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REVIEW ARTICLE

Treatment of upper cervical spine involvement in rheumatoid arthritis patients

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Abstract The cervical spine, especially the upper cervical spine, is a common focus of destruction by rheumatoid arthritis (RA). Because of its potentially debilitating and life-threatening sequelae, cervical spine involvement remains a priority in the diagnosis and treatment of RA. Many studies show that early surgical intervention gives a more satisfactory outcome. Surgery aims to establish spinal stability and to prevent neurological deterioration and injury to the spinal cord, leading to improved neurological function. The recent sophisticated screw-rod-plate technique allows one to obtain a solid fixation of the upper cervical spine with a high possibility of bone union even in RA patients. Although surgery of the occipitoatlantoaxial region is a challenge with many possibilities of serious complications, recent advances in the surgical technique, complete understanding of the anatomy, and precise preoperative evaluation have decreased complication rates. Early consultation with a specialized spine surgeon is mandatory once cervical involvement is suspected in an RA patient because once the patient becomes myelopathic, the rate of long-term mortality increases and the chance of neurological recovery decreases.

Keywords Atlantoaxial subluxation · Rheumatoid arthritis · Surgery · Upper cervical spine · Vertical subluxation

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Introduction

The cervical spine is a common focus of destruction by rheumatoid arthritis (RA), second only to the metacarpophalangeal joints [1]. About 10–85% of patients with RA have neck pain and radiographic evidence of instability, and about 10–60% have neurological deficits [2–6]. In particular, the upper cervical spine (occipitocervical [O–C] and atlantoaxial [C1–2] regions) is the most common site of destruction, leading to high neck or occipital pain, myelopathy, and even sudden death. The disease is progressive and once myelopathy progresses, conservative treatment is ineffective and the prognosis is poor. Therefore, early and aggressive surgical intervention is recommended to avoid neurological deterioration and to improve patient outcome [5–11]. Surgery aims to establish spinal stability and to prevent neurological deterioration and injury to the spinal cord, which should help improve neurological function. However, surgery in the O–C and C1–2 regions is a challenge that carries the possibility of serious complications. In this article, we focus on the treatment of upper cervical spine involvement in RA patients, in particular on atlantoaxial subluxation (AAS) and vertical subluxation (VS), and the outcome of recently developed techniques used in upper cervical spine surgery.

Pathophysiology

The same processes that affect the peripheral joints in patients with RA also affect the spine. Inflammatory synovitis and RA pannus damage ligaments, bones, and synovial joints in the cervical spine, potentially causing instability and subluxation. Neurological deficit may develop mainly from a direct compressive effect on the

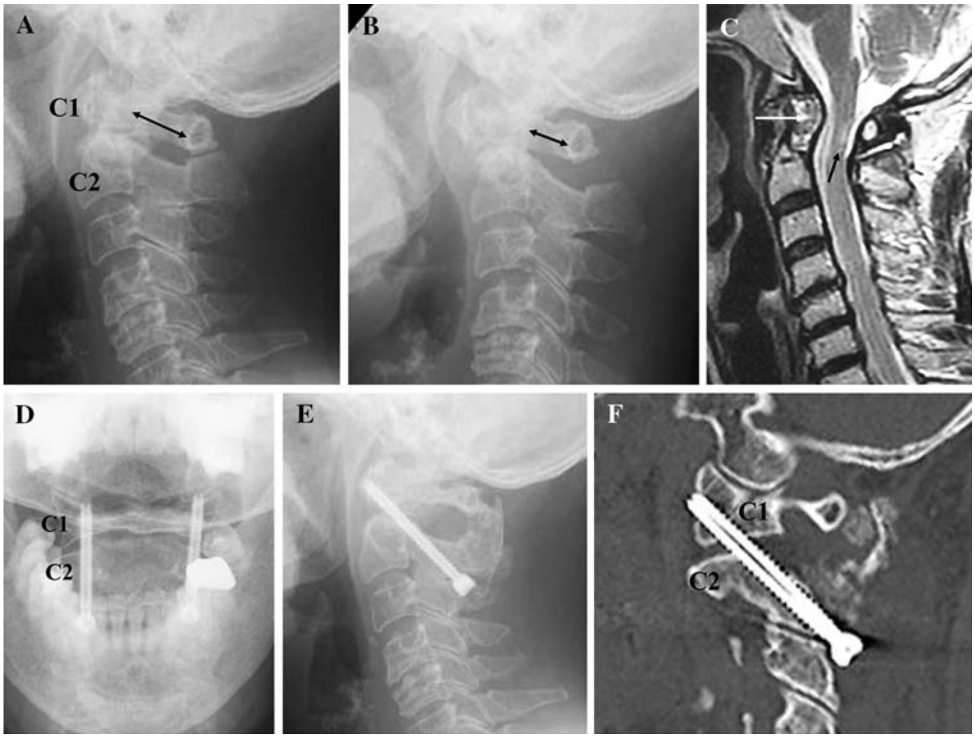

Fig. 1 A 58-year-old female rheumatoid arthritis (RA) patient with atlantoaxial subluxation (*AAS*). She complained of heaviness in the nuchal region, numbness and clumsiness of the hands, and pollakiuria and underwent C1–2 fusion with an iliac bone graft using transarticular screws. **a** Lateral radiogram in the neutral position does not demonstrate AAS but shows a posterior atlantodental interval (*PADI*) of 16 mm. (*arrow*). **b** Lateral radiogram in the flexed position demonstrates AAS with a PADI of 10 mm (*arrow*). **c** Magnetic resonance imaging demonstrated retrodental pannus (*white arrow*), spinal cord atrophy, and a T2-weighted high-intensity lesion in the spinal cord (*black arrow*) at the level of C1. **d** Postoperative radiogram with an *open mouth view* demonstrates the screw positions. **e** Lateral radiogram demonstrates bone union in reduced position 4 months after the operation. The grafted bone was fixed using radioparent polyethylene cable. **f** Postoperative sagittal computed tomography (*CT*) reconstruction demonstrates the ideal screw position

spinal cord or ischemic etiology. Compression of the spinal cord and eventually the brainstem can result from static or dynamic subluxation of the spine or from direct pressure by a synovial retrodental pannus. Further, rheumatoid involvement of the cervical facet joints can lead to stenosis of the nearby vertebral arteries (VA), which in turn leads to ischemia of the spinal cord attributable to the VA contribution to the anterior spinal artery [2].

The most common patterns of instability are AAS (about 65% of RA cervical involvement), followed by VS (or cranial settling or basilar invagination, 20% of RA cervical involvement) and subaxial subluxation (SAS, 15–25% of RA cervical involvement) [2, 10]. The O–C1 and C1–2 joints have a higher risk for pathological involvement (AAS and VS) because they are pure synovial joints lacking intervertebral discs and are thus primary targets for RA.

The C1–2 joint is affected most often because of the consistent involvement of the synovial-lined bursa found between the dens and the transverse ligament. Subsequent weakening and rupture of the transverse, then alar and apical ligaments, combined with erosion of the C1–2 joint can lead to anterior AAS (Fig. 1). Further, C1–2 facets are oriented in the axial plane, and there is no bony interlocking to prevent subluxation [6]. C1 anterior arch defects or dens erosions or fractures sometimes cause posterior AAS. Lateral AAS occurs secondarily to a combination of rotational deformities. Although posterior or lateral AAS has a higher risk of cord compression, anterior AAS predominates, followed by lateral (20%) and posterior (10%) AAS [2, 10].

VS occurs as a result of cartilage and bone destruction at the O–C1 and C1–2 joints. This destruction causes the skull to settle onto the cervical spine and subsequent relative superior migration of the dens into the foramen magnum, where dens compresses the brainstem (Fig. 2). VS is almost always preceded by AAS and usually presents with a more advanced neurological status and a poorer prognosis.

Clinical manifestations

Occipital and high neck pain is one of the most frequent complaints of patients with upper cervical involvement (40–85%) and one of the earliest findings caused by

Fig. 2 A 43-year-old female patient with mutilating RA. She did not demonstrate apparent myelopathy. **a** Lateral radiogram demonstrates severe destruction of the upper cervical spine and subaxial spine. Spontaneous fusion was shown from C2 to C4. **b**, **c** Sagittal CT reconstruction (**b**) and sagittal T2-weighted magnetic resonance imaging (**c**) demonstrate VS with a cervicomedullary angle (α) of 118°, in which the dens compresses the medulla oblongata. **d** O–C4 fusion with an iliac bone graft was performed with a right C3 and C4 pedicle screw and left transarticular screw, taking into consideration the VA course, its dominancy, and the space available for bilateral transarticular screws and pedicle screws. The fusion range was determined after talking with the patient and the rheumatologist in charge. Occipitothoracic fusion was another option for this patient. Deliberate follow-up is necessary as for progression of SAS. **e** Postoperative sagittal CT reconstruction. The dens was withdrawn about 5 mm from the skull during the operation. Compare this figure with (**b**). **f** Sagittal CT reconstruction along the transarticular screw. The screw was inserted into the occipital condyle to reinforce the fixation. **g**, **h** Axial CT at C3 (**g**) and C4 (**h**). Both screws were inserted using a computer-assisted navigation system and were positioned between the spinal canal and transverse foramen (VA, *arrows*) exactly as planned without breaching the cortex

articular destruction. Pain associated with subluxation is generally aggravated by neck motion, and patients may actually describe a clunking sensation or a feeling that the head is falling forward with flexion [2, 10]. Pain that is worse when upright and relieved by recumbency usually results from compression of the greater occipital branch of C2 [10]. Ear pain, mastoid pain, migraine, and facial pain can occur from compression of the C2 sensory fibers supplying the greater auricular nerve or the nucleus of the spinal trigeminal tract [6].

Spinal cord and brainstem compression is most important clinically. However, it is sometimes difficult to diagnose myelopathy because peripheral RA disease masks subtle findings. Hyperreflexia and positive pathological reflexes may be helpful, although it is often false-negative because of tenosynovitis, muscle atrophy, tendon rupture, peripheral nerve entrapment, or articular involvement related to RA. The scapulohumeral reflex is characteristic of upper cervical spine involvement [12]. Clumsiness of the hand, gait disturbances, and the sensation of heaviness or fatigability in the legs can be some of the first signs of early myelopathy [2]. Therefore, cervical spine involvement should be suspected in patients who were previously ambulatory, even if with crutches or a walker, and who become wheelchair-dependent [10]. Lhermitte's sign can be provoked occasionally by flexing the head [2, 6].

Less commonly, patients with RA may present with findings consistent with vertebrobasilar insufficiency [10, 13]. This is associated more commonly with VS [2]. The clinician should be highly suspicious when treating patients presenting with complaints such as vertigo, tinnitus, nausea, vomiting, dysarthria, dysphagia, visual disturbance, diplopia, or cerebellar signs [6, 10]. However, the signs and symptoms of brain stem compression from VS in RA patients mimic those caused by VA stenosis or cranial nerve palsies, which are also seen in RA patients [2].

Natural history and conservative treatment

Cervical spine involvement in RA patients is often progressive and potentially devastating. If left untreated, a large percentage of patients with AAS progress toward more the complex instability patterns of VS. For example, in a study of 106 patients by Pellicci et al. [4], 43% of patients had initial cervical spine involvement, but this percentage increased to 70% by 5 years, and 36% developed neurological progression. In another study, Rana [14] followed 41 AAS patients for 12 years, and 27% of patients showed radiographic evidence of progression, 61% showed no change, and 12% showed less AAS. However, 80% of the patients who had decreased AAS showed deterioration of VS.

Prognosis is also negatively affected once myelopathy appears, and patients may die. Matsunaga et al. [9] reported that RA patients with myelopathy who did not undergo surgical treatment have poor functional recovery and a low survival rate. In their series, without surgical intervention, AAS became aggravated during the follow-up, and 76% of patients experienced neurological deterioration. Crockard and Grob [15] demonstrated that if left untreated, 50% of patients with RA who become myelopathic die within 1 year. Once patients became nonambulatory (Ranawat [16] classification of neurological deficit, IIIB), the poor prognosis is accelerated. Cervical spine involvement is also believed to be associated with sudden death. A classical postmortem study by Mikulowski et al. [17] demonstrated that 11 of 104 patients had AAS with cervical medullary compression and that seven of them had died suddenly. Boden et al. [5] observed clinical symptoms and radiographs of 73 patients managed for rheumatoid involvement of the cervical spine. During an average follow-up period of 7.1 years, neurological deficit developed in 42 patients (58%), 35 of whom had operative stabilization. All seven patients who refused the operation died within 4 years, and five of them died of cord compression.

Conservative treatment such as collar fixation is recommended only to treat patients who have pain but not myelopathy. Therefore, the following principles should be applied when choosing conservative management. Because cervical involvement is associated with the degree of systemic involvement, aggressive medical management is important. In addition, close follow-up is necessary to detect subtle signs of deterioration of myelopathy because many papers stress the importance of early surgical intervention based on the natural history and ineffectiveness of conservative treatments [5–11].

On the other hand, Collins et al. [18] reported that half of RA patients who had cervical instability had no symptoms. Therefore, it is critical to predict who will develop neurological symptoms. For example, in a series of 49 patients, Oda et al. [19] found that none of the patients with minimal peripheral disease had VS, whereas 52% of patients with more erosive disease and 88% of the subset with mutilating disease had advanced VS. However, no single factor is entirely predictive of progression of cervical disease, although a variety of serological and clinical factors are associated with progressive cervical disease. Further, the effects of recent biological agents such as infliximab or etanercept on the prognosis of cervical spine involvement are not known.

Surgical indication

The currently accepted clear indications for surgery are intractable pain and neurological deficit. Pain is the most common complaint, but it can be managed medically or by collar fixation in many patients. However, in some patients, it progresses to untractable pain despite conservative treatment and disturbs activities of daily living. In such patients, surgical arthrodesis greatly reduces or prevents pain and satisfies the patient.

As mentioned, once neurological deficit occurs, surgical intervention is strongly recommended. Cervical collars do not prevent progression of subluxation and neurological deficit, and once myelopathy develops, the prognosis is poor. Earlier surgery in less neurologically involved patients often has a more satisfactory outcome [6, 10, 11, 20] Therefore, surgical intervention should be considered before more profound impairment occurs.

The controversial condition that might make a surgeon hesitate is significant cervical instability or subluxation without neurological deficit and with minimal pain [6, 10, 11]. In high-risk patients, early prophylactic arthrodesis with or without decompression can reduce the potential for paralysis but carries the risks of morbidity or mortality associated with surgical intervention. Currently there is no single reliable method for predicting which patients will become paralyzed. Shen et al. [10] advocated their preference of surgical indication as follows. In patients with normal neurology, observation is acceptable if the posterior atlantodental interval (PADI) (Fig. 1a, b) in flexion is greater than 14 mm and there is minimal evidence of VS. For patients with PADI less than 14 mm in the flexed position, an MRI should be obtained to look for the true space available for the cord (SAC). If the SAC is less than 13 mm or the cervicomedullary angle (Fig. 2c) is less than 135°, prophylactic arthrodesis is recommended. In patients with VS, a more aggressive approach should be considered because of the higher morbidity and poorer prognosis.

On the other hand, it is true that many of the patients under recent advanced medical control do not show progression of AAS or VS, nor present myelopathy for a long time. Therefore, observation may be an option of treatments for these patients and some surgeons adopt less strict surgical indication than that of Shen et al. [10]. In that case, however, close observation is necessary and the patient should be informed of the potential risks of the non-surgical treatment.

Surgical management

The goal of surgical intervention is to safely restore alignment and to obtain a solid arthrodesis, which should preserve or restore neurological function and improve pain. To obtain solid fusion, recent refined implants are generally used because they provide rigid internal fixation.

C1–2 fusion

The surgical management of a reducible AAS is stabilization of the C1–2 segment in the reduced position. This is the most frequently performed operation on the cervical spine in RA patients. Even if the AAS seems to be irreducible on preoperative flexion and extension radiograms, it is sometimes possible to obtain a reduction under general anesthesia. If no bony structure that hinders reduction is observed on preoperative computed tomography (CT), reduction should be tried under general anesthesia. The reduction should be performed not by extension of the neck but by lifting the head upward using a Mayfield clamp in the prone position. Even if a complete reduction is not possible, but an acceptable reduction is obtained, the modern rigid screw fixation method should be able to maintain this position with minimal reduction loss. Confining the fused range to only the C1–2 region reduces postoperative morbidity compared with longer fusions. That is, a larger range of motion of the cervical spine is preserved and the potential for newly developed postoperative SAS decreases [21]. VS does not usually progress after C1–2 fusion [21, 22].

Currently, the posterior approach is used routinely in C1–2 fixation because the recent posterior instrumentation techniques provide more rigid stabilization and probably fewer complications such as infection compared with the anterior transoral approach. Traditionally, posterior wiring with autogenous bone graft, such as the modified Gallie [23] or Brooks and Jenkins [24] methods, has been used. However, the mechanical rigidity of these fixations is inadequate and requires postoperative rigid external fixation such as the halo-vest, and bone union rates are not satisfactory [8, 25, 26].

The most popular fixation method currently is atlantoaxial transarticular screw fixation advocated by Magerl and Seehan [27] coupled with posterior wiring or clamp (Fig. 1). Autogeneous bone graft is performed routinely to obtain bony fusion and to prevent future implant loosening or failure. This method provides more rigid internal fixation compared with traditional methods, and provides fusion rates of around 95%, which surpass those of traditional posterior wiring methods despite elimination of the halo-vest fixation [25, 26, 28–31]. However, VA injury is an inherent risk associated with a screw trajectory and can result in catastrophic consequences such as massive bleeding, cerebellar or brain stem infarction, and death [32–37]. Injury to the dominant VA may be lethal. The published rates of VA injury during transarticular screw fixation are 4.1–8.2% [25, 34, 37]. One reason for these fairly high rates is that VA makes an acute lateral bend in the lateral mass of C2 just under the superior articular facet, a course quite different from the simple vertical course of the VA in the subaxial spine (C3–6) [38]. In addition, some surgeons do not understand this anatomy correctly. Another reason is that the position of this bending point of the artery varies between individuals, and enough space is not available for screw placement in around 20% of patients [34, 39, 40]. In these patients, a screw may breach the cortex and injure the VA even when inserted as planned. Therefore, precise preoperative evaluation of the course and dominancy of each VA is mandatory, in which magnetic resonance angiography or computed tomographic angiography is very useful. If a surgeon understands this unique relationship between the VA and screw trajectories, and is sufficiently skilled to insert the screw exactly as planned based on the preoperative evaluation, it is possible to insert a screw safely in most patients [41–43]. However, if one VA is obstructed, it may be better to avoid inserting a screw on the patent side.

Recently, posterior atlantoaxial fixation using C1 lateral mass screws combined with C2 pedicle screws has become popular, and this technique provides comparable stability to that provided by transarticular screw fixation [44–46].

Some surgeons prefer this procedure to transarticular screw fixation because they believe that the technique is less demanding and decreases the risk of VA injury [10, 45, 47]. However, an anatomical study using CT demonstrated that C2 pedicle screw fixation is not any safer than transarticular screw fixation in relation to VA injury [48, 49]. VA injuries during C1 lateral mass fixation have also been reported [35, 50]; these are encountered rarely during transarticular screw fixation. Massive venous bleeding encountered during a dissection of the lateral mass of C1 is also troublesome. In contrast, this method has several advantages over transarticular screw fixation. First, the reduction maneuver is possible after insertion of the screws, and it is sometimes possible to perform reduction using screws. Second, the technique can be applied to lateral or posterior AAS, in which a transarticular screw may miss catching the C1 lateral mass. Third, it can also be applied without losing stability in patients whose C1 posterior arch is deficient, whereas transarticular screws without posterior wiring provide weaker stability. Lastly, the technique does not necessitate detaching the semispinalis cervicis muscle from spinous process of C2, which may prevent postoperative neck pain or progression of kyphosis.

The relative superiority of these two C1–2 fusion techniques is controversial. Further accumulation of experience and investigation is necessary.

If the course of the VA does not allow the use of a transarticular screw or C2 pedicle screw, or one VA is obstructed, a C2 laminar screw is an alternative technique. The C2 laminar screw can be relatively safely inserted and provides slightly less but acceptable mechanical strength as an anchor [51–54].

O–C fusion

Arthrodesis should be extended superiorly to include the occipital bone (O–C fusion) with or without removing the posterior arch of C1 in patients with VS or irreducible AAS (Fig. 2). In patients with severe VS whose dens compresses the brainstem remarkably, preoperative direct skull traction may withdraw the dens from the skull, relieving the neurological deficit. Preoperative halo-vest fixation is also recommended to prevent further deterioration of the neurological deficit or to improve the status [55]. A halo-vest is also useful for identifying preoperatively the fusion position convenient for the patient. In patients with mild VS, brainstem compression may be relieved only once they are positioned on the operating table under general anesthesia, when cervical traction force is applied (Fig. 2). In many patients with O–C fusion, the modern rigid fixation system with screw, rod, and plate can maintain this obtained reduced position. If the cord or brainstem compression is relieved in the obtained position, decompression is unnecessary. Only stabilization may relieve neurological symptoms even if mild compression remains. On the other hand, if significant compression persists, decompression should be performed. In many patients, adequate decompression is obtained by removing the posterior arch of C1, but transoral odontoid resection may be sometimes necessary when the dens compresses the brainstem anteriorly [7, 8, 15].

In O–C fusion, the recently developed rigid fixation system sometimes uses the C1–2 transarticular screw or pedicle screw as a cervical anchor (Fig. 2). These screws provide the most rigid and reliable anchor for fixation. Abumi et al. [56] used intraoperative distraction and extension of the upper cervical spine to decompress anterior cord compression caused by the dens and fixed the obtained position using cervical pedicle screws. They performed O–C fusion in 19 RA patients and successfully reduced the subluxation and obtained bony fusion with minimal postoperative loss of correction, thus eliminating anterior decompression. The fixation ranges of 13 patients were confined to O–C2 only because of the rigid anchor of the C2 pedicle screw. However, a pedicle screw also has a potential risk of VA injury. In particular, the rate of screw perforation out of the pedicle in degenerative disease or RA is fairly high [48, 49, 57, 58]. To prevent misplacement of the cervical pedicle screw, a computer-assisted navigation system is now used in some institutions (Fig. 2). This system shows the surgeon the position of the screw being inserted on a virtual reality monitor in real time. A dramatic decrease in perforation rates of cervical pedicle screws has been reported when using this system [59, 60].

Surgical outcomes

Reported surgical outcomes vary after operative intervention in RA patients [5, 7, 61]. In 1996, Casey et al. [7] reported that 12.7 and 58% of Ranawat IIIB (unable to walk) patients died within 1 month and 3 years after surgery, respectively. However, the new techniques mentioned above and improved pre- and postoperative management mean that surgical intervention can improve neurological status and short- and long-term prognosis with more certainty. Favorable surgical outcomes have been reported recently even for Ranawat IIIB patients [55, 62] or elderly RA patients [63]. Matsunaga et al. [64] reported the outcomes over more than 10 years in 16 patients who underwent occipito-upper cervical fusion. Occipital pain decreased after surgery in all patients, and neurological symptoms improved by more than one Ranawat class in 75% of the patients. They also reported that the survival rate of the RA patients who underwent O–C fusion was 84% after 5 years and 37% after 10 years. In contrast, all patients who did not receive the operation were bedridden within 3 years after the onset of myelopathy and the survival rate was 0% after 8 years [9].

Surgical complications

Common perioperative serious complications other than VA injury include neurological deterioration, surgical site infection, dysphagia, and dyspnea. Boden et al. [5] reported that postoperative neurological deterioration occurred in 8% patients with Ranawat class III neurological deficit. Nannapaneni et al. [62] reported that among 31 O–C or C1–2 fusion patients, three patients with graft displacement and resubluxation had neurological deterioration. The possibility of surgical site infection is higher than usual because RA patients are treated with medications such as steroids and have poor general condition, including anemia or low blood protein level. Transient and persistent dysphagia or dyspnea caused by pharyngeal obstruction may occur after fixation in malposition of O–C fusion, and RA is a major risk factor for this complication [55, 62, 65]. Keenan et al. [66] reported that the relative shortening of the neck secondary to the vertical migration of the dens causes the soft tissue of the pharynx to become redundant, further compromising the airway. Redlund-Johnell [67] noted that the size of the upper airway can become smaller in patients with RA and temporomandibular joint destruction. Acquired laryngeal deviation, laryngeal mucosal abnormalities, and cricoarytenoid and cricothyroid arthritis can also distort the anatomy of the airway in patients with RA [66, 68, 69]. Surgeons should remember that an adequate fusion angle is mandatory to avoid this catastrophic complication, even in short O–C fusions and especially in RA patients [65]. However, it is sometimes difficult to decide the suitable fixation position on the operating table. Preoperative halo-vest fixation is helpful because the surgeon can identify the most convenient position for the patient and can fix the cervical spine in that position.

The late postoperative complications include loss of reduction, instrumentation failure, malunion, and nonunion. Recently reported fusion rates of upper cervical surgery in RA patients are satisfactory at 90–100% [25, 26, 28, 56, 61]. However, even after solid fusion is obtained, previously asymptomatic levels can develop SAS below the rigid segment. In contrast, VS does not usually progress after C1–2 fusion [21, 22]. Clarke et al. [22] followed 51 RA patients who underwent posterior cervical arthrodesis for 5–20 years. Of the 33 patents with AAS, 39% developed nonsymptomatic (18%) or symptomatic (21%) SAS subsequent to C1–2 fusion. All of the latter patients required extension of their arthrodesis. Kraus et al. [21] compared the incidence of SAS after upper cervical fusion. Of the O–C fusion patients, 36% developed SAS requiring surgery at an average of 2.6 years after fusion. Of the C1–2 fusion patients, 5.5% developed SAS requiring surgery after an average of 9 years after fusion. Yoshimoto et al. [70] reported that 42% of patients who underwent C1–2 fusion showed progression of kyphosis in the subaxial cervical spine, and that C1–2 fixation in a hyperlordotic position led to subaxial kyphosis after surgery. In contrast, Mukai et al. [71] concluded that subaxial alignment is regulated by multiple factors, which are difficult to evaluate correctly, and consequently subaxial change after C1–2 fusion for RA is hard to predict. It should be kept in mind that there is no definitive method to prevent postoperative SAS after upper cervical fusion and, therefore, the clinician should follow each patient deliberately and carefully.

Conclusions

Once myelopathy develops because of cervical involvement in RA patients, early and aggressive surgical intervention is recommended to avoid neurological deterioration and to improve outcome. The recent sophisticated screw-rod-plate techniques allow one to obtain solid fusion of the upper cervical spine surely and safely, and to lessen the risk of complications even in RA patients. Early consultation with a specialized spine surgeon is mandatory if cervical involvement is suspected in an RA patient because once the patient becomes myelopathic, the rate of long-term mortality increases and chance of neurological recovery decreases.

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