Early development and progression of heterotopic ossification in cervical total disc replacement

Clinical article

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Objective. The purpose of cervical total disc replacement (TDR) is to decrease the incidence of adjacent segment disease through motion preservation. Heterotopic ossification (HO) is a well-known complication after hip and knee arthroplasties. There are few reports regarding HO in patients undergoing cervical TDR, however; and the occurrence of HO and its effects on cervical motion have rarely been reported. Moreover, temporal progression of HO has not been fully addressed. One goal of this study involved determining the incidence of HO following cervical TDR, as identified from plain radiographs, and demonstrating the progression of HO during the follow-up period. A second goal consisted of determining whether segmental motion could be preserved and identifying the relationship between HO and clinical outcomes.

Methods. The authors conducted a retrospective clinical and radiological study of 28 consecutive patients who underwent cervical TDR with Mobi-C prostheses (LDR Medical) between September 2006 and October 2008. Radiological outcomes were evaluated using lateral dynamic radiographs obtained preoperatively and at 1, 3, 6, 12, and 24 months postoperatively. The occurrence of HO was interpreted on lateral radiographs using the McAfee classification. Cervical range of motion (ROM) was also measured. The visual analog scale (VAS) and Neck Disability Index (NDI) were used to evaluate clinical outcome.

Results. The mean follow-up period was 21.6 ± 7.0 months, and the mean occurrence of HO was at 8.0 ± 6.6 months postoperatively. At the last follow-up, 18 (64.3%) of 28 patients had HO: Grade I, 6 patients; Grade II, 8 patients; Grade III, 3 patients; and Grade IV, 1 patient. Heterotopic ossification progression was proportional to the duration of follow-up; HO was present in 3 (10.7%) of 28 patients at 1 month; 7 (25.0%) of 28 patients at 3 months; 11 (42.3%) of 26 patients at 6 months; 15 (62.5%) of 24 patients at 12 months; and 17 (77.3%) of 22 patients at 24 months. Cervical ROM was preserved in Grades I and II HO but was restricted in Grades III and IV HO. Clinical improvement according to the VAS and NDI was not significantly correlated with the occurrence of HO.

Conclusions. The overall incidence of HO after cervical TDR was relatively high. Moreover, HO began unexpectedly to appear early after surgery. Heterotopic ossification progression was proportional to the time that had elapsed postoperatively. Grade III or IV HO can restrict the cervical ROM and may lead to spontaneous fusion; however, the occurrence of HO did not affect clinical outcome. The results of this study indicate that a high incidence of HO with the possibility of spontaneous fusion is to be expected during long-term follow-up and should be considered before performing cervical TDR. (DOI: 10.3171/2011.8.SPINE11303)

KEY WORDS • cervical total disc replacement • heterotopic ossification • spontaneous fusion

Cervical total disc replacement is becoming a popular alternative to ACDF in the surgical treatment of degenerative disc disease.\(^\text{18}\) The purpose of cervical TDR is to decrease the incidence of adjacent segment disease through motion preservation.\(^\text{4}\) Heterotopic ossification is a well-known complication following hip and knee arthroplasties.\(^\text{10}\) McAfee et al.\(^\text{13}\) have reported that HO occurs during lumbar disc replacement, and they proposed an HO classification system in 2003. There are few reports about HO in patients undergoing cervical TDR,\(^\text{12,13}\) and the occurrence of HO and its effects on cervical motion have rarely been studied. In addition, temporal progression of HO has not been fully addressed. Hence, one goal of this study included determining the incidence of HO following cervical TDR by using plain radiographs and determining HO progression during the follow-up period. A second goal

Abbreviations used in this paper: ACDF = anterior cervical discectomy with fusion; HO = heterotopic ossification; NDI = Neck Disability Index; NSAID = nonsteroidal antiinflammatory drug; PLL = posterior longitudinal ligament; ROM = range of motion; TDR = total disc replacement; VAS = visual analog scale.
consisted of determining whether segmental motion could be preserved and identifying the relationship between HO and clinical outcomes.

**Methods**

**Patient Population**

The study included 28 consecutive patients who had undergone cervical TDR with Mobi-C prostheses (LDR Medical) between September 2006 and October 2008. The inclusion criteria were radiculopathy and/or myelopathy from disc herniation and other degenerative changes. If the patient had 2 consecutive levels of degenerative disc disease, hybrid surgery consisting of cervical TDR combined with ACDF was performed. The cervical TDR was performed at a mobile nonspondylotic segment. Patients who exhibited postlaminectomy syndrome with kyphotic deformity, translational instability, ossification of the posterior ligament, or active infection were excluded. All surgical procedures were performed by 1 of 2 surgeons (C.K.C. or T.A.J.).

**Surgical Technique**

A standard approach to the anterior cervical spine was performed. After discectomy, the intervertebral space was distracted and held in distraction with a Caspar distractor. There was a difference between the 2 surgeons in the method used to clear the endplates. One surgeon (C.K.C.) performed curettage to clear the endplates in 12 cases, while the other surgeon (T.A.J.) used a drill in 16 cases. During surgery, the operative site was copiously irrigated with normal saline to remove as much bone dust as possible. The uncovertebral joints were left intact, and the PLL was removed. After a trial implant was inserted, the appropriate size, height, and position of the artificial disc were determined using fluoroscopic imaging.

**Device Description**

A single type of cervical artificial disc, the Mobi-C (LDR Medical), was used in all surgeries. The Mobi-C is a 3-piece nonconstrained articulation prostheses with a polyethylene nucleus moving between 2 plates and was designed to be as anatomically similar as possible to the intervertebral disc. The Mobi-C prosthesis is composed of 2 spinal plates consisting of a cobalt-chromium-molybdenum (CoCrMo) alloy (ISO 5832-12) and an ultra-high molecular weight polyethylene mobile insert. The mobile insert is self-centering on the inferior endplate. Each movement of the superior plate induces the mobile insert to reposition on the inferior spinal plate.

**Radiological Evaluation**

Lateral dynamic radiographs were obtained preoperatively and at 1, 3, 6, 12, and 24 months postoperatively. The occurrence of HO was interpreted on lateral radiographs according to the 5 grades in the McAfee classification (Table 1). We also measured cervical ROM to assess the biomechanical effects of HO. Angular motion was measured by drawing a line along the superior endplate of the superior vertebral body and the inferior endplate of the inferior vertebral body. To evaluate the angular ROM, the differences between flexion and extension on radiographs were calculated. All measurements were performed using the Cobb method along with PACS software (Marosis M-view, version 5483, Infinitt Healthcare). The presence of preoperative calcification of the PLL at the surgically treated level was determined using CT.

**Clinical Evaluation**

Nonsteroidal antiinflammatory drugs were not used following surgery. The VAS score and NDI value for each patient were evaluated before surgery and at 1, 3, 6, 12, and 24 months postoperatively. One independent neurosurgeon and 1 research nurse blindly assessed all clinical and radiological outcome data.

**Statistical Analysis**

The results are expressed as the means ± standard deviation. Data were analyzed using a commercially available statistical software package (SPSS for Windows, version 17.0, SPSS, Inc.). A p value < 0.05 was considered statistically significant.

**Results**

**Patient Population**

Twenty-eight patients (21 men and 7 women) with a mean age of 44.4 ± 9.8 years (range 31–61 years) were included in this study. The mean follow-up period was 21.6 ± 7.0 months (range 3–38 months). Nineteen patients underwent a single-level cervical TDR, and 9 patients underwent hybrid surgery consisting of a cervical TDR and ACDF. The most frequently instrumented level was C5–6; the distribution of the instrumented levels is shown in Table 2. Patient participation at each follow-up time was as follows: 28 patients at 1 month, 28 patients at 3 months, 26 patients at 6 months, 24 patients at 12 months, and 22 patients at 24 months. By 24 months after surgery, 4 patients were lost to follow-up. In addition, 2 patients were not evaluated at 24 months but were followed up for > 24 months.

**Radiological Outcomes**

At the last follow-up, 18 (64.3%) of 28 patients had HO (Fig. 1). Grade I HO occurred in 6 patients and Grade II HO occurred in 8 patients. Three patients exhibited Grade...
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TABLE 2: Distribution of instrumented levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TDR Alone (%)</th>
<th>Hybrid (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no.</td>
<td>19</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3–4</td>
<td>1 (5.3)</td>
<td>0 (0.0)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>C4–5</td>
<td>1 (5.3)</td>
<td>3 (33.3)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>C5–6</td>
<td>14 (73.7)</td>
<td>2 (22.2)</td>
<td>16 (57.1)</td>
</tr>
<tr>
<td>C6–7</td>
<td>3 (15.8)</td>
<td>4 (44.4)</td>
<td>7 (25.0)</td>
</tr>
</tbody>
</table>

III HO, and 1 patient had Grade IV HO (Table 3). Of the 19 patients who underwent cervical TDR alone, 11 (57.9%) demonstrated HO, whereas 7 (77.7%) of the 9 patients who underwent hybrid surgery exhibited HO. While HO appeared to be more common in patients who had undergone hybrid surgery rather than TDR alone, the difference was not statistically significant (p = 0.323). Eighteen patients (12 men and 6 women) with a mean age of 44.6 ± 9.7 years demonstrated HO. The mean period at which HO occurred was 8.0 ± 6.6 months postoperatively (range 1–22 months).

The progression of HO was proportional to the follow-up period (Fig. 2). At the 1-month follow-up, 3 (10.7%) of 28 patients demonstrated HO: 1 patient, Grade I; and 2 patients, Grade II. At the 3-month follow-up, HO was detected in 7 (25.0%) of 28 patients: 3 patients, Grade I; and 4 patients, Grade II. At the 6-month follow-up, HO was detected in 11 (42.3%) of 26 patients: 5 patients, Grade I; and 6 patients, Grade II. At the 12-month follow-up, HO was detected in 15 (62.5%) of 24 patients: 6 patients, Grade I; and 3 patients, Grade II. At the 24-month follow-up, HO was detected in 17 (77.3%) of 22 patients: 5 patients, Grade I; 8 patients, Grade II; 3 patients, Grade III; and 1 patient, Grade IV. There was no statistical difference in the occurrence of HO between the 2 surgeons (p = 0.194).

The mean cervical ROM in the patients decreased from 10.0° ± 1.2° to 5.5° ± 1.1° immediately after surgery (p = 0.083); however, the mean cervical ROM was 9.8° ± 3.6° at 1 month postoperatively (p = 0.019; Fig. 3). No significant changes in the cervical ROM were observed at 1, 3, 6, 12, and 24 months after surgery. The cervical ROM was preserved even though Grade I or Grade II HO developed (p = 0.655). Note, however, that Grade III or Grade IV HO led to a restriction in the ROM (p = 0.004). The preoperative cervical ROM in patients with Grade III HO was 11.2° ± 1.9°. The cervical ROM in patients with Grade III HO immediately after surgery was significantly lower (5.0° ± 1.8°; p = 0.060) and was also significantly lower (6.5° ± 2.3°) at 24 months postoperatively (p = 0.061). The preoperative cervical ROM in the patient with Grade IV HO was 11.2°, and this patient's ROM was 8.8° immediately after surgery. The postoperative ROM in the patient with Grade IV HO decreased to 3.2° and 2.0° after 6 and 24 postoperative months, respectively. Preoperative calcification of the PLL at surgery was observed in 5 patients, and all of these patients exhibited HO formation after surgery. However, the occurrence of HO was not significantly different in patients with or without calcification of the PLL prior to surgery (p = 0.066).

![Fig. 1. Early development and progression of HO on radiographs obtained in a 45-year-old man. A: Herniated intervertebral disc at C6–7. B: Immediate postoperative lateral radiograph showing TDR at C6–7. C: One-month postoperative radiograph showing no HO. D: Three-month postoperative radiograph showing Grade I HO. Although the HO is detectable, it is not in the intervertebral space. E: Six-month postoperative radiograph showing Grade II HO growing into the disc space. F: One-year postoperative radiograph showing Grade III HO. Bridging ossification is present, but flexion and extension movement is still possible. G and H: Two-year and 3-year postoperative radiographs showing progression of HO toward near-complete fusion at C6–7.](image-url)
Clinical Outcomes

The VAS score for cervical pain immediately after surgery (2.49 ± 0.77) was significantly lower than the preoperative score (6.36 ± 0.92; p < 0.01; Fig. 4). The mean VAS score decreased at each follow-up evaluation and was significantly lower at the 12-month follow-up evaluation (p < 0.01) compared with the preoperative score. The mean NDI reduced from 18.3 ± 2.55 preoperatively to 10.4 ± 3.77 after 24 months postoperatively (p < 0.01). A comparison of the VAS score and the NDI value among the groups with each grade of HO revealed that there was no statistical significance related to the improvement in clinical outcomes.

Discussion

Cervical TDR can be used to preserve motion of the segment and decrease the incidence of adjacent segment disease, and it is increasing in popularity as an alternative to ACDF in the surgical treatment of degenerative disc disease.1,4,7,9,11 Overall, the clinical outcomes of cervical TDR in other studies have been acceptable and promising.3,15,21 The clinical results in our consecutive series of 28 patients treated with Mobi-C were similar. The patients’ VAS and NDI values showed significant improvement over the entire follow-up period.

Heterotopic ossification is a well-known complication after hip and knee arthroplasties.10 McAfee et al.13 reported that HO occurs in lumbar disc replacement and proposed a classification system for HO in 2003. Spontaneous fusion following cervical TDR has rarely been described, and if reported, it is usually described in the form of a case report. Bartels and Donk2 and Parkinson and Sekhon17 reported cases of spontaneous fusion after cervical TDR in 2005. Mehren et al.14 reported the results of a prospective multicenter study in which HO was categorized into 5 grades using a modified McAfee HO classification scheme. In that study, radiographs of 54 patients (77 implanted prostheses) were analyzed 1 year after cervical TDR with ProDisc-C prostheses. Only 33.8% of the patients had no signs of HO, and the rate of spontaneous fusion 1 year after cervical TDR was unexpectedly high. Subsequently, the clinical outcomes improved significantly and were similar to those in previous reports about cervical TDR. It was concluded that motion preservation after cervical TDR is only guaranteed if spontaneous fusion can be prevented.14 Leung et al.12 studied HO incidence and outcomes in patients treated with Bryan cervical prostheses and reported that 17.8% of 90 treated patients exhibited HO, with 6.7% of the patients having Grade III or IV HO after 1 year of follow-up. A strong association was noted between HO occurrence and the subsequent loss of movement of the implanted disc. Beaurain et al.4 reported intermediate clinical and radiographic results of cervical TDR with Mobi-C prostheses with up to 2 years of follow-up. Among 76 patients, 51 (67.1%) demonstrated HO; Grade III HO occurred at 3 levels (3.9%) and Grade IV occurred at 6 levels (7.9%). In their study, Grade III and Grade IV HO were responsible for fusion at the instrumented level, and the outcomes can be regarded as indicative of nonfunctional prostheses. Note, however, that the presence of HO does not alter the clinical outcomes. Similar to the above-described study, 28 patients in our study underwent cervical TDR with Mobi-C prostheses, and we observed a 64.3% incidence of HO over the 21.6 months of the mean follow-up period. In contrast, Beaurain et al.5 assessed HO occurrence 2 years after surgery, not at shorter follow-up periods. In the present study, we evaluated HO at several follow-ups and unexpectedly established that HO development was present < 1 year after surgery.
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surgery. Moreover, the progression of HO was shown to be directly proportional to the duration of follow-up. In addition, cervical ROM was preserved in patients with Grade I or II HO, whereas cervical ROM was restricted in those with Grade III or IV HO (Table 4).

Although HO is a well-known complication following major joint replacement, the exact cause remains unknown. Chalmers et al. proposed 3 conditions that were needed for HO development: osteogenic precursor cells, inducing agents, and a permissive environment. Ekelund et al. postulated that bone morphogenetic protein is liberated from normal bone in response to venous stasis, inflammation, or diseases of connective tissue attachments to bone, conditions that often accompany immobilization related to trauma. In patients undergoing cervical TDR, trauma to the longus colli is inevitable during exposure of the disc space. Leung et al. postulated that direct trauma to the longus colli was one of the factors facilitating the formation of HO. In their study, Leung and colleagues tried to limit retraction damage to the longus colli but found no association between operative time and the development of HO. In addition, they reported that excessive drilling and opening of the bone canals during chiseling could result in new bone formation. Usually, bony degenerative changes (osteophytes and uncinate hypertrophy) require more extensive bony work to achieve sufficient neural decompression, therefore making hard disc disease a contraindication to motion preservation technology. In relation to surgical bony work during cervical TDR, Puzas et al. suggested that residual bone dust plays an important role in pathological bone formation. Lee et al. also considered that small quantities of bone dust after endplate preparation was the most important factor inducing HO between the discs that replaced vertebral bodies. To overcome these problems, Leung et al. recommended copious irrigation of the operative site with normal saline during milling and again before closure. Most surgeons use similar efforts to reduce the perioperative infection rate, especially during arthroplasties. Therefore, residual bone dust in the operative field is scant.

Authors of several studies have investigated various factors related to the occurrence of HO. There is a report that male sex and increased age are 2 possible risk factors in the development of HO after cervical TDR. In addition, it has been documented that the prophylactic use of NSAIDs or radiation therapy decreases the incidence of HO after arthroplasty. However, age, sex, and the duration of NSAIDs intake had no significant relationship to the occurrence of HO. In the present study, NSAIDs were not used, age was not shown to have a relationship with the development of HO, and HO occurred more frequently in females in our series. Moreover, there was no difference in HO development between the 2 surgeons and in the 2 methods those surgeons used to prepare the endplates. Preoperative calcification of the PLL at the surgically treated level had also been considered to predispose a patient to the occurrence of HO following cervical TDR. Although HO developed without exception in the 5 patients with preoperative calcification of the PLL at the operated level, it was uncertain whether preoperative calcification of the PLL was predisposed to HO in the present study. While many theories attempt to explain the development of HO after cervical TDR, in our opinion the process is multifactorial.

We suggest that the surgical indication for cervical TDR is one of the more important factors. Some authors have speculated that the formation of osteophytes or bony spurs in degenerative spinal disease is associated with the origin of HO. Osteophytes are usually observed in patients with advanced Modic changes in endplates with a severely degenerated disc, especially in elderly patients. Osteophyte formation may eventually lead to arthrosis between 2 adjacent vertebral bodies. Therefore, cervical TDR in patients with osteophytes in degenerative spinal disease may result in the development of HO. Unlike ACFD, cervical TDR aims to preserve motion of the segment and to decrease the incidence of adjacent segment disease. However, if motion of the artificial disc is limited, the artificial disc itself may play a role in the cervical cage between 2 vertebral bodies, and thus arthrosis will be inevitable.

There were several limitations in this study. First, the study involved a small number of patients, and thus the analyses have low statistical power. With 28 patients, we could not perform adequate prognostic factor analysis. Second, surgical procedures consisted of cervical TDR alone or hybrid surgery. The use of 2 different surgical procedures is a limitation to analyzing risk factors associated with HO. Third, the follow-up period of < 2 years is relatively short. Despite these limitations, considering that cervical TDR is a recently developed and adopted alternative to ACFD, we demonstrated that HO is not rare following cervical TDR and that it develops within a short time period, that is, in < 2 years. Further studies with a large number of patients and a longer follow-up period are needed to determine the long-term outcomes with respect to mobility and function, to establish whether HO in cervical TDR increases the likelihood of adjacent segment disease, and to determine whether preoperative calcification of PLL is an HO risk factor.

**Conclusions**

The overall incidence of HO after cervical TDR was relatively high. Unexpectedly, HO development was observed at < 1 year after surgery and its progression was proportional to the elapsed postoperative time. However, the occurrence of HO did not affect clinical outcome. Grade III or IV HO can restrict cervical ROM and may lead to spontaneous fusion. Therefore, before performing

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**Table 4: Review of previous studies of heterotopic ossification in cervical TDR**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Artificial Disc</th>
<th>No. of Pts</th>
<th>FU (mos)</th>
<th>HO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leung et al., 2005</td>
<td>Bryan disc</td>
<td>90</td>
<td>12</td>
<td>17.8</td>
</tr>
<tr>
<td>Mehren et al., 2006</td>
<td>ProDisc-C</td>
<td>54</td>
<td>12</td>
<td>66.2</td>
</tr>
<tr>
<td>Beaurain et al., 2009</td>
<td>Mobi-C</td>
<td>76</td>
<td>24</td>
<td>67.1</td>
</tr>
<tr>
<td>Lee et al., 2010</td>
<td>Bryan disc, Prestige</td>
<td>48</td>
<td>14</td>
<td>27.1</td>
</tr>
<tr>
<td>Present study</td>
<td>Mobi-C</td>
<td>28</td>
<td>21</td>
<td>64.3</td>
</tr>
</tbody>
</table>

* FU = follow-up; Pts = patients.
cervical TDR, surgeons should consider that a significant incidence of HO, together with ultimate spontaneous fusion, must be expected during long-term follow-up.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Chung, Lee. Acquisition of data: Lee. Analysis and interpretation of data: Lee. Drafting the article: Lee. Critically revising the article: all authors. Reviewed the final version of the manuscript on behalf of all authors: Chung. Statistical analysis: Lee. Administrative/technical/material support: Chung, Jahng. Study supervision: Chung, Jahng.

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