Heterotopic Ossification in Cervical Disk Surgery Is Still a Problem. What Are the Key Factors for a Solution?

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■ BACKGROUND: **The aim of our study was to determine the presence of heterotopic ossifications (HO) in a series of patients with cervical disk arthroplasty treated with different type of prosthesis, as well as to analyze the most suitable systems for diagnosis.**

■ METHODS: **A retrospective study of patients with cervical disk disease treated with cervical arthroplasty between May 2005 and December 2009, was performed. Patients were divided into 3 groups, depending on the prosthesis implanted: (Group A: Baguera prosthesis, Group B: ProDisc prosthesis, and Group C: PCM prosthesis). The presence of heterotopic ossifications was evaluated with both, simple radiology and computed tomography.**

■ RESULTS: **As a summary of the results on motion preservation, computed tomography scans showed that 63% of the cervical arthroplasties in Group A presented good mobility at the first check point (December 2010), whereas cervical arthroplasties in Group B and Group C had 74% and 65% severe motion restrictions, respectively (Grade III or Grade IV, according to McAfee classification). The differences between groups were statistically significant when comparing Groups A and B, and Groups A and C ($P < 0.05$), but there were no differences between Groups B and C ($P < 0.05$). At the second check point (December 2014), the good mobility was just preserved in the 26% of the disk replacements (all in Group A).**

■ CONCLUSIONS: **Our results showed that, although cervical disks provide optimal mid-term results, the incidence of HO seems to increase with time. Long term studies, with a larger sample size should be conducted to evaluate the appearance of HO and cervical motion after total disk replacement.**

INTRODUCTION

Cervical disk arthroplasty has been postulated in recent years as an alternative to cervical fusion with arthrodesis in the treatment of cervical radiculopathy and myelopathy, after conservative treatment has failed. It is known that the cervical arthrodesis provides good clinical and radiologic results[1]; however, this technique also could decrease the range of cervical motion and increase the risk of adjacent segment degeneration.[2] In addition, there are many studies that support the benefits of cervical disk arthroplasty against cervical fusion, increasing its popularity in recent years as an alternative to fusion.[3,4] Nevertheless, cervical arthroplasty is not exempt from risks such as the development of hematomas, hypersensitivity reactions, and the creation of heterotopic ossifications (HO), which lead to a reduction in motion. For this reason, some authors recommend long-term follow-up prospective studies to define the indications of this technique.[5] We sought to determine the presence of HO in our series of patients with cervical disk arthroplasty, depending on the type of prosthesis implanted, and to analyze the most suitable systems for diagnosis as well.

MATERIALS AND METHODS

A retrospective, single-center study of patients with cervical disk disease treated with cervical arthroplasty between May 2005 and December 2009 was performed. The objective was to evaluate the

Key words
- Anterior
- Cervical
- Cervical arthroplasty
- Discectomy
- Heterotopic ossification

Abbreviations and Acronyms
CT: Computed tomography
HO: Heterotopic ossifications

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Citation: World Neurosurg. (2016) 96:585-590.
http://dx.doi.org/10.1016/j.wneu.2016.08.078

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

Table 1. CT Scan Analysis Showing the Presence of HO in Each Group

Grade of HO	Total, *n* (%)	Group A, No. Patients (%)	Group B, No. Patients (%)	Group C, No. Patients (%)	*P* Value
Grade 0	6 (9.1%)	6 (22.2%)	_	_	A–B: <0.001 A–C: 0.001 B–C: nonsignificant
Grade I	13 (19.7%)	11 (40.7%)	2 (10.5)	_	
Grade II	15 (22.7%)	5 (18.5%)	3 (15.8%)	7 (35.0%)	
Grade III	28 (42.4%)	4 (14.8%)	11 (57.9%)	13 (35.0%)	
Grade IV	4 (6.1%)	1 (3.7%)	3 (15.8%)	_	
Total no. patients (%)	66 (100%)	27 (40.9%)	19 (28.7%)	20 (30.3%)	

CT, computed tomography; HO, heterotopic ossifications.

presence of HO, both by simple radiology and computed tomography (CT). The data were analyzed at 2 specific check points, a first analysis carried out in December 2010 and a second one at the end of 2014 in the same group of patients.

The patients who were included in the review met the following criteria: 1) symptomatic cervical disk disease diagnosed by magnetic resonance imaging, caused by herniated disk, spondylosis, or a loss of disk height at 1 or 2 levels; 2) patients who had not responded to traditional treatment after at least 16 weeks; 3) between 35 and 75 years of age; and 4) written informed consent provided for surgery.

The exclusion criteria were as follows: 1) presence of disease at 3 or more levels; 2) allergy to any component of the disk prosthesis; 3) posttraumatic cervical deformity; 4) cervical instability defined by the presence of a translation greater than 3 mm; 5) facet joint degeneration; 6) osteoporosis; 7) active infection; 8) tumor; or 9) pregnancy.

The patients underwent surgery in our institution according to the implant authorized at that time. In our retrospective analysis of consecutive cases, the patients were classified into 3 groups, depending on the type of prosthesis that was implanted. The 3 models of disk prosthesis studied were Baguera (Spineart Geneva SA, Geneva, Switzerland), ProDisc (DePuy Synthes Spine, Raynham, Massachuetts, USA), and PCM (NuVasive, San Diego, California, USA). The patients who were operated with Baguera were assigned to Group A, the patients with ProDisc to Group B, and patients with PCM to Group C.

The presence of HO was evaluated on plain radiographs and CT by 3 professionals (a radiologist, an orthopedic surgeon, and a spine surgeon) blinded to the patient who used the classification of McAfee[6] for grading. Grading was as follows:

- Grade 0: no HO;
- Grade I: islands of bone not within the margins of the disc and not interfering with motion;
- Grade II: bone within the margins of the disc but not blocking motion;
- Grade III: bone within the margins of the disc and interfering with motion of the prosthesis; and
- Grade IV: bony ankyloses.

Statistical Analysis

The quantitative variables are presented as mean and standard deviation. In those cases that do not follow a normal distribution, the median and interquartile range was given. Testing was performed with the Kolmogorov-Smirnov test. The qualitative data are presented by frequency distribution. The χ^2 test was used to analyze the association of qualitative variables. In the event that the number of cells with expected values was less than 5 and greater than 20%, the Fisher exact test was applied. The comparison of quantitative variables was performed with the Mann-Whitney U test for the independent samples due to the sample

Table 2. X-ray Analysis Showing the Presence of HO in Each Group

Grade of HO	Total, *n* (%)	Group A, No. Patients (%)	Group B, No. Patients (%)	Group C, No. Patients (%)	*P* Value
Grade 0	22 (33.3%)	18 (66.7%)	4 (21.1%)	_	A–B: <0.001 A–C: 0.001 B–C: nonsignificant
Grade I	14 (21.2%)	4 (14.8%)	4 (21.1%)	6 (30.0%)	
Grade II	11 (16.7%)	1 (3.7%)	7 (36.8%)	3 (15.0%)	
Grade III	16 (24.2%)	1 (3.7%)	4 (21.1%)	11 (55.0%)	
Grade IV	3 (4.5%)	3 (11.1%)	_	_	
Total no. patients (%)	66 (100%)	27 (40.9%)	19 (28.7%)	20 (30.3%)	

HO, heterotopic ossifications.

Table 3. Comparison of Cervical Motion Grade Among Groups

Grade of HO	Total, *n* (%)	Group A, No. Patients (%)	Group B, No. Patients (%)	Group C, No. Patients (%)	*P* Value
Grade 0–I	19 (28.8%)	17 (63.0%)	2 (10.5%)	–	A–B: <0.001 A–C: 0.001 B–C: nonsignificant
Grade II	15 (22.7%)	5 (18.5%)	3 (15.8%)	7 (35.0%)	
Grade III–IV	32 (48.5%)	5 (18.5%)	14 (73.7%)	13 (65.0%)	
Total No of patients (%)	66 (100%)	27 (40.9%)	19 (28.7%)	20 (30.3%)	

HO, heterotopic ossifications.

size. The interrelations of quantitative variables were calculated by the Spearman correlation coefficient. The data were analyzed with the SPSS package, version 20.0 (IBM SPSS Statistics for Windows, IBM Corp, Armonk New York, USA). Those values of P lower than 0.05 were considered statistically significant.

RESULTS

A total of 66 consecutive patients who underwent cervical disk replacement between May 2005 and May 2009 were evaluated. The series was composed of 41 male (62%) and 25 female (38%) patients, with a mean age of 47.2 ± 11.1 years (range, 37–74 years). Fifty-four patients (82%) underwent 1-level surgery and 12 (18%) a 2 consecutive cervical levels surgery.

Patients were distributed into 3 groups: Group A ($n = 27$), Group B ($n = 19$), and Group C ($n = 20$). There were no statistically significant differences in the age, sex, or levels of surgery distribution among groups ($P > 0.05$). We found also no relationship between the number of levels treated and the grade of HO ($P > 0.05$).

The mean blood loss was 38 mL (range, 33–45 years), with no statistically significant differences among groups ($P > 0.05$). No relation between bleeding and grade of HO ($P > 0.05$) was observed. The mean follow-up was 30.2 ± 9.2 months (range, 12–50 months) in the analysis conducted in 2010. In Group A, the mean follow-up was 26.2± 2.9 months (range, 20–30 months), in Group B, 33.7 ± 13.2 months (range, 12–50 months), and in Group C, 33.2 ± 6.5 months (range, 18–48 months). There were not statistical differences between Group B and C; however, this difference was statistically significant compared with Group A ($P < 0.05$). The results obtained with the CT scan analysis showed the presence of HO in all groups (Table 1). The analysis of X-rays in the same patients showed that the results between Groups A and B and Groups A and C were statistically significant ($P < 0.05$), whereas there were no statistical differences between Groups B and C ($P > 0.05$) (Table 2). These data showed that 43.9% of the intervertebral levels had the same degree of HO according to the classification of McAfee in both CT and conventional radiology; however, 56.1% had greater scores in this classification with CT than with conventional radiology and therefore showed greater levels of HO in CT than in simple radiology images. The differences between the 2 radiologic methods were statistically significant ($P < 0.05$).

With regard to cervical motion, and based on the greatest quality data through the CT scan, HO in grade 0 and I were found in 28.8% of the patients (17 in Group A, and 2 in Group B). Grade II was identified in 22.7% of implanted prosthesis (5 in Group A, 3 in Group B and 7 in Group C). Grade III or IV were found in 48.5% of cervical prostheses, being 5 from Group A, 14 from Group B and 13 from Group C (Table 3). Differences were statistically significant among groups ($P < 0.05$) for the nonrestricted motion (HO Grade 0 and I), and for the total restricted range of motion (HO Grade III and IV), whereas there were no differences in partially reduced motion (HO Grade II). In summary, 63% of Group A cervical arthroplasties showed good motion at the first study check point, whereas Group B and Group C had 74% and 65%, respectively, severe motion restrictions due to the high degree of HO.

A second checkpoint of analysis was carried out at the end of 2014.The mean follow-up period was 79.4 ± 9.16 months

Table 4. Presence of HO in Each Group, Measured by CT at the Second Checkpoint (79 Months' Follow-Up)

Grade of HO	Total, *n* (%)	Group A, No. Patients (%)	Group B, No. Patients (%)	Group C, No. Patients (%)	*P* Value
Grade 0	2 (3.0%)	2 (7.4%)	–	–	A–B: <0.001 A–C: 0.001 B–C: nonsignificant
Grade I	6 (9.1%)	6 (22.2%)	–	–	
Grade II	19 (28.8%)	9 (33.3%)	2 (10.5%)	8 (40.0%)	
Grade III	26 (39.4%)	6 (22.2%)	12 (63.1%)	8 (40.0%)	
Grade IV	15 (22.7%)	5 (18.5%)	6 (31.6%)	47. (20.0%)	
Total no. patients (%)	66 (100%)	27 (40.9%)	19 (28.7%)	20 (30.3%)	

HO, heterotopic ossifications; CT, computed tomography.

Table 5. Presence of HO in Each Group, Measured by X-rays at the Second Checkpoint (79 Months' Follow-Up)

Grade of HO	Total, *n* (%)	Group A, No. Patients (%)	Group B, No. Patients (%)	Group C, No. Patients (%)	*P* Value
Grade 0	6 (9.1%)	6 (22.2%)	–	–	A–B: <0.001 A–C: 0.001 B–C: nonsignificant
Grade I	7 (10.6%)	7 (25.9%)	–	–	
Grade II	11 (16.7%)	4 (14.8%)	3 (15.8%)	4 (20.0%)	
Grade III	18 (27.3%)	7 (25.9%)	5 (26.3%)	6 (30.0%)	
Grade IV	24 (36.4%)	3 (11.1%)	11 (57.9%)	10 (50.0%)	
Total no. patients (%)	66 (100%)	27 (40.9%)	19 (28.7%)	20 (30.3%)	

HO, heterotopic ossifications.

(range, 60–98 months). As for the first check point, the follow-up length was statistically different in Group A compared with Groups B and C ($P < 0.05$). The assessment of CT results and the results observed in HO analysis with the X-rays are shown in Tables 4 and 5, respectively. Figures 1 and 2 show examples of CT and X-ray images. The differences between groups were statistically significant when we compared Groups A and B and A and C ($P < 0.05$), but there were no differences between Groups B and C.

DISCUSSION

Unlike cervical fusion, cervical disk prosthesis restore and maintain motion of the treated segment and decrease the number of complications related to arthrodesis, such as degeneration of the adjacent segment, morbidity of the autologous bone graft's site, and potential infections when using grafts coming from hospital's bone bank.[7] The indications and contraindications of cervical disk prosthesis have been well reported in the literature[8,9]; however, because of the variety of available cervical artificial disks, characteristics, such as type of joint, amount of bone removal for accurate placement, contact surface, arc of motion, footprint, and primary and secondary fixation, must be taken into account. The surgeon should indicate the best prostheses for each patient depending on the aforementioned features.[10]

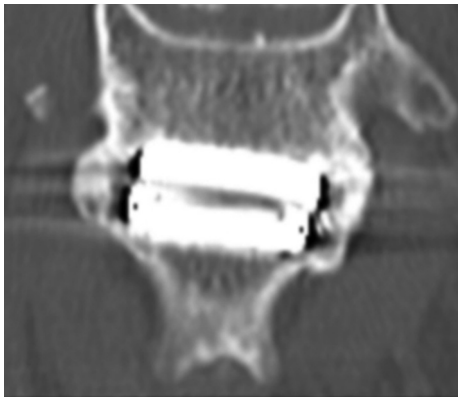

Figure 1. Computed tomography scan image of Group C cervical prosthesis at the second check point (79 months' follow-up).

The implant selection before performing a cervical disk surgery is a key factor, because placement is not the only factor that determines its feasibility. Therefore, it is necessary to take into account other factors such as biomechanics of the implants, degree and levels of instability, or patient's anamnesis (age, sex, comorbidities such as osteoporosis, smoking, etc.).[11]

The range of motion will be defined by the characteristics of the prosthesis, and the surgical technique. Recent studies supporting the benefits of cervical disk arthroplasty, over cervical fusion have contributed to an increase on its popularity[3,4]; however, cervical disk arthroplasty also encompasses risks. These risks include complications derived from the anterior approach itself and from its definitive placement between both endplates. The complications related to the implantation of the prosthesis can be divided into early complications, such as increased cervical pain, retropharyngeal hematoma, or vertebral fracture, and late complications, which include migration, failure of the prosthesis, postoperative kyphosis, adjacent segment degeneration, hypersensibility reactions, or HO.[12] Therefore, as discussed previously, some authors recommend the performance of long-term studies to confirm whether cervical disk arthroplasty grants better outcomes than anterior cervical fusion.[5] The adverse effects of cervical disk arthroplasty include late migration, fusion of device, or HO, which causes reduction in motion at different degrees.[13]

HO is defined as the formation of mature lamellar bone in nonskeletal soft-tissue areas.[14] Although the true etiology of HO is unknown, its incidence is greater in male patients, those with ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, spinal cord and brain injuries, and patients undergoing large joint arthroplasties.

The first reference related to HO after cervical disk arthroplasty was posted by Parkinson in 2005.[15] The patient described in this case report was a woman with a cervical disk prosthesis located between C5 and C6 that showed a limited motion due to bone formation around the implant. Subsequently, there have been more cases published about this complication. The incidence of HO is variable. It ranges from the total absence of spontaneous mergers after two years follow up, as described by Heller et al.,[3] to a 67% posted by Beaurain et al.[16] The differences between them make us pay attention to the guidelines on nonsteroidal anti-inflammatory drugs prescribed in every case after surgery.

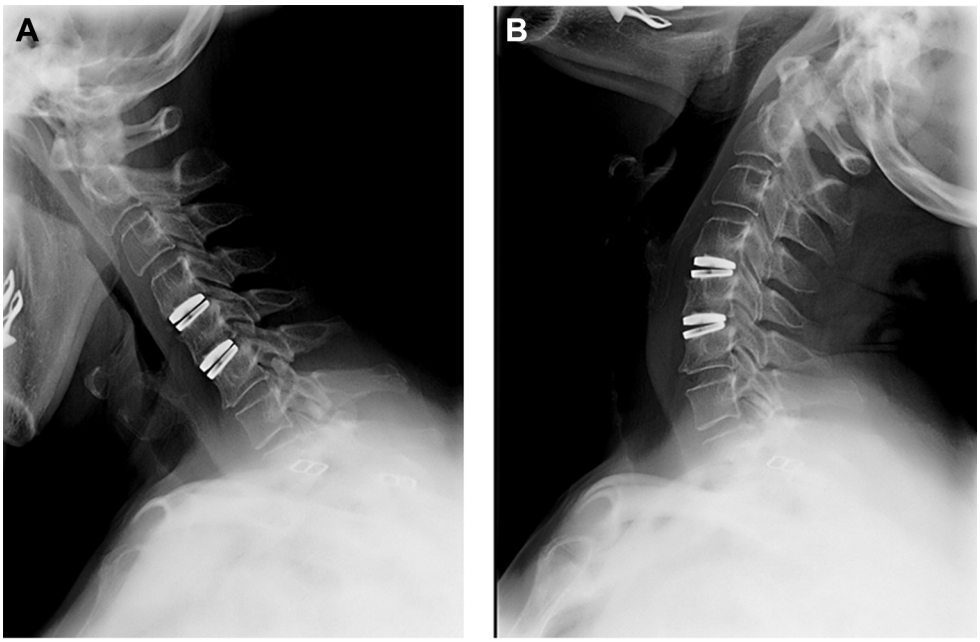

Figure 2. X-ray lateral views of Group A cervical prosthesis at the second check point (79 months' follow-up). (**A**) Flexion; (**B**) extension.

In the present study, the patients implanted with more anatomical cervical disk prosthesis showed better results in terms of HO, maybe as the result of the shorter follow-up.

Surgical time and blood loss also should be taken into account. It has been well reported that the greatest HO grades occur during long surgical operations with more blood loss. It is also important to reduce the amount of remaining residual cartilage after cleaning of the endplates, through abundant irrigation of saline solution to better clean all traces.[17]

Several limitations of the study need to be mentioned, such as its retrospective design. In addition, the time to implant each prosthesis and its relation with HO or with the potential risk of X-ray radiation were not measured. We must say, as well, that the sample size was relatively small, and the follow-up period was heterogeneous among groups. Despite the face we obtained good results, the indication of cervical disk arthroplasty remains controversial, because we have observed that those mobile disks trend to develop ossifications over time.

Spine surgeons should validate the necessity of arthroplasty as primary indication, given that disk prosthesis eventually ends in fusion. Is arthroplasty a useful approach? To answer this question, we believe that long-term randomized studies are needed. These studies will allow us to obtain appropriate clinical and radiologic findings to compare both techniques and properly define the directions of each one.

CONCLUSIONS

Although cervical disks provide optimal mid-term results, the incidence of HO seems to increase over time, even though no clinical significance has been proved to date. On the basis of these results, long-term follow-up studies, with a larger number of patients, are necessary to confirm the presence of HO and the grade of cervical motion after implanting a cervical prosthesis. From the point of view of radiological assessments, CT seems to be an optimum diagnostic method to determine the presence of HO because if its greater sensitivity and reliability; however, the benefit-risk balance should be considered, taking into account factors such as risk radiation and associated costs.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 10 May 2016; accepted 17 August 2016

Citation: World Neurosurg. (2016) 96:585-590.
http://dx.doi.org/10.1016/j.wneu.2016.08.078

Journal homepage: ***www.WORLDNEUROSURGERY.org***

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