonstrate the association with multivariate analysis^[27]. Frequently, azathioprine is recommended to be continued in the perioperative time period with some physicians recommending holding the day of surgery^[8,38]. Similarly, sulfasalazine is typically recommended to be continued perioperatively with some physicians holding it the day of surgery. In one retrospective study, sulfasalazine was associated with a lower risk of perioperative infection^[39]. In all cases, renal function, which affects the elimination of many DMARDs, must be closely monitored^[8,38].

The American College of Rheumatology does not provide recommendations on the perioperative management of nonbiologic DMARDs due to conflicting data^[40]. Medication management requires a risk-benefit discussion between patients, surgeons, and rheumatologists.

Biologics

TNF- α Inhibitors: Multiple studies have evaluated the perioperative risk of TNF- α inhibitors as compared to traditional DMARDs. A single prospective study demonstrated that TNF- α inhibitors compared to other DMARDs were associated with reduced complications of infection and wound healing with TNF- α inhibitor use^[41]. In a retrospective cohort study, there was no difference in adverse events for surgical wounds, time for wound healing, or duration of fever when comparing TNF- α inhibitors and DMARDs. TNF inhibitors were held at the time of surgery^[42]. In contrast, in a retrospective evaluation comparing patients who used traditional DMARDs versus TNF- α inhibitors, there was an increased risk of surgical site infection with TNF- α inhibitors, OR 21.8. All of these patients had stopped TNF- α 2-4 wk before surgery. Further, there was a higher rate of deep venous thrombosis^[43].

A retrospective parallel cohort demonstrated no increased risk of infection with continuation of TNF- α inhibitor therapy perioperatively (8.7%) as compared to cessation (5.8%). The highest risk for perioperative infection in this study was previous surgical site infection^[39]. In a cohort of patients treated with TNF- α inhibitors, there was no difference in rates of complications if the therapy was stopped greater than 5 half-lives prior to surgery versus not stopped. Also, there was no difference if it was stopped 2 half-lives before surgery as compared to less than 2 half-lives or not discontinued^[44].

In a retrospective cohort of 16 patients all of whom were treated with TNF- α inhibitor therapy, there were no perioperative infections either in the group who continued the therapy or those who discontinued. There was a single episode of RA disease flare that occurred in a patient who stopped etanercept at the time of triple arthrodesis of the ankle^[45]. In a retrospective evaluation of 30 patients who underwent 50 surgical procedures, there were no episodes of major infections in either patients who continued or discontinued the TNF- α therapy.

There were 3 cases which experienced delay in wound healing by 1-2 wk. It is not specified if these were in individuals who continued or discontinued their therapy. There were higher rates of flare in those who discontinued therapy at the time of surgery rather than those that continued ($P = 0.02$) with overall rate of 12% flares in the cohort^[46].

A retrospective review of a cohort of patients treated with infliximab with mean of 4 wk between infliximab infusion and surgery revealed low rates of infection (3.8%, 2 cases). There was no association with the time duration of latest infliximab infusion and infection^[47].

A separate retrospective analysis of 91 patients who underwent orthopedic surgery revealed that TNF- α inhibitor therapy was associated with serious postoperative infection (septic arthritis, osteomyelitis, or deep wound infection) in multivariate analysis, OR 5.3^[48]. In a retrospective review of patients with RA who underwent total knee arthroplasty, a total of 268 replacements in 248 patients, the cohort included patients who were treated with TNF- α inhibitor therapy versus those who were not. Of those treated with TNF- α inhibitors, 87% were recommended to discontinue therapy in the perioperative period with the remaining 13% having no documentation regarding the recommendation. There were 10 episodes (4.3%) of infection with a single deep joint infection. There was no difference in the rates of infection^[49].

A further retrospective evaluation of total hip and total knee arthroplasties reported that 5.7% of cases had superficial surgical site infections while 0.7% experienced infections requiring removal of the artificial joint prosthesis. In multivariate logistic regression, the use of biologic DMARDs (OR, 5.69) was associated with infection. When evaluating individual TNF- α inhibitors, infliximab (OR, 9.80) and etanercept (OR, 9.16) when adjusted for disease duration were associated with increased risk of infection. TNF- α inhibitors were stopped prior to surgery^[50].

Cohorts of RA patients treated with and without biologics were compared in a review of patients in whom infliximab, etanercept, adalimumab, and tocilizumab had been stopped between 2-4 wk before surgery. There was no difference in complications of wound healing. The rates of infection were very low with 4 infections out of 554 surgeries and no association was found with biologic therapy^[51].

Clinical guidelines vary in regard to their recommendations of TNF- α inhibitor management in the perioperative period^[52,53]. Some guidelines do not provide specific details but rather recommend weighing the risks of infection/wound healing with risk of flare with discontinuation^[54]. American College of Rheumatology guidelines recommend holding biologic therapy for at least 1 wk before and after surgery with further adjustment to that time frame depending on the pharmacokinetics of the individual agent^[40].

Other biologic therapy: Less information is available re-

garding other biologic therapy in the perioperative setting. Tocilizumab was evaluated in the perioperative setting of 161 surgeries. Tocilizumab was held for mean of 23.5 d with range of 1-71. Three (1.9%) surgical site infections occurred. Wound healing delays occurred in 20 (12.4%). There were high rates of concurrent corticosteroid use (74.5%). Multiple logistic regression demonstrated corticosteroid use, foot surgery, and spinal surgery as risks for delayed wound healing^[55]. In a smaller cohort of 22 patients treated with tocilizumab, no postoperative infections occurred. Surgery occurred in between infusions of tocilizumab with a mean of 16.1 d from the previous infusion. No patient required a delay in the next infusion^[56].

Seven patients who underwent 8 surgeries were being treated with abatacept. The mean discontinuation time prior to surgery was 15.9 d with a total time of discontinuation of 33.1 d. None of these patients experienced surgical site infections or delays in wound healing^[57].

Finally, a review of 133 patient undergoing 140 surgeries (including 94 orthopedic surgeries) on average 6.4 mo following a last rituximab infusion reported a postoperative infection rate of 6.7%, including one death due to septic shock^[58]. With little data available to guide decisions, an individualized plan is required for management of non-TNF biologic therapy.

AT TIME OF SURGERY

Stress dose corticosteroids

Corticosteroid use is a major risk factor for infection in patients with RA^[59]. This risk is dose related emphasizing the importance of balancing risks of adrenal insufficiency with infection^[60]. Not all patients receiving corticosteroids require stress dosing to prevent adrenal insufficiency. There is not a single dose cut-off that can be utilized to determine which patients may be at risk, as even low dose corticosteroids can lead to disruption of the hypothalamic-pituitary axis^[61]. An ACTH stimulation test when performed with a normal result is predictive of an appropriate response during surgery^[62]. Using 250 μ g of cosyntropin, a cortisol value at time point zero, 30 or 60 min following injection greater than or equal to 20 μ g indicates a normal response^[8].

In patients requiring stress dose corticosteroids in the perioperative timeframe, the dose required depends on the type of surgery. Most orthopedic surgeries such as joint replacement are representative of a moderate surgical stress. Other examples of moderate surgical stress beyond arthroplasties include hemicolectomy. A severe surgical stress would include major cardiothoracic surgery. Examples of minor surgical stress include dental procedures, colonoscopy, and inguinal hernia repair. On the day of the procedure, hydrocortisone 50-75 mg or methylprednisolone 10-15 mg intravenously can be used with the dose tapered to the routine corticosteroid dose in 1-2 d^[63].

Airway management

Rheumatoid arthritis can result in wide ranging involve-

ment of the larynx including cricoarytenoid arthritis and rheumatoid nodules^[64,65]. The use of laryngeal mask airway can exacerbate laryngeal rheumatoid arthritis, which may be undiagnosed prior to surgery^[66]. This possibility must be included in the differential diagnosis in the setting of acute upper airway obstruction particularly following extubation^[67]. An emergent cricothyroidotomy is sometimes required for treatment^[68].

AFTER SURGERY

Postoperative complications

Patient with RA must be followed closely in the postoperative time period as well. Patients with RA suffer higher rates of prosthetic joint infections compared to matched controls with osteoarthritis (hazard ratio of 4). The risk is increased in the setting of revision arthroplasty and previous prosthetic infection^[69]. Data from a large registry in Norway revealed the risk of revision of arthroplasty of the hip or knee for infection to be higher in patients with RA as compared to osteoarthritis^[70].

Staphylococcus was the most likely infectious cause of total joint arthroplasty infection in the setting of TNF- α inhibitor therapy according to a case control study. In multivariate analysis, primary arthroplasty or revision within the previous year (odds ratio, OR, 88.3) and prednisone use (OR, 5.0 per 5 mg/d) were identified as risk factors for infection^[71]. In 200 episodes of prosthetic joint infection, the rate of 5 year survival free of treatment failure was 56%. The rates of survival free of treatment failure were highest with 2-stage exchange (79%) followed by resection arthroplasty (61%) with the lowest rates occurring with debridement and retention of components (32%)^[72].

A meta-analysis demonstrated the increased risk of total hip arthroplasty dislocation in patients with RA as compared to osteoarthritis, OR 2.74. In terms of overall rates of revision for hip arthroplasty, there was a higher rate of revision within 5 years of patients with RA as compared to osteoarthritis, OR 1.33. There was no difference in infection rates between 6-10 years following revision arthroplasty. After 10 years, there were lower rates of revision in patients with RA, OR 0.28. In terms of revision for knee arthroplasty, there was a higher rate in the first years for patients with RA with OR 1.24. There was no difference detected after 5 years. There was no difference in 90 d mortality or venous thromboembolism rates between patients with RA *vs* osteoarthritis^[73].

Patients with RA require special attention because of their disease, treatments and comorbidities in the perioperative period. Despite the decreased rates of orthopedic surgeries for RA patients, surgery continues to be a modality that is required for some patients^[74]. Successful perioperative management requires a multidisciplinary approach including orthopedic surgeons, rheumatologists, anesthesiologists and radiologists.

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