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Bone Bulletin

Volume 2 | Issue 1 Article 7

2024

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Bone Bulletin | *Vol. 2, No. 1, 2024*

Article – Clinical Medicine

Shoulder Arthroplasty in Patients with Inflammatory Arthritis: Preoperative and Perioperative Management of Disease Modifying Anti-Rheumatic Drug Therapy

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Introduction

Inflammatory arthritis is a debilitating systemic autoimmune and inflammatory disease that leads to joint damage, resulting in significant pain and disability. Rheumatoid arthritis (RA) is the most common inflammatory arthritis typically associated with advanced arthritic changes of the glenohumeral joint as well as with rotator cuff tears.[20] Since the introduction of disease modifying anti-rheumatic drug (DMARD) therapy, patients diagnosed with inflammatory rheumatic diseases have observed improvements in pain management and functional outcomes, alongside a reduction in the occurrence of upper limb arthroplasties.[16] Nonetheless, total joint arthroplasty still remains common in the treatment of RA.[8,14]

One recognized challenge in shoulder arthroplasty in the context of inflammatory arthritis is the perioperative management of anti-inflammatory medications. Approximately 75-84% of patients undergoing arthroplasty take traditional DMARDs or biologics.[14] Management of these medications currently varies across rheumatology organizations. For instance, the American College of Rheumatology recommends withholding tumor necrosis factor (TNF)-α inhibitors for more than a week prior to surgery, British Society recommends withholding for 3-5 times the half-life of the drug, and Canadian Rheumatology Association propose withholding for 2 half-lives of the drug.[14,22,31] Understanding the appropriate timing for discontinuing or continuing these medications is a critical element of perioperative management in shoulder arthroplasty, as it involves balancing the potential risks of post-operative disease flares with concerns for poor wound healing and infection.

Wound Healing

Impaired wound healing in patients undergoing shoulder arthroplasty surgery with concomitant use of anti-inflammatory medications is a concern due to the potential interference of these medications with the normal healing process. Clinical consequences of these immunosuppressive effects include dehiscence of incision site, wound infection and delayed open-wound healing. Corticosteroids inhibits the inflammatory phase of wound healing through inhibited prostaglandin synthesis as well as reduced neutrophil, macrophage, and lymphocyte activities. Granulation tissue formation is also decreased due to decreased fibroblast proliferation and decreased epithelial regeneration. Steroid-induced vasoconstriction due to prostaglandin E2 inhibition decreases oxygen and nutrient supply to injured tissues, further reducing the rate of wound healing. RA patients with chronic use of corticosteroids (>three years) demonstrated significantly increased wound complications compared to patients with RA without steroid use when undergoing orthopedic surgery.[12] Furthermore, patients with RA may be already predisposed to wound complications due to reduced skin thickness, independent of corticosteroid use.[5]

Immunosuppressants, in general, have a lower impact on wound healing. Methotrexate use in elective orthopedic surgery was not associated with increased risk of wound complications, although one study by Bridges et al. showed that patients who continued methotrexate until <4 weeks before surgery showed significantly higher rates of wound dehiscence.4,5 RA patients receiving biological DMARDs such as TNF-α inhibitors and undergoing orthopedic surgery demonstrated no significant difference in healing complications.[2,5]

Infections

Shoulder periprosthetic infection (PJI) is a serious complication of shoulder arthroplasty with negative health implications. Patients with underlying RA are at 1.8- to 4-fold higher risk of PJI compared to those undergoing arthroplasty for other etiologies such as osteoarthritis, attributed to their immunosuppressive medications.[30] High doses of steroids and TNF-α inhibitor therapy within one year of surgery has been shown to increase the risk of subsequent infection in patients undergoing orthopedic procedures.[34] Corticosteroid injections within four weeks of shoulder arthroplasty was also shown to be linked to higher rates of PJI.[1] Methotrexate therapy's effect on infection risk has been mixed. A randomized controlled trial failed to show any differences in infection rates among patients who continued vs discontinued the use of methotrexate.[19] However, another study showed an increase rate in infection in patients who continued the drug during the perioperative period.[29]

Given the high risk of PJI in patients who have RA and are on anti-inflammatory medications, the use of

antibiotic-impregnated cement during total joint arthroplasty is recommended. However, there are no current studies on the PJI rates in RA patients who had antibiotic-impregnated cement and those who did not.[18,34]

Impaired Bone Healing and Implant Survival

Immunosuppressive medications can adversely affect bone healing, thereby increasing the risk of implant failure in orthopedic surgery. Bone healing is characterized by the inflammatory, repair and remodeling phase.[26] Robust bone formation is dependent on the initial local and systemic inflammatory responses as well as the inter-cellular communication between immune cells and mesenchymal stromal cells. Pro-inflammatory cytokines such as TNF-α and prostaglandins play a key role in bone metabolism.[26] Chronic use of anti-inflammatory medications and immunosuppressive medications can suppress these response and delay bone healing. In vitro study of methotrexate's effect on the cells of osteoblastic lineage showed that the medication inhibited the proliferation, but not differentiation of osteogenic cells.[28] Infliximab and leflunomide has also been shown to have a significant inhibitory effect on osteogenic cell proliferation.[25]

Osseointegration refers to a direct bone-to-metal interface without interposition of non-bone tissue.[27] An implant is considered osseointegrated when there is no progressive relative movement between the implant and the bone with which it has direct contact. Therefore, robust osseointegration is an important predictor of long-term implant survival. RA patients with anti-inflammatory medication use demonstrate poorer intrinsic healing potential, which contributes to excessive implant micromotion and instability. Mechanical stress and implant micromotion was associated with significantly higher likelihood of osseointegration and eventual implant failure.[27]

Rotator Cuff Failure

A critical perioperative consideration for shoulder arthroplasty in the setting of inflammatory arthritis is rotator cuff function. Cuff tears in rheumatoid patients are extremely common (20%-100%), and lead to poorer functional outcomes, superior humeral migration and earlier component failures.[11,21,23] Khan et al. showed that rotator cuff failure was more prominent in long-term follow up, with 9 out of 12 RA patients having clinical and radiological evidence of failure of the cuff at minimum 10 year follow up.[21]

Therefore, one important consideration in surgical treatment of RA patients is the failure of subscapularis healing. Access to the glenohumeral joint is performed through a deltopectoral approach and often requires the takedown of the subscapularis tendon. Lesser tuberosity osteotomy and subscapularis peel are two techniques commonly used today, and both options portend good results with proper repair of the muscle. However, failure of the tendon repair can readily occur especially in RA patients, leading to shoulder pain, internal rotation weakness, increased passive external rotation, and anterior instability.[3] Biomechanical studies reported a 24.8% increase in maximum glenohumeral contact force with a subscapularis deficiency, while infraspinatus and supraspinatus deficiency resulted in a 11.3% decrease in contact force.[6] The significant increase in contact force in the context of a deficient subscapularis suggests a worse effect on glenoid implant fixation.

Perioperative Management of Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy and Biologics

Utilization of immunosuppressive medications is high in RA patients.[14] 75–84% of patients undergoing arthroplasty are on DMARDs or biologics, while 80% are on corticosteroids.[14,17,32] These medications pose a challenge during the perioperative period and clear guidelines for perioperative medication management are necessary.

DMARDs and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)

Methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or apremilast has been recommended to continue throughout the perioperative period. Methotrexate is the most-studied DMARD in the treatment of RA. In a prospective randomized study of 388 RA patients undergoing elective orthopedic surgery, patients were allocated to either continuing methotrexate (Group A) or discontinuing the drug two weeks prior to and after surgery (Group B). A third group had no exposure to methotrexate (Group C). Infection rates and flares at six weeks post-operation showed no difference across the groups, demonstrating that continuation of methotrexate does not increase the risk of either infections or of surgical complications in RA patients.[19] There is limited evidence on the safety profile of other csDMARDs, such as sulfasalazine, hydroxychloroquine or leflunomide. Previous observational studies and systematic literature review found no relationship between the included drugs and the risk of postoperative infections.15,16,18 Therefore, continuation of these agents is recommended. However, patients with a history of severe or recurrent PJI may elect to withhold medications prior to surgery.

Immunosuppressants such as mycophenolate mofetil, azathioprine, cyclosporine and tacrolimus are more

commonly used for autoimmune diseases other than RA, such as systemic lupus erythematosus. Patients undergoing arthroplasty and concomitantly treated with one or more of these therapies showed increased risk of pneumonia, sepsis and PJI.[16] However, these postoperative adverse events have not been specifically linked to medication use. Given the uncertainty, these medications are recommended to be continued throughout the perioperative period in patients with severe SLE and undergoing arthroplasty. In patients with less severe SLE, current recommendations suggest withholding 1 week prior to surgery.

Biologics

Increased risk of infection in patients taking TNF inhibitors (TNFi) has been well-recognized.[33] Multiple series demonstrate increased surgical site infections and PJI with the use of TNFi, with the highest risk occurring within the first 6 months of therapy.[10,17] However, the evidence of association between perioperative timing of biologics and infection is largely inconclusive.[13,18] George et al. showed that there was no increase in infection within 30 days of surgery in patients who received infliximab <4 weeks prior to surgery compared to 8-12 weeks. Similarly, there was no increase in the rate of PJI in patients receiving infliximab infusions <4 weeks versus 8–12 weeks.[13] Additionally, a meta-analysis showed that postoperative infection risk was not decreased in those patients stopping TNFi prior to orthopaedic surgery.[24] Despite the lack of consensus on whether withholding TNFi before surgery improves postoperative outcomes, current recommendations support stopping all biologics for a short duration with surgery planned for the end of the dosing cycle. The decision to refrain from administering the biologics was grounded on the presumption that the levels of active drug would be diminished by the end of the dosing interval. However, surgery within the dosing cycle may be elected if symptoms are severe and the disease has been challenging to control. Medications can be restarted approximately two weeks after surgery after wounds have healed.

Corticosteroids

Corticosteroid therapy is widely used in the setting of RA. High levels and chronic corticosteroid use has been associated with greater risk of infection in RA patients undergoing arthroplasty.[14] Additionally, a study of 432 patients with RA undergoing elective THA and TKA demonstrated that patients with higher corticosteroid exposure were more likely to have hyperglycemia and other complications.[7] The study also showed that the risk of short-term complications is increased by 8.4% for every 10-mg increase in corticosteroid dose. Studies have also identified extended corticosteroid exposure as a significant risk factor for PJI and mortality.[9] Stopping long-term corticosteroid therapy abruptly during surgery carries the risk of adrenal insufficiency leading to severe hypotension and death. Therefore, administration of a supraphysiologic, or "stress doses" at the time of surgery in order to prevent adrenal insufficiency was previously considered. However, the evidence on the benefits of stress doses is limited. The current guidelines suggest that patients receiving long-term corticosteroid for their rheumatic conditions should continue preoperative daily dose of corticosteroid rather than administering stress doses on the day of the surgery.

These guidelines provide important information for clinicians and patients to better understand the risks and benefits regarding the management of perioperative antirheumatic medications. However, it is important to note that the level of evidence to support these recommendations are mostly low[18] and gaps exist in the current information base. Continued research is necessary to develop a more robust set of evidence to support these recommendations. Furthermore, the above recommendations are based on the guidelines set out by the American College of Rheumatology/American Association of Hip and Knee Surgeons (ACR/AAHKS). There are no guidelines currently available specific to shoulder arthroplasty, and most clinicians performing shoulder arthroplasty follow the ACR/AAHKS perioperative guidelines. Perioperative management of antirheumatic medications in the setting of shoulder arthroplasty may differ. Therefore, additional research on the management of these drugs specific to shoulder arthroplasty is necessary.

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