Perioperative and anesthetic management of patients with rheumatoid arthritis

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Our understanding and management of rheumatoid arthritis (RA) have greatly improved, but perioperative and anesthetic management remain challenging. RA is not limited to joints; systemic evaluation is thus required when planning perioperative management. Especially, careful airway evaluation is needed; management of airway-related arthritis is challenging. A multidisciplinary approach is essential to prevent complications without exacerbating RA disease activity. Guidelines published in 2017 are available for perioperative management of anti-rheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. However, the guidelines focus only on anti-rheumatic medications, and do not consider all aspects of perioperative management (including anesthesia). Here, we discuss the perioperative and anesthetic management of patients with RA.

Keywords: Arthritis, rheumatoid; Anesthesia; Operation; Surgery

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder that mainly affects the synovial joint [1,2]. However, the precise etiology remains unknown, although the inflammation is autoimmune in nature. RA is characterized by symmetrical erosive polyarthritis, most commonly of the joints of the hands and feet [3]. However, RA can affect internal organs, i.e., can be systemic. Patients with RA commonly require orthopedic surgery under anesthesia for RA management or surgery unrelated to RA [4]. This study reviews perioperative and anesthetic issues in RA patients.

CLINICAL FEATURES, DIAGNOSIS, AND MANAGEMENT OF RA

RA typically presents as persistent and painful joint swelling with morning stiffness. Usually, the small joints of the wrist and hand are involved, but the atlanto-axial joints and large joints (such as those of the hip and knee) may also be affected. Joint inflammation and destruction with muscle atrophy...
and weakness cause pain. Progressive joint synovial inflammation triggers cartilage degradation and bone erosion, and ultimately joint destruction with laxity/disintegration of the tendon and ligament [3]. For example, the hand joints exhibit swan neck and boutonniere deformities, which may require surgical correction [5]. The diagnosis of RA is partly clinical (joint involvement and long symptom duration) and partly based on laboratory findings. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA include the presence of autoantibodies (rheumatoid factor and anti-cyclic citrullinated peptide antibody) and an acute phase reactant (C-reactive protein), along with a high erythrocyte sedimentation rate [6,7]. The goal of management is clinical remission or maintenance of low-level disease activity via early aggressive use of conventional and targeted synthetic agents, and biological disease-modifying anti-rheumatic drugs (DMARDs) [8]. These improve symptoms, inhibit disease progression, maintain joint function and facilitate the performance of activities of daily living [9].

PRE- AND INTRA-OPERATIVE CONSIDERATIONS

Detailed RA history-taking, including RA disease severity and duration, systemic involvement, and medication status, is essential to avoid missing a subtle symptom or sign [10]. Careful physical examination, especially of the airway, is also essential when planning anesthesia. A low body mass index (“rheumatoid cachexia”) may indicate sustained, poorly controlled disease. As RA increases morbidity and mortality, mechanical ventilator support should be considered postoperatively [4]. Apart from joint disabilities, systemic complications and current medications must be reviewed prior to anesthesia. The goals of anesthetic management are establishment of a safe airway with preservation of cervical spine integrity (via careful positioning and manipulation); successful management of any systemic condition, and prevention of RA progression and disease-related-complications.

RA-related joint problems

The joint deformities caused by bone and cartilage destruction impact anesthetic management as follows. First, joint deformities affect patient positioning and hinder vascular assessment and evaluation of regional anesthesia. The need for appropriate positioning during surgery requires additional surgical support and time, which is associated with postoperative adverse effects. Finally, axial joint deformities render the cervical spine unstable, which makes intubation difficult. However, RA patients with axial joint disorders are often asymptomatic, so careful assessment thereof is essential prior to anesthesia.

Airway-related joint disorder

1) Atlanto-axial subluxation

The range of motion (flexion and extension) of the cervical spine should be assessed preoperatively. Attenuation of the transverse ligament and erosion of the odontoid process can cause atlanto-axial subluxation (AAS) and, in turn, atlanto-axial instability and spinal cord compression, with or without compression of the vertebral arteries [4]. During airway management, neurological complications (including quadriplegia and sudden death) can occur, but are fortunately rare. The anesthesiologist must be aware that the standard sniffing position for endotracheal intubation using a laryngoscope involves head hyperextension and neck flexion, and may thus exacerbate AAS and cause neurological injury [11]. The clinical symptoms of an AAS neurological disorder are difficult to distinguish from those of simple joint or muscle disorders and peripheral neuropathy. Moreover, the proportion of patients with such symptoms is low. Based on plain radiographs, the prevalence of AAS was estimated as 3% to 44% [12,13]. Preoperative plain radiography of the cervical spine has been recommended for all RA patients, as it can reveal cervical spine instability [14]. However, no evidence-based guidelines or consensus have emerged. If a plain radiograph reveals narrowing of the atlanto-axial joint space, airway management may be difficult [15]. Anesthetic management should be based on radiographic data; it is essential to prevent or minimize neurological and vascular complications. Magnetic resonance imaging (MRI) is better for assessing the cervical spine than radiography, although the data correlate weakly with clinical symptoms. If a neurological sign is present, cervical spine MRI is essential. The risk of AAS increases over time and is higher in seropositive patients and those with more severe RA. Involvement of the sub-axial cervical spine is less common than AAS, and limitation of cervical spine motion makes central venous access difficult.
2) Temporomandibular joint disorders
Temporomandibular joint disorders can be associated with difficulties in mouth-opening and mastication, but may also be asymptomatic. However, careful airway examination, including using the Mallampati test with the mouth open and mandible protruding, is essential to prevent airway accidents. If an RA patient exhibits cervical spine instability, or a limitation of neck motion or mouth-opening, airway management may be difficult; awake fiberoptic bronchoscopy-guided endotracheal intubation is recommended in such cases [16].

3) Cricoarytenitis
Cricoarytenitis is associated with hoarseness, stridor, and a foreign body sensation in the larynx; a laryngeal mass is also occasionally observed. When one of these symptoms or signs is observed, the larynx should be directly examined. Difficulty in airway management should be anticipated such that appropriate equipment is available. Endotracheal intubation should be avoided if possible; if not, the endotracheal tube should have the smallest possible diameter. Use of a face mask or supra-glottic airway device should be preferred. Awake fiberoptic bronchoscopy-guided endotracheal intubation is sometimes recommended for such patients, although surgical tracheostomy under local anesthesia is an alternative [17]. Close observation of airway obstruction caused by edema is required during recovery from extubation.

4) Other joint disorders with skin lesions
A joint deformity, or thin and fragile skin makes intravenous assessment difficult. A wrist joint deformity may render the radial artery inaccessible. Preoperatively, the range of motion of affected joints should be assessed to optimize patient positioning during and after surgery. Careful positioning during surgery is essential. All pressure points should be secured to avoid pressure sores. Chronic steroid use triggers osteoporosis; such patients must be manipulated gently. Eye care should also be considered; 15% of RA patients suffer from keratoconjunctivitis and are thus at risk of corneal ulceration, especially when prone [18].

Regional anesthesia obviates the need for airway management. However, joint deformities make it difficult to palpate anatomical landmarks. Central neuraxial block using non-steroidal anti-inflammatory drugs (NSAIDs) does not increase the risk of hematoma. All procedures must be aseptic; immunsuppressive agents increase the risk of infection.

RA-related systemic complications
RA-related systemic complications were summarized in Table 1. Although no preoperative evaluation guideline is available for RA patients, RA does not appear to increase the risk of perioperative mortality [19]. Careful preoperative evaluation of extraarticular complications is required when planning anesthesia. Arterial blood gas analysis, a pulmonary function test, and echocardiography may be required, depending on the systemic complications. As RA patients do not exhibit the classical symptoms and signs of cardiovascular disease, it is easy to miss the disease. RA patients are at increased risk of atherosclerosis (stroke and myocardial infarction) [20,21]. The presentation is usually insidious and triggers sudden cardiac death [22]. Heart failure is a major cause of death in the absence of a history of ischemic heart disease, in contrast to non-RA patients [23,24]. A higher body mass index is associated with a higher cardiovascular mortality rate in the general population. However, RA patients with a lower body mass index have a higher likelihood of cardiovascular mortality due to rheumatoid cachexia and sustained and poorly controlled chronic inflammation [25]. Cardiac arrhythmia is an important cause of sudden death in RA patients; it is associated with rheumatoid nodules, amyloidosis, and ischemic heart disease [22]. The chronic inflammation seen in RA is likely to affect the vessels, although this remains to be confirmed. Anemia is common in RA patients, and is attributable to chronic disease or medications such as glucocorticoids and NSAIDs. RA patients are more likely to require perioperative blood transfusions. The effects of RA on the pharmacokinetics and pharmacodynamics of the drugs used to induce anesthesia remain poorly understood. RA-associated systemic disorders (especially hepatic and renal disorders) and RA medications change drug pharmacokinetics and pharmacodynamics. Therefore, the drugs should be carefully titrated.

Medications for RA
To control or manage RA, various medications were used (Table 2). NSAIDs and glucocorticoids are commonly used to relieve pain and decrease joint inflammation. Janssens and Hartstein [16] stated that the adverse effects of opioids outweigh the benefits; opioids are nonetheless used for pain relief. Conventional NSAIDs and glucocorticoids increase the risk of gastrointestinal bleeding; prophylaxis for gastrointes-
Long-term glucocorticoid use is problematic because they increase the infection rate and wound-healing complications in a dose-dependent manner. Normally, the adrenal gland secretes about 8 to 10 mg of cortisol daily. Perioperative glucocorticoid coverage is required by patients on a prednisolone dose > 10 mg/day to control the surgical stress response [26]. Although the transient increase in cortisol secretion in response to stress varies among individuals, it is typically up to 50 mg/day for minor procedures and 75 to 150 mg/day for more complex ones; it rarely exceeds 200 mg/day (Table 3) [27]. The blood glucose level and blood pressure should be closely monitored. The use of nitrous oxide to induce anesthesia should be avoided in patients on methotrexate to treat folate depletion. Patients on glucocorticoids or DMARDs are susceptible to infection; strict application of an aseptic technique and appropriate antibiotic prophylaxis are required [28].

Conventional and biological DMARDs have been used to slow disease progression and prevent joint destruction and deformity. The 2017 guidelines of the American College of Rheumatology/American Association of Hip and Knee Surgeons suggest that conventional synthetic DMARDs (meth-

Table 1. Extraarticular and systemic aspects of rheumatoid arthritis that must be considered during perioperative and anesthetic management

| Organ                        | Extraarticular involvement                                                                 |
|------------------------------|------------------------------------------------------------------------------------------|
| Neurological system          | Central neuropathy<br>Peripheral neuropathy, carpal tunnel syndrome<br>Autonomic neuropathy |
| Ocular system                | Kerato-conjunctivitis                                                                     |
| Cardiovascular system        | Pericarditis, pericardial effusion, cardiac tamponade<br>Valvular heart disease (usually regurgitation)<br>Conduction abnormality<br>Granulomatous disease<br>Endocarditis or myocarditis<br>Coronary artery disease |
| Respiratory system           | Reduced chest wall compliance (costochondral disease)<br>Pleural effusion<br>Restrictive lung disease<br>Pulmonary nodule |
| Hematological system         | Anemia [chronic disease, iron deficiency (bleeding) and bone marrow suppression from medication]<br>Thrombocytopenia<br>Felty’s syndrome<br>Lymphoma |
| Hepatic system               | Hepatic fibrosis<br>Hepatomegaly with splenomegaly<br>Hypoalbuminemia                      |
| Renal system                 | Glomerulonephritis<br>Tubulointerstitial nephritis<br>Amyloidosis                         |
| Skin                         | Fragile skin<br>Pyoderma gangrenosum<br>Sicca syndrome<br>Scleritis<br>Scleromalacia perforans |
| Musculoskeletal system       | Osteoporosis                                                                              |
otrexate, leflunomide, hydroxychloroquine, and sulfasalazine) can be continued in patients undergoing elective joint surgery; however, this remains controversial in clinical practice [26,29,30]. All current biological and targeted synthetic DMARDs should be stopped prior to surgery (at the end of a dosing cycle for biological DMARDs). Tofacitinib must be withheld for at least 7 days. Medications may be restarted when the wound is healing well without any sign of infection [26,28,29].

**POSTOPERATIVE MANAGEMENT**

Airway and breathing status should be closely monitored after successful anesthesia. The possibility of tracheal edema, and thus a need for re-intubation, should be borne in mind. Standard breathing exercises should be initiated as soon as possible to prevent the development of respiratory problems, and postoperative pain should be appropriately controlled to allow for early recovery and mobilization. Howev-

Table 2. Common adverse effects associated with medications for rheumatoid arthritis and recommendations on how to deal with them during elective surgical procedures

| Medication                  | Adverse effect                                                                 | Administration during surgical procedures                                      |
|-----------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Corticosteroid              | Hypertension, infection, electrolyte imbalance, weight gain, glucose intolerance, adrenal insufficiency, fragile skin | See Table 3                                                                   |
| Conventional DMARDs         |                                                                               |                                                                                 |
| Methotrexate                | Pulmonary toxicity, bone marrow suppression, hepatotoxicity, infection         | Continue                                                                       |
| Hydroxychloroquine          | Retinal toxicity, cardiotoxicity, blood dyscrasia                              | Continue                                                                       |
| Sulfasalazine               | Central nervous system symptoms, granulocytopenia, hemolytic anemia            | Continue                                                                       |
| Leflunomide                 | Hepatotoxicity, myelosuppression infection, pulmonary toxicity                 | Continue                                                                       |
| Biologic DMARDs             |                                                                               |                                                                                 |
| TNF inhibitor               |                                                                               |                                                                                 |
| Etanercept, infliximab, adalimumab, golimumab | Infection, drug-induced lupus, neurologic deficit, heart failure, hepatitis B reactivation | Withhold before surgery and schedule surgery at the end of the dosing cycle: Week 2 (SQ) or week 9 (IV) |
| Rituximab                   | Infection, infusion reaction, cytopenia, hepatitis B reactivation              | Withhold before surgery and schedule surgery at the end of the dosing cycle: Month 7 Week 5 (IV) |
| Tocilizumab                 | Infection, cytopenia, increased liver enzyme, dyslipidemia                     | Withhold before surgery and schedule surgery at the end of the dosing cycle: Week 2 (SQ) or week 5 (IV) |
| Abatacept                   | Infection                                                                      | Withhold before surgery and schedule surgery at the end of the dosing cycle: Week 2 (IV) |
| JAK inhibitor (tofacitinib, baricitinib, upadacitinib) | Infection, neutropenia, increased liver enzyme, dyslipidemia                 | Withhold at least 7 days prior surgery                                           |

DMARD, disease-modifying anti-rheumatic drug; TNF, tumor necrosis factor; SQ, subcutaneous; IV, intravenous; IL, interleukin; JAK, Janus kinase.
er, the use of opioids for postoperative pain management requires caution, as they can affect airway management. Appropriate perioperative thromboprophylaxis is required [4]. RA patients tend to exhibit delayed ambulation, associated with hypercoagulability. Any sign of infection should be carefully monitored, and any immunosuppressive agent temporarily stopped.

**CONCLUSIONS**

The perioperative management of RA patients is summarized in Fig. 1. Prior to anesthesia, careful preoperative evaluation is required to prevent complications and minimize injury. Anesthetic management strategies must consider RA-related systemic problems and postoperative management should be individualized.
Conflict of interest
No potential conflict of interest relevant to this article was reported.

REFERENCES
1. Kim KW, Kim BM, Won JY, et al. Tocotrienol regulates osteoclastogenesis in rheumatoid arthritis. Korean J Intern Med 2021;36(Suppl 1):S273-S282.
2. Sung YK, Kim H, Cha SJ, Kim SH, Ndosi M, Cho SK. Developing the Korean Educational Needs Assessment Tool (Korean ENAT) in rheumatoid arthritis: cross-cultural validation using Rasch analysis. Korean J Intern Med 2021;36:1014-1022.
3. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320:1360-1372.
4. Zisa D, Goodman SM. Perioperative management of rheumatic disease and therapies. Med Clin North Am 2021;105:273-284.
5. Park JW, Hwang JS, Gong HS. Rheumatoid hand surgery in the era of biologic therapy: a rheumatologist-oriented overview. J Rheum Dis 2021;28:192-201.
6. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-2581.
7. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-1588.
8. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2021;73:1108-1123.
9. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3-15.
10. Aires RB, de Carvalho JF, da Mota LM. Pre-operative anaesthetic assessment of patients with rheumatoid arthritis. Rev Bras Reumatol 2014;54:213-219.
11. Takenaka I, Urakami Y, Aoyama K, et al. Severe subluxation in the sniffing position in a rheumatoid patient with anterior atlantoaxial subluxation. Anesthesiology 2004;101:1235-2137.
12. van Eijk IC, Nielen MM, van Soesbergen RM, et al. Cervical spine involvement is rare in early arthritis. Ann Rheum Dis 2006;65:973-974.
13. Lahio K, Soini I, Kautiainen H, Kauppi M. Can we rely on magnetic resonance imaging when evaluating unstable atlantoaxial subluxation? Ann Rheum Dis 2003;62:254-256.
14. Kwek TK, Lew TW, Thoo FL. The role of preoperative cervical spine X-rays in rheumatoid arthritis. Anaesth Intensive Care 1998;26:636-641.
15. Calder I, Calder J, Crockard HA. Difficult direct laryngoscopy in patients with cervical spine disease. Anaesthesia 1995;50:756-763.
16. Janssens M, Hartstein G. Management of difficult intubation. Eur J Anaesthesiol 2001;18:3-12.
17. Samanta R, Shoukrey K, Griffiths R. Rheumatoid arthritis and anaesthesia. Anaesthesia 2011;66:1146-1159.
18. Fombon FN, Thompson JP. Anaesthesia for the adult patient with rheumatoid arthritis. Contin Educ Anaesth Crit Care Pain 2006;6:235-239.
19. Yazdanyar A, Wasko MC, Kraemer KL, Ward MM. Perioperative all-cause mortality and cardiovascular events in patients with rheumatoid arthritis: comparison with unaffected controls and persons with diabetes mellitus. Arthritis Rheum 2012;64:2429-2437.
20. Min HK, Kim HR, Lee SH, et al. Four-year follow-up of atherogenicity in rheumatoid arthritis patients: from the nationwide Korean College of Rheumatology Biologics Registry. Clin Rheumatol 2021;40:3105-3113.
21. Kim SH, Lee SH, Kim HR, Min HK. Cardiovascular disease risk calculators to reflect the subclinical atherosclerosis of coronary artery in rheumatoid arthritis: a pilot study. BMC Rheumatol 2021;5:39.
22. Gabriel SE. Why do people with rheumatoid arthritis still die prematurely? Ann Rheum Dis 2008;67 Suppl 3(Suppl 3):iii30-iii34.
23. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2011;63:522-529.
24. Nicola PJ, Maradit-Kremers H, Roger VL, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005;52:412-420.
25. Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis Rheum 2004;50:3450-3457.
26. Hresko AM, Got CJ, Gil JA. Perioperative management of immunosuppressive medications for rheumatoid arthritis. J Hand Surg Am 2022;47:370-378.
27. Liu MM, Reidy AB, Saatee S, Collard CD. Perioperative steroid management: approaches based on current evidence. Anesthesiology 2017;127:166-172.
28. George MD, Baker JF. Perioperative management of immunosuppression in patients with rheumatoid arthritis. Curr Opin Rheumatol 2019;31:300-306.
29. Goodman SM, Springer B, Guyatt G, et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. Arthritis Care Res (Hoboken) 2017;69:1111-1124.
30. Goodman SM, George MD. ‘Should we stop or continue conventional synthetic (including glucocorticoids) and targeted DMARDs before surgery in patients with inflammatory rheumatic diseases?’ RMD Open 2020;6:e001214.