Surgical treatment outcome on a national cohort of 176 patients with cervical manifestation of rheumatoid arthritis

ABSTRACT

Purpose: Rheumatoid arthritis (RA) affecting the cervical spine results in instability and deformity that can be divided into the subtypes C1–C2 horizontal (atlantoaxial instability), C0–C2 vertical (basilar invagination), subaxial, and combined instabilities. The aim of this study was to compare the surgical treatments and outcomes of RA-related deformity and instability in a population-based setting.

Patients and Methods: All patients with RA in the national Swespine register from January 1, 2006, to March 20, 2019, were assessed. Baseline characteristics, surgical treatments, European Myelopathy Scale (EMS), Neck Disability Index, the Visual Analog Scale for neck and arm pain as well as pre- and postoperative imaging were analyzed. The follow-up time points were at 1-, 2-, and 5 years after surgery.

Results: A total of 176 patients were included. There were 62 (35%) patients with C1–C2 horizontal instability, 48 (27%) with C0–C2 vertical instability, 19 (11%) patients with subaxial instability, 43 (24%) patients with combined instability, and 4 patients without instability served as controls. The EMS improved in the C1–C2 horizontal instability group after fusion surgery ($\Delta = 2.6$) but remained within baseline confidence intervals in the other groups. All patients regardless of instability improved in pain. The subaxial instability had the highest risk of death within 5 years after surgery (11/19, 58%). The most dangerous complications due to implant failure were seen in patients instrumented with laminar hooks.

Conclusion: The neurological outcome after fusion surgery is poor and the death rate is high in patients with cervical RA-related instability and deformity.

Keywords: Cervical deformity, cervical instability, European myelopathy score, rheumatoid arthritis, surgical treatment

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting the peripheral joints with chronic synovitis resulting in bony erosions and ligamentous laxity. RA affects 0.5%–1.0% of the population in Europe[1] and twice as many women as men.[2] In 42% of RA patients, the cervical spine is involved in an early stage, within 2 years following diagnosis,[3] and in 10%–25%, the lesions progress over time to atlantoaxial instability (AAI).[4,5] Early treatment with disease-modifying antirheumatic drugs (DMARDs) has decreased the incidence of cervical instability to 5% within the first 10 years following diagnosis.[6]

Synovitis and pannus formation affect the joints and the main stabilizing ligaments of the atlantooccipital and atlantoaxial
joints as well as the medial C1–C2 joint resulting in C1–C2 horizontal instability (AAI) [Figure 1a]. Continuous erosions of the atlantoaxial joints may lead to the collapse of the C1 lateral masses resulting in cranial migration of the odontoid process into the foramen magnum, C0–C2 vertical instability, for example, basilar invagination [Figure 1b]. Basilar invagination increases the risk of brainstem injury and sudden death.[7] Destabilization of the subaxial facet joints is a late phenomenon in the rheumatoid process causing multilevel spondylolisthesis yielding the characteristic “staircase” deformity [Figure 1c].[8]

Surgery is indicated in patients with myelopathy, progressive neurological deficit, instability with the risk of compression of the neural elements, and chronic intractable pain unresponsive to analgesics. Surgery can provide substantial improvement in symptoms and particularly pain reduction.[4] The continuation of DMARD therapy throughout the perioperative period is safe.[9] A more recent explanation model by Goel is that instability manifested at the facets is the primary point of pathogenesis causing lateral mass collapse and buckling of the posterior longitudinal ligament, resulting in the form of a pannus. The retro-odontoid pannus in RA need not to be directly addressed, and the surgical effort should be focused on the AAI.[10] Restoring the anatomical craniovertebral alignment in patients with atlantoaxial dislocation may be achieved with manual distraction of the facets of the atlas and the axis and placement of bone graft or metal spacers within the joint together with atlantoaxial screw fixation.[11,12]

The national Swedish Spine Registry (Swespine) was founded in 1993. Cervical spine procedures have been included in Swespine since 2006.[13] Ninety-five percent of the spine surgery units in Sweden are affiliated with this register and they report 75% of all spine surgeries in the country. We used the Swespine register with the primary goal of evaluating the improvement of myelopathy expressed as changes in the European Myelopathy Scale (EMS) after 1, 2, and 5 years of follow-up after surgical treatment with decompression or decompression and fusion for myelopathy and/or cervical instability in patients with RA. Secondary objectives were to evaluate neck disability, quality of life, neck and arm pain as well as complications and secondary surgeries.

PATIENTS AND METHODS

In this prospective, register-based study of a national cohort, data were collected for all Swedish patients with RA undergoing surgery of the cervical spine, registered in Swespine, since the beginning of the registration of cervical procedures on January 1, 2006. Final follow-up information was entered on March 20, 2019. Inclusion criteria were patients with RA and myelopathy or neck pain due to cervical arthritis with or without instability, which had any kind of surgical treatment (anterior or posterior surgery, with or without instrumentation). RA was diagnosed based on the revised criteria for the classification of RA formulated by the committee of the American Rheumatism Association.[14] Exclusion criteria were previous cervical surgery, fracture, ankylosing spondylitis, infections, or neoplasm.

Data collection and outcomes

Patients completed baseline and postal follow-up questionnaires as well as validated patient-reported outcome measures (PROMs) without any assistance from the operating surgeon.[15-17] Preoperative patient data included routine demographics, smoking habits, work status, sick leave, duration of neck pain, attitude toward returning to work, use of analgesics, fine motor skills, and PROMs including the EMS, Neck Disability Index (NDI), European Quality of Life Five Dimensions (EQ-5D), and the Visual Analog Scale (VAS) separately for arm and neck pain. The surgeons reporting to Swespine recorded data including diagnosis, surgical treatment, operated levels, neurological impairment, Ranawat grading,[18] presence of instability, type of implant used, and any perioperative complications. Follow-up questionnaires and PROMs were sent to the patients after 1, 2, and 5 years, postoperatively. The follow-up questionnaire included questions to the patients about change in neck pain and manual dexterity after surgery, global assessment, amount of time they were absent from work after surgery, if their work was physically heavy or if they changed to easier task assignments, if they exercised or changed their exercise routines after surgery, if they suffered from dysphagia or hoarseness more than one month after surgery or had other complications and adverse events (thrombosis, emboli, and antibiotic treatment).

EMS is a 5-item, self-administered questionnaire measuring walking ability, hand function, coordination, bladder and bowel function, and paresthesia and pain. The scale ranges from 5 to 18, with lower scores reflecting more severe deficits. The score is to be interpreted as normal: 17 + 18 pts, Grade 1: 13–16 pts, Grade 2: 9–12 pts, and Grade 3: 5–8 pts.[19] Internal consistency within patients using EMS, measured by Cronbach’s alpha with a score of 1 representing perfect correlation, is 0.68–0.77.[20]

NDI measures neck disability and the score is ranging from 0 to 50, with higher scores indicating severe disability. In order to deal with items which may have been mistakenly overlooked by the patient, the NDI was transformed into a percentage (range: 0%–100%).[21]
Quality of life was measured by EQ-5D ranging from −0.5–1, with higher scores reflecting a better quality of life. EQ-5D health ranges from 0 to 100, with higher scores indicating better health. VAS for neck and arm pain ranges from 0 to 10, with higher scores indicating more severe pain. The minimum clinically important difference is 15%–17% for NDI, 0.24 for EQ-5D, and 2.5 for VAS of the neck and arm.

Imaging
Preoperative plain radiographs, preoperative magnetic resonance imaging with T1- and T2-weighted images in sagittal and axial planes, and pre- and postoperative computed tomography (CT) scans were retrieved for all included patients and from all the hospitals performing cervical spine surgery in Sweden. The images were screened for cervical deformity and instability due to RA.

The nomenclature used in the registry was used for simplicity to divide the different deformities into the following groups:

1. C1–C2 horizontal instability (AAI) [Figure 1a]. Measurements used to define C1–C2 horizontal instability were the anterior atlantodental interval, <3 mm being normal for adults, and the posterior atlantodental interval, >13 mm.
2. C0–C2 vertical instability, i.e. basilar invagination [Figure 1b]. Measurement used to define C0–C2 vertical instability was the vertical atlantoaxial index as it is a modern method made for CT that measures the relationship of atlas and axis. Normal = 0.80 (range: 0.76–0.85).
3. C2–Th1, subaxial, instability – spondylolisthesis and/or kyphosis [Figure 1c]. Definition of spondylolisthesis-antrolis thesis of > 2 mm on cervical radiographs taken in the neutral position with the patient sitting.
4. Combined instability [Figure 1d].

Study oversight
This study was approved by the Swedish ethics review board.

Figure 1: (a) C1–C2 horizontal instability (A1: extension, A2: flexion), (b) C0–C2 vertical instability, (c) C2–Th1 subaxial instability, (d) Combined instability

Figure 2: Consort diagram
board (Dnr 2017/450 and 2019-00913). Since 1998, Swespine has been entirely patient based and all participants provided oral and written informed consent. The Swespine register is owned and governed by the Swedish Society of Spinal Surgeons (www.4s.nu) with public financial support.

**Statistical analysis**

All statistical analyses were performed in R,\(^{(29)}\) version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Baseline characteristics, surgical treatment methods, and deaths are presented from the raw data set of the available cases. For the Kaplan–Meier curve, pairwise multiple comparison was performed with Benjamin–Hochberg procedure. An end date of July 1, 2019, was used.

**Table 1: Baseline characteristics within groups and as total**

| Patient characteristics | No instability, n (%), C1-C2, C0-C2, C2-Th1 | Combined instability, n (%) | Total, n (%) |
|-------------------------|---------------------------------------------|-----------------------------|--------------|
| Male                    | Male                                       | Male                        | Male         |
| Age (years), mean (SD)  | 64.75 (15.11)                              | 65.10 (11.68)               | 65.10 (11.68) |
| Smoking                 | 0 (0)                                      | 3 (4.84)                    | 3 (4.84)     |
| BMI, mean (SD)          | 22.93 (1.75)                               | 24.74 (8.66)                | 24.74 (8.66) |
| Number of levels, mean (SD) | 2.5 (1)                               | 2.21 (0.61)                 | 2.21 (0.61) |
| Unemployed              | 0 (0)                                      | 4 (6.45)                    | 4 (6.45)     |
| Sick leave              | 0 (0)                                      | 9 (14.52)                   | 9 (14.52)    |
| Disability pension      | 1 (25)                                     | 8 (12.90)                   | 8 (12.90)    |
| Retired                 | 1 (25)                                     | 25 (40.32)                  | 25 (40.32)   |
| Heavy work              | 2 (50)                                     | 10 (16.13)                  | 10 (16.13)   |
| Fine motor skill        | 1 (25)                                     | 30 (48.39)                  | 30 (48.39)   |
| Preoperative EMS, mean (SD) | 16.75 (0.96)                             | 12 (5.89)                   | 12 (5.89)    |
| Preoperative NDI, mean (SD) | 31.5 (22.65)                             | 36.2 (22.39)                | 36.2 (22.39) |
| Preoperative EQ-SD, mean (SD) | 0.51 (0.39)                             | 0.3301 (0.31)               | 0.3301 (0.31) |
| Preoperative VAS neck, mean (SD) | 7.5 (4.35)                              | 5.5 (3.13)                  | 5.5 (3.13)   |
| Hospital time (days), mean (SD) | 4 (2.45)                                | 4.02 (2.87)                 | 4.02 (2.87)  |

**Table 2: Surgical treatment method and deaths within groups**

| Patient characteristics | No instability, n (%), C1-C2, C0-C2, C2-Th1 | Combined instability, n (%) | Total, n (%) |
|-------------------------|---------------------------------------------|-----------------------------|--------------|
| Anterior decompression and fusion | -                                          | -                           | 1 (2)        |
| Anterior corpectomy and fusion | -                                          | -                           | 6 (32)       |
| Posterior laminectomy | 1 (25)                                     | 1 (2)                       | 1 (2)        |
| Posterior laminctomy and fusion | -                                          | 12 (25)                     | 12 (25)      |
| Posterior fusion only (no decompression) | 3 (75)                                    | 55 (89)                     | 55 (89)      |
| Other types of surgery, not specified | -                                          | -                           | 3 (6)        |
| Information missing | -                                          | 1 (2)                       | 1 (2)        |
| Hooks or wire | 1 H                                        | 10 H, 7 W                   | 3 H          |
| Deaths | 0                                          | 15 (24)                     | 19 (44)      |

**Statistical analysis**

Inter-observer reliability between the author’s assessment of instability and the registering surgeon was evaluated by unweighted Cohen's kappa test (two categorical variables; the author’s and the original assessments). \(\kappa < 0.20\) is considered to be poor agreement, \(\kappa = 0.21–0.40\) is fair agreement, \(\kappa = 0.41–0.60\) is moderate agreement, \(\kappa = 0.61–0.80\) is good agreement, and \(\kappa = 0.81–1.00\) equals very good agreement.

For the outcome analyses and time plots, missing values were replaced with multiple imputations using chained equations as implemented in the R package MICE, generating 20 imputations. Using ANCOVA, we compared the mean 1-year outcome values between the treatment groups, adjusted for sex, age (continuous), number of levels (ordered), body mass index (continuous), retired (yes vs. no), sick leave (yes vs. no), disability pension (yes vs. no), and the attitude toward returning to work after surgery (positive vs. negative).

**Table 2: Surgical treatment method and deaths within groups**

| Patient characteristics | No instability, n (%), C1-C2, C0-C2, C2-Th1 | Combined instability, n (%) | Total, n (%) |
|-------------------------|---------------------------------------------|-----------------------------|--------------|
| Anterior decompression and fusion | -                                          | -                           | 1 (2)        |
| Anterior corpectomy and fusion | -                                          | -                           | 6 (32)       |
| Posterior laminectomy | 1 (25)                                     | 1 (2)                       | 1 (2)        |
| Posterior laminctomy and fusion | -                                          | 12 (25)                     | 12 (25)      |
| Posterior fusion only (no decompression) | 3 (75)                                    | 55 (89)                     | 55 (89)      |
| Other types of surgery, not specified | -                                          | -                           | 3 (6)        |
| Information missing | -                                          | 1 (2)                       | 1 (2)        |
| Hooks or wire | 1 H                                        | 10 H, 7 W                   | 3 H          |
| Deaths | 0                                          | 15 (24)                     | 19 (44)      |
RESULTS

We included 190 RA patients who were operated on their cervical spine. Preoperative imaging was located and retrieved for 176 patients [Figure 2]. The mean age at the time of surgery was 67 years (range: 33–89 years), and a majority of the patients were women 143 (81%). There were no radiologic signs of instability in four of the patients, forming the small control group. The patients were divided according to their instabilities resulting in 62 patients with C1–C2 horizontal instability, 48 patients with C1–C2 vertical instability, 19 patients with subaxial instability, and 43 patients with combined instability. Baseline characteristics within the groups and as total are presented in Table 1.

Different types of surgery were performed within the groups: anterior decompression and fusion (2 patients), anterior corpectomy and fusion (6 patients), posterior laminectomy (3 patients), posterior laminectomy and fusion (48 patients), posterior fusion only (no decompression) (105 patients), and other types of surgery, not specified (10 patients) [Table 2]. In the

Figure 3: Outcome after 1-, 2-, and 5 years of follow-up. The bars indicate 95% of confidence interval. 3A: EMS = European Myelopathy Scale, 3B: NDI = Neck Disability Index, 3C: EQ-5D = European Quality of Life 5 Dimensions, 3D: VAS-neck = Visual Analog Scale for neck pain, 3E: VAS-arm = Visual Analog Scale for arm pain, 3F: Kaplan-Meier Survival Curve
C1–C2 vertical instability group, 30 patients (63%) were fused without being decompressed or having their deformity reduced. Three patients were reduced by C1–C2 facet spacers together with posterior fusion according to Goel.\

Overall, 61 patients (35%) died between the first registration in Swespine at January 1, 2006, and the retrieval of the file at March 20, 2019 [Table 2].

The inter-observer reliability between the author’s assessments of instability measured on preoperative imaging and the registering surgeon’s assessment, presented a moderate agreement between raters with a correlation coefficient (kappa value) of 0.48 ($P < 0.05$).

**Outcome**

- **EMS:** The only group improving 1 year after surgery is the C1–C2 horizontal instability group. The C1–C2 vertical instability group is improving 2 years after surgery but is worsened back to baseline values at 5 years of follow-up. The control group gets worse at 2 years of follow-up [Figure 3a]

Figure 4: Examples of complications with laminar hooks used for posterior instrumentation in patients with rheumatoid arthritis. (a) The hook is loose and compresses the medulla, (b) the hook is loose causing loss of sagittal balance and chin on chest deformity

- **NDI:** All groups improve significantly except for the subaxial instability group, which deteriorates 2 years after surgery [Figure 3b]
- **EQ-5D:** All groups improve significantly except for the control group that needs 2 years to improve and then deteriorates to baseline values at 5 years of follow-up [Figure 3c]
- **VAS neck:** All groups improve significantly at 1 year of follow-up [Figure 3d]
- **VAS arm:** All groups improve significantly at 1 year of follow-up [Figure 3e]
- **Survival:** The risk of deceasing is high in all groups, but the subaxial instability group is performing worse ($P = 0.038$ in pairwise comparison with the horizontal instability group) [Figure 3f].

When 1-year improvements, i.e. the adjusted ∆ values (∆ = 1-year value minus baseline value, adjusted for baseline values), were compared, there were no differences between the groups [Table 3].

**Reoperations**

Eighteen patients had 22 reoperations. The reasons for reoperations were pseudarthrosis or implant failure (11), infection (5), chronic implant-related pain (2), residual or restenosis (2), and postoperative bleeding (2) [Table 4]. The most dangerous implant failures were the ones caused by the laminar hooks [Figure 4].

**DISCUSSION**

All groups improve in pain and quality of life after fusion surgery, but the myelopathy is only successfully managed within the C1–C2 horizontal instability group. All other groups remain within their baseline confidence interval on the EMS at all times. The subaxial instability group is the most vulnerable group with more severe signs of myelopathy both at baseline and at follow-ups that perform worse in neck disability and have the highest risk of death within 5 years after surgery.

| Table 3: The outcome, i.e., the delta value (Δ = 1-year value minus baseline value) with confidence intervals (CI), for each PROM and within each instability group |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| No instability, Δ (CI)          | C1-C2 horizontal, Δ (CI)        | C0-C2 vertical, Δ (CI)          | C2-T1 instability, Δ (CI)       | Combined instability, Δ (CI)    | ANCOVA*, P                       |
| EMS                             | 0.16 (−0.04-0.37)               | −2.62 (−3.41–−1.82)             | −0.68 (−1.47-0.12)             | −1.09 (−1.71–−0.48)             | −0.93 (−1.44–−0.41)              | 0.36 |
| NDI                             | 12.08 (9.20-14.95)              | 10.91 (7.37-14.45)              | 14.39 (11.14-17.56)            | 2.41 (−0.35-5.17)               | 7.4 (4.96-9.84)                  | 0.90 |
| EQ-5D                           | −0.04 (−0.07–−0.02)             | −0.25 (−0.3–−0.2)               | −0.28 (−0.33–−0.22)            | −0.18 (−0.23–−0.13)             | −0.16 (−0.21–−0.11)              | 0.73 |
| EQ-5D health                    | −35.63 (−38.67–−32.58)          | −9.12 (−13.16–−5.08)            | −18.91 (−22.72–−15.11)         | −7.6 (−11.27–−3.92)             | −12.55 (−16.21–−8.9)             | 0.51 |
| VAS neck                        | 5.43 (5.02-5.83)                | 3.21 (4.75-3.67)                | 3.4 (2.88-3.93)                | 2.1 (1.6-2.6)                   | 2.59 (2.01-3.17)                 | 0.56 |
| VAS arm                         | 1.2 (0.73-1.67)                 | 1.17 (0.64-1.69)                | 0.98 (0.38-1.57)               | 2.05 (1.47-2.63)                | 1.6 (0.99-2.21)                  | 0.57 |

*Adjusted for sex, age, smoking, body mass index, unemployed, sick leave, disability pension, number of degenerated levels, the attitude toward returning to work after surgery, and baseline values for each outcome. CI - Confidence interval, EMS - European Myelopathy Scale, NDI - Neck Disability Index, EQ-5D - European Quality of Life Five Dimensions, VAS - Visual Analog Scale, Δ - 1 year value minus baseline value
As described by Casey et al.\textsuperscript{7,17} and Paimela et al.,\textsuperscript{8} horizontal instability appears to be the first cervical spine involvement characteristics of RA, followed by vertical and subaxial instability. Traditionally anterior transoral odontoid resection and posterior fusion is the recommended surgical treatment for C1–C2 vertical instability,\textsuperscript{31} but in recent years, reduction of the basilar invagination by C1–C2 facet spacers described by Goel\textsuperscript{160,176} has been introduced as the optional treatment leaving the anterior transoral odontoid resection unnecessary. Despite these recommended treatment methods for C1–C2 vertical instability, 63\% of the patients registered in Swespine were surgically treated with posterior fusion only even though the results are known to be unsatisfactory.\textsuperscript{32} The high percentage of the chosen treatment of posterior fusion only is most likely the reason why the C1–C2 vertical instability group did not improve in myelopathy after surgery. Three patients were treated with reduction by facet spacers according to Goel.\textsuperscript{160} If this method is wider spread and the number of registered patients treated with this method is increased, the results remain to be evaluated.

Laminar hooks were shown to have the most dangerous postoperative complications [Figure 4], exposing the patient to higher risks than that of pseudarthrosis after screw fixation. We, therefore, recommend avoiding laminar hooks in RA patients with the exception of atlas claws that had no complication rate of loosening or dislocating.

In some patients, the destabilizing processes are presenting simultaneously in the upper and subaxial spine (Group 4: combined instability), but in other patients, the inflammatory processes proceeded to the subaxial spine after C1–C2 fusion. The subaxial instability, however, may be treated when and if it occurs and no results from our study indicate the need for prophylactic surgery.

The strength of our study is that it reflects a national setting and not just a few clinics or surgeons. Besides, pre- and postoperative radiographs were able to be retrieved and assessed in 176/190 patients. It is also important to note that this study was not supported by industrial partners.

Limitations are patients lost to follow-up, a deficient registration of complications and reoperations, and\textsuperscript{34} the shortcomings of the EMS questionnaire when used in patients with systemic rheumatic joint disease. Sources of error may occur related to poor walking ability and handgrip, where reasons other than myelopathy may be the destruction of joints in legs, feet, arms, and hands. We used an RA control group that suffered from neck pain and disability but without any signs of radiographic instability. This control group presented values on the limit to the normal range on the EMS score at baseline and worsened after 2 years by one point on the EMS score, which is questionable if it is clinically important.

Even though DMARDs have lowered the incidence of cervical instability in RA patients substantially, these groups of patients suffering from instability remain. Cervical RA deformities differ from other patient groups, for example, degenerative or congenital deformities, and thus, they should not be treated the same way. To our surprise it seems like in Sweden, treatment guidelines are not implemented overall and local routines are still predominant. The authors compared their evaluation of the patient’s cervical instability on preoperative imaging with the registered instability, registered on Swespine by the surgeon who treated the patient, and found that there was a discrepancy between the assessments (a moderate agreement of 0.48). This indicates that the knowledge of RA instability and deformity is not as widespread among spine surgeons as we might assume. This article is a reminder of current recommendations:

In C1–C2 vertical instability, decompression of the spinal cord is obtained either directly by resecting the odontoid process or indirectly through reduction of the deformity with C1–C2 facet spacers.
In subaxial instability, long instrumentations are preferred over short ones, with pedicle screws at the cranial and caudal points of the fixation C2 to Th2–3 for example. The use of laminar hooks should be avoided.

Continuous education and highlighting of publications on treatment guidelines are needed to preserve high-quality surgical treatment of cervical RA instabilities and deformities in future, especially as this group of patients will be less common with modern medical therapy.

**CONCLUSION**

To aim for the wide spread high-quality surgical treatment of this complex patient population throughout a nation, continuous education is of outmost importance. In situ fusion of RA patients with vertical instability without decompression or reduction of the deformity will not result in improvement of the myelopathy. Laminar hooks as anchors should be avoided as they may cause devastating complications. Patients with subaxial instability have a higher risk of decease.

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**Conflicts of interest**

There are no conflicts of interest.

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