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ORIGINAL ARTICLE

Neurologic Outcome of Surgical and Conservative Treatment of Rheumatoid Cervical Spine Subluxation: A Systematic Review

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Objective. **Rheumatoid arthritis commonly involves the upper cervical spine and can cause significant neurologic morbidity and mortality. However, there is no consensus on the optimal timing for surgical intervention: whether surgery should be performed prophylactically or once neurologic deficits have become apparent.**

Methods. **A systematic review of the literature was performed to analyze neurologic outcome (Ranawat) and survival time (Kaplan-Meier) after surgical or conservative treatment using the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) and GRADE (Grading of Recommendations, Assessment, Development and Evaluation system) criteria.**

Results. **Twenty-five observational studies were selected. No randomized controlled trials (RCTs) could be found. All of the studies had a high risk of bias. Twenty-three studies reported the neurologic outcome after surgery for 752 patients. Neurologic deterioration rarely occurred in Ranawat I and II patients. Ranawat III patients did not fully recover. The 10-year survival rates were 77%, 63%, 47%, and 30% for Ranawat I, II, IIIA, and IIIB, respectively. The Ranawat IIIB patients had a significantly worse outcome. Another 185 patients treated conservatively were described in 7 studies. Neurologic deterioration rarely occurred in Ranawat I patients, but was almost inevitable in Ranawat II, IIIA, and IIIB patients. The Kaplan-Meier analysis showed a 10-year overall survival rate of 40%.**

Conclusion. **There are no RCTs that compared surgery with conservative treatment. In observational studies, surgical neurologic outcomes were better than conservative treatment in all patients with cervical spine involvement, and in asymptomatic patients with no neurologic impairment (Ranawat I) the outcomes were similar; however, the evidence is weak. Survival time of surgical and conservative treatment could not be compared.**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects synovial joints. Immunologic dysfunction results in hypertrophy of the synovial tissue, causing erosion of the articular cartilage and subchondral bone (1,2). Surrounding supportive structures are also weakened, resulting in axial instability. In particular, in the atlantoaxial complex of the upper cervical spine (C-spine), RA can cause degeneration of these ligaments, leading to laxity, instability, and subluxation of the vertebral bodies in 17–85% of cases (3–5). In the majority of cases, these radiologic abnormalities remain asymptomatic for years, but patients with progressive upper C-spine involvement nonetheless do run the risk of severe neurologic complications or even sudden death during conservative treatment with disease-modifying antirheumatic drugs (DMARDs). Once neurologic deficits occur, progression seems inevitable, although the speed of decline is highly variable. The first signs and symptoms are pain at the back of the head caused by compression of the greater occipital nerve (Arnold's neuralgia), followed by sensory and eventually motor loss of strength in the arms and legs (5). It is hypothesized that repeated minor spinal cord traumata result in neuronal oligodendroglial cell death and spinal cord atrophy (6). On the basis of findings of radiologic surveys, the prevalence of progressive cervical subluxation is high, reportedly ranging from 43% to 80% (7).

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The role of C-spine surgery in the treatment of asymptomatic patients with RA remains controversial (1). The timing of an operation for cervical instability in RA has been discussed recently. Opinions and recommendations regarding early prophylactic surgical intervention differ and are only based on retrospective studies (8,9). The primary surgical objectives are to relieve neural compression by reduction of subluxation or direct decompression, and/or achieve stabilization of affected segments and reduce pannus formation. Generally accepted indications for surgical intervention include atlantoaxial subluxation (AAS) with intractable pain and/or neurologic deficits, severe vertical translocation with compromise of the vertebral artery, or evidence of increased signal intensity within the spinal cord on T1-weighted magnetic resonance imaging sequences (1). Some studies showed a possible decrease in AAS by active conservative treatment (10,11) and antirheumatic drugs with DMARDs and biologics (12,13). Active conservative treatment includes not only medical treatment, but also patient education, physical training of the deep muscles, and collars.

Our hypothesis is that surgical treatment of patients with C-spine involvement without neurologic signs and symptoms is more effective than (active) conservative treatment and delaying surgery until (severe) neurologic deficits develop. The main objective of this systematic review was to evaluate the neurologic outcome and survival of patients after surgery compared with conservative treatment.

MATERIAL AND METHODS

This systematic review was performed according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria for a systematic, standardized, and detailed approach (14), with recommendations by the Grading of Recommendations, Assessment, Development and Evaluation system (GRADE) (15,16).

Search strategy. PubMed and EMBase were searched using the following keywords (medical subject headings terms): rheumatoid arthritis, cervical spine, atlantoaxial, subluxation, surgery, surgical treatment, fixation, natural course, and conservative treatment. Besides these criteria, the surgical technique should fulfill the current criteria of craniocervical stabilization. The full search strategy is available upon request from the corresponding author. References of retrieved articles and relevant overview articles were checked to identify additional studies. Articles were also found in the authors' own files.

Study selection. Two reviewers (JFCW and WCP) independently checked the title, keywords, and abstract to identify eligible articles. A consensus meeting was held to discuss disagreements. All types of studies (randomized, prospective, retrospective, case–control) were eligible for inclusion. Reports were included if they met the following inclusion criteria: 1) RA population, 2) C-spine, 3) surgical or conservative treatment, 4) followup period reported, 5) neurologic outcome classified according to Ranawat or clear description of the neurologic status with baseline and followup measurements, and 6) mortality reported. In unclear cases, the final decision was made on the basis of the entire study. All types of surgical fixation techniques were included. Conservative treatment included physical therapy, cervical collars, active physical treatment, and rheumatic drugs.

Neurologic classification (Ranawat). There are various classifications to describe the severity of neurologic impairments as a result of rheumatic inflammatory disease. The most commonly used and validated classifications consist of the Ranawat classification (17) and the Myelopathy Disability Index (MDI) (18). The Ranawat classification consists of 3 classes and is the most commonly used scale. Class I patients have no neurologic deficits, class II patients have subjective weakness with hyperreflexia and/or dysesthesia, and class III patients have objective findings of weakness and longtract signs (IIIA: able to walk, IIIB: quadriparetic and unable to walk, bedridden, or requires the use of a wheelchair). The MDI is a validated questionnaire consisting of 10 functional items derived from the Health Assessment Questionnaire. However, the MDI is not commonly used in clinical practice and the literature. For this review, the Ranawat classification was used as a prognostic and outcome variable. If studies described the neurologic status of the patients with the possibility to transpose this to the Ranawat scale, those studies were also selected. The neurologic outcome for the different Ranawat subgroups of both surgical and conservative treatment of patients with C-spine involvement (especially AAS) is described.

Outcome (mortality). To analyze the mortality rates for each Ranawat subgroup, Kaplan-Meier survival analyses were performed. Studies for these survival analyses had to meet the following requirements: the followup time was registered for all of the patients (dead or alive), and only the patients with a Ranawat class at baseline and during followup were used in the Kaplan-Meier analyses. All causes of death were taken into account.

Methodologic quality and data extraction. Although observational studies do not provide valid evidence of the effectiveness of interventions, we assessed the quality of the observational studies to identify flaws in the design of the studies. Checklists for cohort and case–control studies recommended by the Dutch Cochrane Centre (Cochrane Collaboration) were used for quality assessment of the studies (19). There was no evidence available regarding a scale of quality using this checklist. Data concerning study population (age, sex, Ranawat at baseline), outcome (Ranawat during followup and survival/mortality), intervention (surgical or conservative treatment), and followup were independently extracted by 2 reviewers (JFCW, WCP). Data on homogeneous patient populations were analyzed. Statistical pooling was performed using SPSS, version 11.0 statistical software (SPSS, Chicago, IL). The GRADE system was used to offer recommendations for the management of this patient population by performing a sequential assessment of the quality of evidence, followed by assessment of the balance between benefits and risks (15).

Table 1. Results of the quality assessment (Dutch Cochrane Collaboration Checklists)

Author, year (ref.)	Patients defined	Absence of selection bias	Treatment defined	Appropriate outcome measurement	Blinded outcome	Sufficient followup time	No selective loss to followup	Groups comparable confounding factors	Overall quality (max. 8)
Casey et al, 1996 (20)	+	+	+	+	–	+	+	+	7
Sandhu et al, 2003 (21)	+	+	+	+	–	+	+	–	6
Tanaka et al, 2005 (22)	+	–	+	+	–	+	+	+	6
Omura et al, 2002 (23)	+	–	+	+	–	+	+	–	5
Matsuyama et al, 2005 (24)	+	–	+	+	–	+	+	–	5
Matsunaga et al, 2000 (25)	+	–	+	+	–	+	+	–	5
Matsunaga et al, 2003 (26)*	+	–	+	+	–	+	+	–	5
Nannapaneni et al, 2005 (27)	+	–	+	+	–	+	+	–	5
Mizutani et al, 2002 (28)	+	–	+	+	–	+	+	–	5
Ronkainen et al, 2006 (29)	+	–	+	+	–	+	+	–	5
Thompson and Meyer, 1985 (30)	+	–	+	+	–	+	+	–	5
Eyres et al, 1998 (31)	+	–	+	+	–	+	+	–	5
Boden et al, 1993 (32)	+	–	+	+	–	+	+	–	5
Crockard et al, 1986 (33)	+	–	+	+	–	+	+	–	5
Clark et al, 1989 (34)	+	–	+	+	–	+	+	–	5
Santavirta et al, 1991 (35)	+	–	+	+	–	+	+	–	5
Chan et al, 1992 (36)	+	–	+	+	–	+	+	–	5
Larsson and Toolanen, 1986 (37)	+	–	+	+	–	+	+	–	5
Christensson et al, 2000 (8)	+	–	+	+	–	–	+	–	4
Moskovich et al, 2000 (45)	+	–	+	+	–	+	–	–	4
Van Asselt et al, 2001 (39)	+	–	+	–	–	+	+	–	4
Schmitt-Sody et al, 2008 (40)	+	–	+	+	–	+	–	–	4
Falope et al, 2002 (41)	+	–	+	–	–	+	+	–	4
Sunahara et al, 1997 (42)	+	–	+	+	–	+	–	–	4
Fujiwara et al, 2000 (43)	+	–	+	+	–	+	–	–	4
Grob et al, 1999 (44)	+	–	+	–	–	+	+	–	4

* Same observational study as reported by Matsunaga et al (25).

RESULTS

Study selection. In total, 1,598 references were identified in the literature search; 1,540 were excluded on the basis of the abstract, title, and keywords. Hard copies of 58 articles were screened, resulting in 25 original studies that met the inclusion and exclusion criteria (8,20–44).

Description of study characteristics. We could not find any randomized controlled trials (RCTs). There were 25 observational studies: 2 prospective studies and 23 retrospective studies (1 case–control). Eighteen studies described surgical treatment alone, 5 described both surgical and conservative treatment, and 2 described conservative treatment only. One observational study was described in 2 studies, and both are shown in Table 1 (25,26). The methodologic quality of the studies is summarized in Table 1. Twenty-two of the 25 studies had a quality score of 4 or 5 of 8, reflecting low methodologic quality and a high risk of bias.

Outcome of surgery: neurologic outcome (Ranawat classification). In Tables 2 and 3, relevant data on the selected studies are shown with the baseline and postop-

Table 2. Characteristics of the studies describing surgical treatment*

Author, year (ref.)	Type of study	N	Age, years†	Sex, F:M	Followup, months‡
Thompson and Meyer, 1985 (30)	Retrospective	12	53 (25–68)	10:2	36 (7–84)
Crockard et al, 1986 (33)	Retrospective	14	58 (19–78)	11:3	14.6 (6–48)
Larsson and Toolanen, 1986 (37)	Retrospective	29	54 (29–72)	20:9	12–60
Clark et al, 1989 (34)	Retrospective	41	57 (34–82)	36:5	40 (23–74)
Santavirta et al, 1991 (35)	Retrospective	38	56 (35–77)	30:8	>120
Chan et al, 1992 (36)	Retrospective	19	54 (26–78)	14:5	60 (4–120)
Boden et al, 1993 (32)	Retrospective	35	60 (35–79)	21:14	84 (24–192)
Casey et al, 1996 (20)	Prospective	134	63	110:24	6
Eyres et al, 1998 (31)	Retrospective	26	62 (32–82) 75 (66–88)	21:5	24–78
Grob et al, 1999 (44)§	Retrospective	39	63 (47–81)	32:7	41.5 (25–66)
Christensson et al, 2000 (8)	Retrospective	83	65 (36–81)	61:22	7 (1–17)
Moskovich et al, 2000 (45)	Retrospective	92	62 (12–83)	119:31	6
Matsunaga et al, 2000 (25)	Retrospective	16	65	13:3	120
Van Asselt et al, 2001 (39)§	Retrospective	55	67 (42–84)	46:9	3–24
Omura et al, 2002 (23)	Retrospective	11	55 (43–70)	11:0	39.8 (14–60)
Mizutani et al, 2002 (28)	Retrospective	10	74	9:1	46.8
Falope et al, 2002 (41)	Retrospective	25	64 (36–80)	31:9	36 48
Sandhu et al, 2003 (21)	Retrospective	21	65 (47–83)	14:7	25.5 (17–61)
Matsunaga et al, 2003 (26)	Case–control	19	65	13:3	120
Matsuyama et al, 2005 (24)	Retrospective	20	59 (52–66)		60 (32–192)
Nannapaneni et al, 2005 (27)	Retrospective	32	67	25:7	39
Tanaka et al, 2005 (22)	Retrospective	26	53 ± 5.7	6:20	240–288
Ronkainen et al, 2006 (29)	Retrospective	86	62 ± 9.0		90 (60–118)
Schmitt-Sody et al, 2008 (40)	Retrospective	34	62 ± 10	23:5	54 ± 26

* The pre- and postoperative Ranawat classification are shown.
† Values are the mean (range), mean, or mean ± SD.
‡ Values are the mean (range), range, mean, or mean ± SD.
§ These studies are excluded because of lack of data, or because the postoperative Ranawat classification was not listed.

erative Ranawat classes. The total number of surgically treated patients was 852. The postoperative Ranawat classification was lacking for 100 (12%) of these patients. For the other 752 patients (88%), the preoperative and postoperative Ranawat classifications were reported (preoperative: 190 Ranawat I, 166 Ranawat II, 223 Ranawat IIIA, and 173 Ranawat IIIB). Mean ages for the different Ranawat classes could not be calculated. The mean postoperative followup period for determining the neurologic outcome was 45 months (range 1–288 months). In Table 3, the change in Ranawat class during followup is specified and compared with the baseline status. These results are shown in Figure 1. Almost all of the patients with Ranawat I (182 [96%]) showed no deterioration in their neurologic status, and only 4 patients (2%) deteriorated to class IIIA or IIIB. In fact, 88 patients (53%) with Ranawat II improved to grade I, 66 patients (40%) did not change, and only 12 patients (7%) deteriorated to class III. One hundred twenty-five Ranawat IIIA patients (56%) improved 1 or 2 Ranawat classes after surgical treatment, 77 patients (35%) were unchanged, and 21 patients (9%) became bedridden or required a wheelchair (IIIB). Thirty-seven Ranawat IIIB patients (21%) improved at least 2 classes after surgical fixation, 65 patients (38%) improved to Ranawat IIIA and became ambulant, and the remainder (71 [41%]) did not significantly improve and remained severely neurologically disabled (IIIB) (Figure 1).

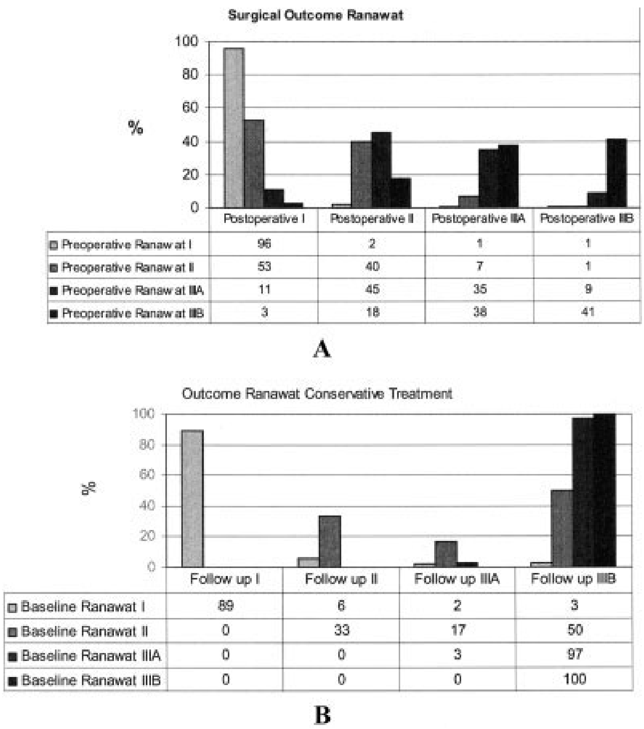
Outcome of surgery: mortality. Data on 509 patients (60%) were available for the survival/mortality analysis (preoperative: 107 Ranawat I, 68 Ranawat II, 160 Ranawat IIIA, and 174 Ranawat IIIB). The outcomes of Ranawat I and II did not exhibit a statistically significant difference ($\alpha < 0.3$). The mortality for Ranawat I compared with IIIA was significantly lower ($\alpha < 0.02$). There was no statistically significant difference in mortality between Ranawat II and IIIA. The mortality rate for Ranawat IIIB was significantly worse compared with all of the other Ranawat classifications ($\alpha < 0.0001$). The Kaplan-Meier graphs are shown in Figure 2. After 60 months, 13%, 20%, 26%, and 43% of the patients died in the Ranawat groups I, II, IIIA, and IIIB, respectively. After 120 months, these percentages increased to 23%, 37%, 53%, and 70%, respectively.

Outcome of conservative treatment: neurologic outcome (Ranawat classification). The 7 studies describing conservatively treated patients and their characteristics are shown in Table 4. A total of 185 patients were treated conservatively. A clear description of the conservative treatment was often not described. The mean age was 51

Table 3. Postoperative (postop) change in Ranawat classification during followup compared with the baseline Ranawat class

Author, year (ref.)	Preoperative Ranawat I				Preoperative Ranawat II				Preoperative Ranawat IIIA				Preoperative Ranawat IIIB			
	Postop I	Postop II	Postop IIIA	Postop IIIB	Postop I	Postop II	Postop IIIA	Postop IIIB	Postop I	Postop II	Postop IIIA	Postop IIIB	Postop I	Postop II	Postop IIIA	Postop IIIB
Thompson and Meyer, 1985 (30)	6	0	0	0	2	2	0	0	1	0	0	0	0	0	0	1
Crockard et al, 1986 (33)	0	0	0	0	1	0	0	0	0	11	0	1	0	0	2	0
Larsson and Toolanen, 1986 (37)	16	0	0	0	4	0	0	0	6	0	3	0	0	0	0	0
Clark et al, 1989 (34)	19	0	0	0	6	15	0	0	0	5	0	0	0	0	0	0
Santavirta et al, 1991 (35)	26	2	0	2	2	0	0	0	1	1	0	0	0	2	0	2
Chan et al, 1992 (36)	9	0	0	0	3	1	0	0	0	0	4	0	0	0	0	2
Boden et al, 1993 (32)	0	0	0	0	9	0	0	0	1	1	1	2	0	7	7	7
Casey et al, 1996 (20)	0	0	0	0	0	0	0	0	6	40	18	11	4	7	11	17
Eyres et al, 1998 (31)	7	0	0	0	2	9	0	0	1	3	1	0	1	2	0	0
Christensson et al, 2000 (8)	47	0	0	0	19	4	0	0	3	7	6	0	0	0	0	0
Moskovich et al, 2000 (45)	2	1	0	0	8	12	6	1	2	13	22	2	1	2	8	10
Moskovich et al, 2000 (45)*	0	0	0	0	4	3	2	0	1	14	12	1	0	0	7	1
Matsunaga et al, 2003 (26)	0	0	0	0	2	0	0	0	1	6	1	1	0	1	0	2
Omura et al, 2002 (23)	0	0	0	0	0	3	0	0	0	0	0	0	0	0	3	5
Mizutani et al, 2002 (28)	2	0	0	0	0	0	0	0	0	4	1	0	0	0	1	2
Falope et al, 2002 (41)	0	0	0	0	0	5	0	0	0	0	9	0	0	0	6	5
Sandhu et al, 2003 (21)	4	0	0	0	2	2	0	0	0	6	1	0	0	0	5	1
Matsuyama et al, 2005 (24)	0	0	0	0	0	0	0	0	0	0	0	0	0	6	8	6
Nannapaneni et al, 2005 (27)	0	0	0	0	0	0	0	0	0	0	0	0	0	4	14	6
Nannapaneni et al, 2005 (27)*	0	0	0	0	0	0	0	0	0	0	0	0	0	2	20	9
Nannapaneni et al, 2005 (27)*	0	0	0	0	0	0	0	0	0	0	0	0	0	5	19	5
Tanaka et al, 2005 (22)	23	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Tanaka et al, 2005 (22)*	23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ronkainen et al, 2006 (29)	14	1	2	0	21	10	5	0	3	2	3	2	0	0	0	3
Schmitt-Sody et al, 2008 (40)	7	0	0	0	7	3	0	0	0	1	6	2	0	0	0	2
Total: 752	182	4	2	2	88	66	11	1	25	100	77	21	6	31	65	71

* These studies had several more followup Ranawat measurements.



	Postoperative I	Postoperative II	Postoperative IIIA	Postoperative IIIB
Preoperative Ranawat I	96	2	1	1
Preoperative Ranawat II	53	40	7	1
Preoperative Ranawat IIIA	11	45	35	9
Preoperative Ranawat IIIB	3	18	38	41

	Follow up I	Follow up II	Follow up IIIA	Follow up IIIB
Baseline Ranawat I	89	6	2	3
Baseline Ranawat II	0	33	17	50
Baseline Ranawat IIIA	0	0	3	97
Baseline Ranawat IIIB	0	0	0	100

Figure 1. **A**, The percent change in Ranawat classification during followup after surgical treatment is shown, stratified according to the preoperative Ranawat class. **B**, The change in Ranawat classification of conservatively treated patients in the different baseline Ranawat classes is shown.

years. The mean followup time was 80 months (range 12–288 months). In total, 169 patients (91%) had a registered Ranawat classification at baseline and during followup (112 Ranawat I, 6 Ranawat II, 37 Ranawat IIIA, and 14 Ranawat IIIB). One hundred Ranawat I patients (89%) remained Ranawat I, whereas 7 patients (6%) deteriorated to class II and 5 patients (5%) deteriorated to class III. Patients classified as Ranawat II did not improve (2 [33%] stayed in class II), and 4 of 6 patients deteriorated to class III during followup (1 [17%] deteriorated to class IIIA and 3 [50%] decreased to class IIIB). Ranawat IIIA or IIIB patients did not improve, and almost all of the patients deteriorated during the followup (36 [97%] of 37 Ranawat IIIA patients deteriorated to a bedridden or nonambulant class IIIB situation). Once patients were classified as Ranawat IIIA or IIIB, there was no chance of improvement and neurologic deterioration was almost inevitable (Table 4 and Figure 1).

Outcome of conservative treatment: mortality. Data on 97 patients (52%) were available for the survival analysis. In the rest of the cases, survival or mortality was unknown. In the graph in Figure 2, all of the different Ranawat classes were grouped together. The Kaplan-Meier analysis could not be stratified per Ranawat classification because of scarcity of data. After 60 months, 37% of the patients died. After 120 months, this percentage increased to 58%.

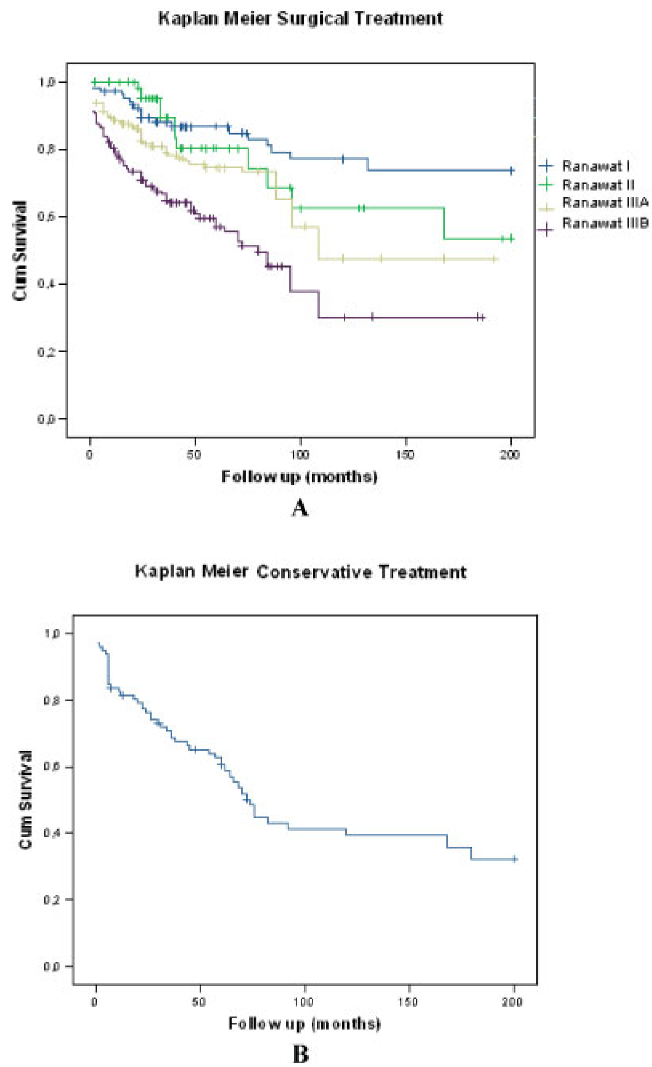


Figure 2. **A**, Kaplan-Meier survival plot for surgically treated patients in the different Ranawat classifications. Survival in Ranawat I was significantly better than IIIA ($\alpha = 0.02$) and IIIB ($\alpha = 0.000$). Ranawat II was not significantly worse than IIIA ($\alpha = 0.131$). Patients in Ranawat IIIB had a significantly worse outcome compared with those in I, II, and IIIA ($\alpha = 0.000$). The 10-year survival rates were 77%, 63%, 47%, and 30% for Ranawat I, II, IIIA, and IIIB, respectively. **B**, Kaplan-Meier survival graph for patients treated conservatively. Because of the scarcity of data, the survival graph could not be shown according to Ranawat classification. The overall 10-year survival rate was 40%. This Kaplan-Meier analysis consisted of 97 conservatively treated patients.

DISCUSSION

The literature has been systematically reviewed to evaluate the outcome for patients with mainly upper C-spine involvement as a result of RA after surgical and conservative nonoperative treatment. To our knowledge, this is the first systematic review of literature on this subject. No RCTs have been performed so far. This review included only observational studies (retrospective, prospective, case–control, case series) that used the Ranawat classification (or clear description of the neurologic status) at baseline and during the followup period. Twenty-five

Table 4. Characteristics of studies describing patients receiving conservative treatment

Author, year (ref.)	Type of study	No. of patients	Age, years*	Sex, M:F	Followup, months†	Baseline Ranawat class, no.	Followup Ranawat class, no.
Boden et al, 1993 (32)	Retrospective	7	59 (50–84)	1:6	84 (24–192)	I, 0	I, 0
						II, 2	II, 0
						IIIA, 3	IIIA, 2
						IIIB, 2	IIIB, 5
Sunahara et al, 1997 (42)	Retrospective	21	62.6 (43–69)	4:17	60 (36–84)	I, 0	
						II, 0	
						IIIA, 16	
						IIIB, 5	IIIB, 21
Fujiwara et al, 2000 (43)	Retrospective	91	43		60	I, 91	I, 81
						II, 0	II, 5
						IIIA, 0	IIIA, 2
						IIIB, 0	IIIB, 3
Omura et al, 2002 (23)	Retrospective	6	62 (47–74)	1:5	39.8 (14–62)	I, 0	I, 0
						II, 0	II, 0
						IIIA, 4	IIIA, 0
						IIIB, 2	IIIB, 6
Falope et al, 2002 (41)	Retrospective	15	65		(12–60)	I, 0	Unknown
						II, 2	
						IIIA, 3	
						IIIB, 9	
Matsunaga et al, 2003 (26)	Case–control	21		4:17	51 (12–96)	I, 0	I, 0
						II, 2	II, 0
						IIIA, 14	IIIA, 0
						IIIB, 5	IIIB, 21
Tanaka et al, 2005 (22)	Retrospective	24	52 ± 7.2	5:19	(240–288)	I, 22	I, 8
						II, 2	II, 5
						IIIA, 0	IIIA, 1
						IIIB, 0	IIIB, 0
					(96–144)	I, 22	I, 19
						II, 2	II, 4
						IIIA, 0	IIIA, 0
						IIIB, 0	IIIB, 0

* Values are the mean (range), mean, or mean ± SD.
† Values are the mean (range), mean, or (range).

studies were included (23 surgical studies and 7 studies on conservative treatment) to obtain an impression of the neurologic outcome (Ranawat classification) and mortality rate during followup. The methodologic quality of the majority of studies was poor (score of 4 or 5 of possible 8); therefore, most studies had a high risk of bias.

A total of 752 patients underwent surgical fixation for any of the possible rheumatic involvements of the C-spine, and their neurologic outcomes were evaluated according to the Ranawat classification. Different fixation or decompression procedures were used (anterior/posterior). The mean age of the group was 62 years. For patients with a preoperative Ranawat I or II classification, it was highly probable that they would remain in the same class or improve after surgery. Approximately half of all of the patients with a preoperative Ranawat IIIA classification improved 1 or 2 classes after surgical treatment. Once patients were classified as Ranawat IIIB, the chances of full recovery were small: 38% improved and became ambulant and 41% remained nonambulant after surgery.

For the Kaplan-Meier survival analyses, 509 (of 852) patients were eligible. The Kaplan-Meier survival analysis was stratified for Ranawat class. The approximate 10-year survival rates are 75% for Ranawat I, 65% for Ranawat II, 50% for Ranawat IIIA, and 30% for Ranawat IIIB. Ranawat IIIB patients had a significantly worse outcome compared with all of the other Ranawat classes after surgical treatment.

The review of the literature on conservative treatment of C-spine involvement by the rheumatic inflammatory process showed that very little is known about the neurologic outcome and mortality for this group of patients. Most studies lacked a clear description of the way patients were treated nonoperatively. The 7 studies included in this review contained only a few patients (n = 185 total patients). The mean age was 51 years. In total, 169 patients (91%) had a registered Ranawat classification at baseline and during followup, most of whom were Ranawat I (n = 112) and IIIA (n = 37). The majority of patients classified as Ranawat I at baseline did not deteriorate with conservative treatment during followup. Once patients were Ranawat II, IIIA, or IIIB at baseline, neurologic deterioration during followup was inevitable. The survival analysis of all conservatively treated patients (Ranawat I, II, IIIA, and IIIB) showed that in this relatively small group, there is a tendency that patients have a higher mortality rate.

Currently, surgical treatment of the C-spine for RA involvement is a relatively safe procedure with low morbidity and mortality rates, especially among patients with Ranawat I and II. However, patients classified as Ranawat I and II who are treated conservatively seem to have a good neurologic outcome and survival as well.

The functional results of surgery on nonambulatory patients with RA (Ranawat IIIB) are often disappointing, with high rates of postoperative morbidity and mortality (6). Once cervical myelopathy is established, mortality appears to be common for both surgical and conservative patients (6,20,27). Once patients are in group IIIA or IIIB, it cannot be expected that they will improve neurologically with conservative treatment. However, due to sparse data, the life expectancy of the conservatively treated patients could not be calculated per Ranawat classification. If Ranawat IIIA or IIIB patients are treated surgically, there is a chance of neurologic improvement. A large subset of patients with craniovertebral junction rheumatic myelopathy may reach Ranawat IIIB. Surgery (despite high morbidity and mortality) might be the best therapeutic option available to this subgroup of patients. Improvement of even one grade in Ranawat score from class IIIB to class IIIA has been suggested to be associated with an improvement in quality of life and survival (27). The strong likelihood of surgical complications, the poor survival, and the limited prospects for functional recovery of nonambulant patients make a strong case for earlier surgical intervention. At a late stage of disease, most patients will have irreversible cord damage (20,23). Several authors concluded that prophylactic atlantoaxial fusion is better than conservative treatment in their studies, but again, RCTs supporting these conclusions are lacking (9,20,22,23,40,43,46,47).

Operative stabilization of the rheumatoid C-spine in the presence or absence of a neurologic deficit for patients who have AAS and a posterior atlantoodontoid interval of 14 mm or less, patients who have AAS and at least 5 mm of basilar invagination, and patients who have subaxial subluxation and a sagittal diameter of the spinal canal of 14 mm or less is recommended by Boden et al (32). Maybe in the future, the incidence of AAS will decrease in the setting of a more aggressive pharmacologic treatment strategy aimed at remission and new medical therapies for RA. However, a study performed by Neva et al in 2006 (48) showed that many patients still develop atlantoaxial pathology as a result of RA. Should patients with RA be actively studied for AAS or other cervical instability, even when cervical symptoms are minor? This question cannot be answered with the available clinical evidence.

This review has several shortcomings. Only observational studies were identified, most of which had a retrospective study design with a high risk of selection bias and confounding. Most studies had small sample sizes and different followup periods; only one study included controls. An important difference with the surgical group is the mean followup period to determine neurologic outcome. The mean followup time for the surgical group was 45 months, compared with 80 months for the conservative treatment group. This may impact the results of the treatment outcomes. Publication bias is inevitable in observational studies and constitutes the main threat to the validity of meta-analysis of observational studies. The material of this systematic review has been collected mainly from surgically orientated studies, in which the decision not to operate has sometimes been based on the poor general condition (and prognosis) of the patient. By pooling all of the data, a large population that had been treated over time is described and the outcome gives an impression of the neurologic outcome and the mortality. However, the reported effects may be an overestimation of the true effects of surgery and conservative treatment as a result of publication bias. Because of the high grade of the selection and publication bias, the Kaplan-Meier graphs of the 2 treatment strategies cannot be compared directly. No conclusions could be drawn from the differences in survival.

This review of the literature shows that surgical neurologic outcomes were superior to conservative treatment in all of the patients, and in the patients who were asymptomatic (Ranawat I), surgically and conservatively treated patients had similar outcomes. However, the evidence is weak. Because of the scarcity of data, the survival time for the conservatively treated patients could not be presented in subgroups of patients with different Ranawat classifications. Therefore, a comparison between surgery and conservative treatment is not possible.

What is lacking is a prospective RCT that gives information about the outcome (Ranawat and survival) of surgically or conservatively treated patients with AAS without neurologic deficits (Ranawat I and II). In 2006, the first international multicenter RCT on this subject was started: The Delphi Trial—I(RCT)^2 (5).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Wolfs had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wolfs, Kloppenburg, Fehlings, van Tulder, Boers, Peul.

Acquisition of data. Wolfs, Peul.

Analysis and interpretation of data. Wolfs, Kloppenburg, Fehlings, van Tulder, Boers, Peul.

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