

THE INFLUENCE OF HETEROTOPIC OSSIFICATION ON CLINICAL AND RADIOLOGICAL OUTCOMES AFTER TOTAL LUMBAR DISC REPLACEMENT WITH M6-L PROSTHESIS: A MULTICENTER STUDY

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Objective. To assess the degree of influence of heterotopic ossification on the motion amplitude of the operated segment and on clinical outcomes in patients after total intervertebral disc replacement.

Material and Methods. Results of total replacement of the intervertebral disc with the M6-L prosthesis were analyzed in 74 patients aged 23–45 years. Follow-up period was 36 months. The motion amplitude of operated segments and the degree of heterotopic ossification were estimated. Clinical outcomes were analyzed based on pain syndrome severity according to the VAS and on the level of the back pain-related quality of life according to the Oswestry index.

Results. Signs of heterotopic ossification were found in 27 (36.4%) patients: Grade I - in 11 (14.8%), Grade II - in 14 (18.9%), and Grade III - in 2 (2.7%). The mean values of the motion amplitude of operated segments, VAS score and Oswestry index in the group of patients without signs of heterotopic ossification were 11.2° \pm 2.7°, 2.8 \pm 1.2 cm and 17.3 \pm 6.5%, respectively, and those in the group of patients with signs of heterotopic ossification - 11.5° \pm 1.2°, 3.4 \pm 1.8 cm and 19.8 \pm 7.3%, respectively.

Conclusion. Heterotopic ossification following total lumbar disc replacement occurs in 36.4 % of cases. High grade of heterotopic ossification reliably affects the amplitude of segment motion, though there was no significant influence on clinical results in patients.

 $\textbf{Key Words:} \ intervertebral \ disc, \ degeneration, \ fusion, \ total \ replacement, \ heterotopic \ ossification.$

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To date, spinal fusion is the gold standard of surgical treatment of degenerative lumbar disc disease [4, 7]. This type of surgery can completely eliminate pathological mobility and instability in an affected spinal motion segment and, as a result, provide pain relief in the lower back. However, rigid fixation leads to disruption of the normal biomechanics of an operated segment, which serves as an inducing factor in the development of adjacent segment degeneration [4].

Total disc replacement as a modern alternative surgical treatment of degenerative disease is becoming increasingly popular in many neurosurgical clinics around the world. The goal of disc replacement is to restore and maintain the physiological range of motion in

a spinal motion segment, which will prevent degeneration of adjacent segments and eliminate pain in the back [19, 20]. Studies on the use of artificial discs have clearly demonstrated their high effectiveness in relation to clinical and instrumental outcomes in patients with disc degeneration (compared to spinal fusion). However, there is an active discussion in the world literature on complications of total disc replacement that adversely affect clinical outcomes. One of these complications is heterotopic ossification (HO) that refers to disorders characterized by bone formation in tissues that normally have no osteogenic properties [13]. HO leads to a limited range of motion in an operated segment, which turns an artificial disc into the cage and

hinders protection of adjacent segments from degeneration. In the world literature, there are single reports on the problem of HO after total disc replacement, and their results are largely contradictory. Furthermore, we did not find studies examining the influence of HO after disc replacement with a M6-L prosthesis.

The study purpose was to assess the influence of HO on the range of motion in an operated segment and on clinical outcomes in patients after total disc replacement.

Material and Methods

The study included 74 patients (46 males and 28 females) aged 23–45 years (mean age, 36.7 ± 5.9 years) who underwent

surgery for single-level degenerative disc disease at the Center of Neurosurgery of the Railway Clinical Hospital at the Irkutsk-Passenger Station, Neurosurgical Department of the Krasnoyarsk Regional Hospital, and Neurosurgical Unit of the 1477th Naval Clinical Hospital (Vladivostok). The follow-up period was 36 months. In all cases, a disc was replaced with a M6-L prosthesis.

The range of motion in an operated spinal motion segment was assessed based on the data of functional spondylograms (Fig. 1). Spondylography was performed in all patients before and after surgery as well as on examination at 6, 12, 24, and 36 months after disc replacement. The degree of HO was assessed using the classification by McAfee et al. [15]; the occurrence of HO foci was analyzed according to an original method by Park et al. [17], based on dividing the peripheral area of implant into 9 zones (Fig. 2). Clinical outcomes were analyzed in term of the pain intensity (VAS) and back pain quality of life (Oswestry Disability Index (ODI)). Parameters of the motion range in operated segments, VAS, and ODI in patients with signs of HO were compared to those in patients without signs of HO. Statistical processing of the data was carried out using the Microsoft Excel 2010 software. Descriptive statistics are presented in the form $M \pm SD$, where M is the mean value, and SD is the standard deviation. The statistical confidence of the data was determined using the Mann-Whitney U test. Differences were considered significant at p < 0.05.

Results

Signs of HO were found in 27 (36.4 %) patients with implanted disc prostheses. According to the classification by McAfee et al. [15], HO cases were graded as follows: Grade I – 11 (14.8 %) cases, Grade II – 14 (18.9 %) cases, Grade III – 2 (2.7 %) cases, and Grade IV – no cases. The mean values of motion range in an operated segment, VAS score, and ODI for each HO grade are presented in Table 1. Comparison of radiological and clinical outcomes in patients with and without HO is shown in Fig. 3.

An analysis of the motion range of an operated segment revealed no significant differences between patients with Grade I and II HO and patients without signs of HO. On the other hand, the range of motion of a segment in patients with Grade III HO was significantly lower than in patients without signs of HO (p = 0.024). Comparison of the mean parameters of VAS and ODI in these groups revealed no statistically significant differences (VAS: p = 647, p = 0.144, p = 0.414; ODI: p = 0.525; p = 0.263; p = 0.334 for Grade I, II, and III HO, respectively).

Assessment of the occurrence of HO foci in a group according to the method by Park et al. [17] showed that HO foci were detected in zones 1–6 in 32 (82 %) cases according to lateral spondylography and in zones 7–9 in 7 (17.9 %) cases according to spondylography in an anterior-posterior projection (Table 2). It is worth noting that HO progressed from Grade I to Grade II within a 6 month follow-up period in 2 (2.7 %) patients. In the remaining cases, there was no increase in the HO grade in operated segments.

Discussion

The formation of HO foci is a frequent complication after hip replacement [5, 6]; the rate of HO formation after this surgery varies from 0.6 to 61.0 %. As the total disc replacement technique has been developed and actively implemented in common clinical practice, the HO problem has become topical in modern spinal neurosurgery. In 2003, McAfee et al. [15, 16], based on the Brooker's classification of HO grades after hip replacement, proposed their classification of HO in patients after total disc replacement. Later, this classification was supplemented by P. Sukhomel et al. [1]. This issue, in particular the development of HO after total cervical disc replacement, was addressed in several studies. For example, Jackson et al. [11] analyzed the rate of formation of HO foci and their effect on clinical outcomes in patients after cervical disc replacement. The authors found that only 33.8 % of patients had no signs of HO formation, and the rate

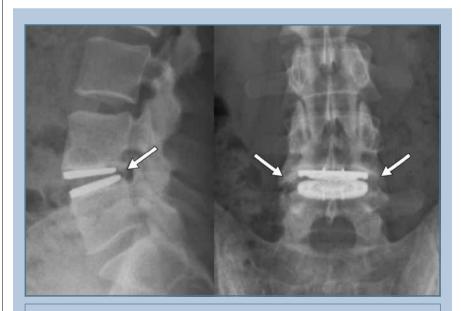


Fig. 1
Spondylograms of the lumbosacral spine in lateral and anterior-posterior projections: 12 months after implantation of the M6-L artificial intervertebral disc; there are signs of Grade II–III heterotopic ossification according to the McAfee classification [15]

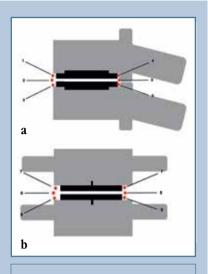


Fig. 2
Occurrence of heterotopic ossification foci according to Park et al. [17]:
a – a lateral projection; b – an anterior-posterior projection

of spontaneous ankylosis of operated segments amounted to 45.0 %.

The issue of HO after total lumbar disc replacement was also addressed in several studies. According to Tortolani et al. [24], in a clinical series of 276 patients with total lumbar disc replacement using a Charite™ prosthesis, signs of HO developed in 4.3 % of the cases after two years. In this case, the authors did not find any significant differences in the range of motion in operated segments and in clinical outcomes between patients with and without HO. The same authors demonstrated that HO foci in 11 out of 12 cases formed within 3 months

after surgery. The authors claim that the risk of HO development is almost zero 6 months after disc replacement. On the other hand, Lemaire et al. [12] clearly demonstrated the development of HO foci in 3 % of patients after disc replacement within a 10-year follow-up period. In this case, all HO cases were noted as early as five years of follow-up. According to other studies [4, 22, 25], HO after lumbar disc replacement develops in 1.4 83.0 % of cases.

In our study, the prevalence rate of HO is 36.4 %, which agrees with the international literature data. We believe that this relatively high prevalence rate of HO is explained by targeted assessment of all operated segments using the McAfee classification [15, 16]. HO foci were found to be capable of developing and progressing during the entire follow-up period. That is why the true rate of HO development after disc replacement can be evaluated only within a longer follow-up period.

In this study, we have demonstrated that only high grade (III) HO significantly affects the range of motion in an operated segment. Grade I or II HO does not significantly affect this indicator. However, it remains unclear whether preservation of the range of motion in an operated segment is associated with good clinical outcomes in patients after total disc replacement. There were no statistically significant differences in clinical outcomes between patients with HO (even high grade) and without it. In general, our findings are in agreement with the data of other studies. For example, Putzier et al. [18] reported that patients

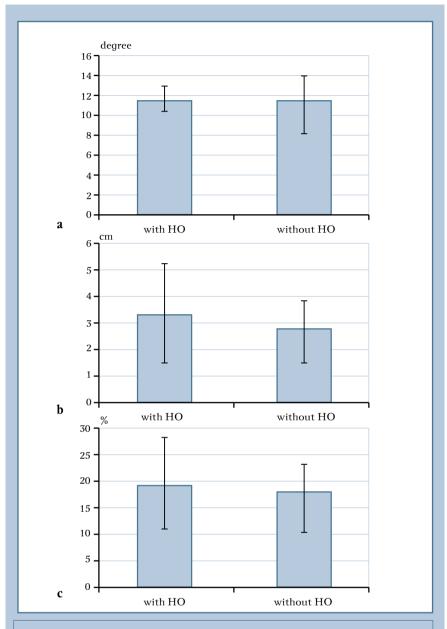
with HO and spontaneous ankylosis of an operated spinal motion segment had mainly good clinical outcomes. However, further large multicenter studies are required to evaluate more reliably the effect of a segment's motion range on clinical outcomes in patients after total disc replacement.

At present, pathophysiology of the development of HO foci is not fully understood. However, HO is believed to result from abnormal differentiation of pluripotent mesenchymal cells into osteoblasts. A study by Wosczyna et al. [26] showed that implantation of a demineralized bone matrix into the skeletal muscles of animals was followed by formation of ectopic bone foci. Later, Shi et al. [21] confirmed these data. Furthermore, the authors proved that a bone matrix implanted in the skeletal muscle produced bone morphogenetic proteins (BMPs) promoting growth and differentiation of mesenchymal stem cells into osteoblasts. To date, a number of bone morphogenetic proteins are known. In this case, the formation of HO foci is most often associated with hyperproduction of BMP-4 [2]. An important role in the pathogenesis of HO formation is played by arachidonic acid metabolism resulting in production of prostaglandin E2 (PGE2). High PGE2 concentrations were found to be associated with the development of HO [8]. This was confirmed by Fransen et al. [10] who demonstrated the efficacy of non-steroidal antiinflammatory drugs (NSAIDs) in preventing formation of HO foci.

The genetic predisposition of patients plays an important role in the develop-

Table 1 The range of motion in the operated segment, pain intensity according to VAS, and quality of life according to the Oswestry index for each grade of heterotopic ossification according to the McAfee classification [15], $M \pm SD$

Ossification grade	Number of patients, n (%)	Range of motion in segment, degree	VAS, cm	Oswestry index, %
0	47 (63.5)	11.2 ± 2.7	2.8 ± 1.2	17.3 ± 6.5
I	11 (14.8)	15.7 ± 3.1	4.5 ± 2.9	21.9 ± 9.4
II	14 (18.9)	11.6 ± 2.5	3.3 ± 1.5	17.7 ± 4.6
III	2 (2.7)	5.7 ± 1.3	4.2 ± 0.9	25.5 ± 8.9
IV	0	_	-	-



Puc. 3Radiological and clinical outcomes in patients with and without signs of heterotopic ossification (HO): **a** – the range of motion in the operated segment; **b** – pain intensity according to the VAS; **c** – quality of life according to the Oswestry index

ment of HO foci. For example, a mutation in the 2q23-24.9 gene encoding the BMP type 1 receptor leads to activation of intracellular signaling pathways responsible for the formation of ectopic bone tissue [23]. On the other hand, a deletion of the noggin gene may cause increased expression of the BMP-4 gene

[9]. In the nearest future, studies of the genetic code will identify impairments responsible for the development of various pathological conditions, including HO, as well as enable the creation of effective methods for their molecular genetic therapy.

Table 2				
Occurrence of heterotopic ossification foci				
around the implant according to Park et al.				
[17]				
Zone	Cases of heterotopic			
	ossification, % (n)			
1	7.6 (3)			
2	7.6 (3)			
3	20.5 (8)			
4	30.7 (12)			
5	5.1 (2)			
6	10.2 (4)			
7	5.1 (2)			
8	7.6 (3)			
9	5.1 (2)			
Total	100.0 (39)			

A surgical technique for total disc replacement was shown to influence the development of HO foci. A paper by Maida et al. [14] describes some risk factors associated with the formation of HO after total disc replacement: gross tissue dissection accompanying an operative approach, leading to local skeletal hyperostosis; hemorrhages near the implant; placing of hemostatic materials in the treated segment area. In our study, all cases of total lumbar disc replacement involved the anterior pararectal retroperitoneal approach to the lumbosacral spine with strict observance of the anatomical and topographical relationships between organs and soft tissues. At the stage of discectomy and preparation of the bed for the disc prosthesis, we used microsurgical technique involving an OPMI Pentero 900 operating microscope. We believe that removal of the lig. longitudinale posterius is the obligatory stage of total disc replacement because this ligament can be the source of a pool of mesenchymal stem cells capable of differentiating into mature osteoblasts, with the subsequent formation of ectopic bone foci [3]. Therefore, for thorough prevention of HO formation after disc replacement, we recommend using a surgical approach with minimal soft tissue damage, a microsurgical technique involving an operating microscope,

removal of the *lig. longitudinale posterius*, careful hemostasis without placing of hemostatic materials near the implant, administration of NSAIDs, and early activation of patients. These recommendations will reduce the rate of HO formation and size of HO foci.

In our clinical series, the location pattern of HO foci was as follows: most foci were located anterior and posterior to the artificial disc (82 %), and only 17.9 % of foci were located lateral to the prosthesis. This location of HO foci is most likely related to the biomechanical features of the lumbosacral spine; in contrast to lateral flexions, flexion-extension movements are more characteristic of the lumbosacral spine. Another potential cause for the pattern of HO locations may be the sensitivity of spondylography. In spondylography in an anterior-pos-

terior projection, the L4–L5 and L5–S1 segments are tilted anteriorly and are not parallel to the X-ray path, which complicates detailed visualization of regions located lateral to the artificial disc. In this case, MSCT can be useful for assessing the occurrence of HO foci.

Of course, this study has some short-comings. First, a small number of respondents were included in the study. Second, the follow-up period was three years only, which excludes objective assessment of HO occurrence after disc replacement. Third, only one type of a disc prosthesis (M6-L) was studied.

Conclusion

The study clearly demonstrated that HO after total lumbar disc replacement occurred in 36.4 % of patients during a

three-year follow-up period. Grade I and II HOs (McAfee classification [15]) do not affect the range of motion in operated segments and clinical outcomes (pain intensity according to the VAS and quality of life according to the Oswestry index). Grade III HO significantly affects the range of motion in segments. However, there is no statistically significant effect of high grade HO on clinical outcomes in this group of patients.

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