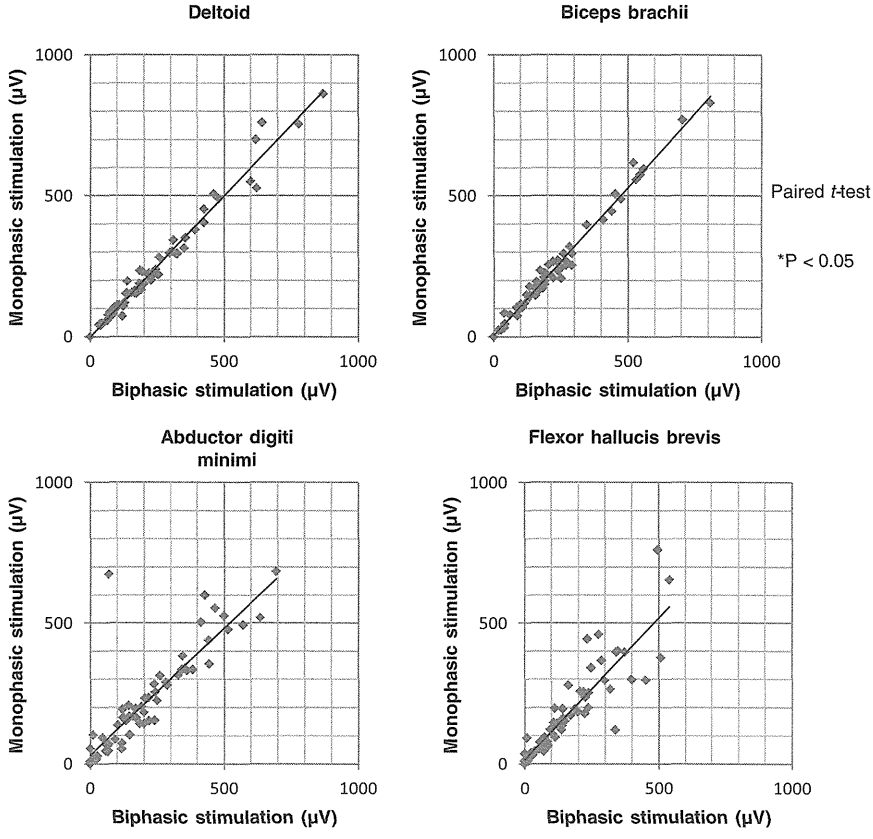

Figure 4. TCE-MEP amplitude of the same muscles was compared between the 2 stimulation methods in each patient. TCE-MEP indicates transcranial electrical motor evoked potential.

Del and Bic responded similarly to both stimulation methods. In 2 patients with a JOA motor function score of 2, ADM was evoked unilaterally by monophasic stimulation but bilaterally by biphasic stimulation. For FHB, cases in which monophasic stimulation evoked potentials either unilaterally or on neither side were evoked by biphasic stimulation either bilaterally or unilaterally. When biphasic stimulation did not evoke potentials in any muscles, these muscles also showed no potentials under monophasic stimulation (Figure 3).

TCE-MEP amplitude of the same muscles was compared between the 2 stimulation methods in each patient. The amplitude of the dominant muscles under monophasic stimulation (left or right muscles stimulated through the right or left anode, respectively) was similar to that under biphasic stimulation, except that the TCE-MEP amplitude of Bic was significantly larger under the latter method (paired *t* test, $P < 0.0001$, Figure 4).

Examination 2

In the biphasic stimulation group, data were collected from 100 patients (71 males, 29 females) aged 64.5 ± 12.7 (26–89) years with upper and lower extremity JOA motor function scores of 2.00 ± 1.21 (−1–4) and 1.94 ± 1.19 (0–4) points, respectively. There were 60 cases of cervical spondylotic myelopathy, 4 of cervical disc herniation, 23 of ossification of the posterior longitudinal ligament of the cervical spine, 8 of extramedullary spinal cord tumor, 2 of cervical spondylotic amyotrophy, 1 of ossification ligamentum flavum, and 2 of rheumatoid spondylitis. In the monophasic stimulation group, 100 patients (77 males, 23 females) aged 63.0 ± 12.6 (35 to 89) years with upper and lower extremity JOA motor function scores of 2.16 ± 1.13 (−2–4) and 2.00 ± 1.20 (0–4) points, respectively, were categorized into 60 cases of cervical spondylotic myelopathy, 10 of cervical disc herniation, 25 of ossification of the posterior longitudinal ligament of the cervical spine, 2 of extramedullary spinal cord tumors, 1 of atlantoaxial subluxation, and 2 of upper cervical pseudotumor. There were no significant differences in type of disorder, sex, age, or upper or lower extremity JOA motor function scores between the groups.

Under biphasic stimulation, we could not obtain valid TCE-MEPs for intraoperative monitoring in 1 case, and we gave an actual warning to the surgeon in 9 cases, in 7 of which the surgeon discontinued surgery temporarily or removed the causal factor in response. Waveforms were recovered in only 4 cases, but none of the 7 developed postoperative paralysis. The remaining 2 cases, in which the surgeon did not respond, did not recover the waveforms and segmental motor paralysis developed in 1 of the cases (*i.e.*, the Schwannoma case). No postoperative paralysis was observed in the 90 cases requiring no intraoperative warning. If we had disregarded TCE-SCEP and applied the warning threshold[16] to TCE-MEP monitoring, warnings would have been given in 10 cases and not in 89 cases. No postoperative paralysis developed in 7 of the 10 cases when the surgeon responded promptly. However, in 1 of the remaining 3 cases in which the surgeon did not respond, postoperative paralysis occurred. With the exclusion of 1 case without valid TCE-MEPs and 7 cases of prompt response, the sensitivity and

specificity of TCE-MEP monitoring using the biphasic method would have been 100% and 97.8%, respectively.

Under monophasic stimulation, we could not obtain valid TCE-MEPs in 1 case and we gave actual warnings in 4 cases. The surgeon responded in all cases, but waveforms resumed in only 1 case; in the other 3 cases, 1 (*i.e.*, the meningioma case) developed postoperative segmental motor paralysis. No postoperative paralysis was observed in 95 cases requiring no intraoperative warning. If we had disregarded TCE-SCEP and applied the warning thresholds[16] to TCE-MEP monitoring, warnings would have been given in 11 cases and not in 88 cases. Of these 11 cases, the surgeon responded in 4, 1 of which developed postoperative paralysis. Of the 7 cases in which the surgeon did not respond, waveforms recovered in only 4 cases, but none of the 7 developed postoperative paralysis. In addition, no paralysis was observed in cases requiring no warning. With the exclusion of the 1 case without valid TCE-MEPs, 4 cases with a prompt response, and 4 cases with spontaneous waveform recovery despite the surgeon's lack of response, the sensitivity and specificity of TCE-MEP monitoring using the monophasic method would have been 100% and 96.7%, respectively.

There were no signs of complications such as burns, tooth damage, alveolar ridge injury, or seizures in either group.

DISCUSSION

In examination 1, although TCE-MEPs in patients with severe paralysis were difficult to evoke by biphasic or monophasic stimulation, the derivation rates were generally the same or higher under biphasic stimulation than under monophasic stimulation. This might have been due to the firing of pyramidal neurons in the brain by the opposite rectangular pulse despite the absence of firing evoked by the initial 200-mA monophasic stimulation. Alternatively, it might have been caused by anterior horn cells in the spinal cord segments firing due to activation of the contralateral descending pathway by the opposite rectangular pulse despite the absence of firing evoked by the initial monophasic stimulation. In addition, similar TCE-MEP amplitudes were obtained by both methods, although biphasic stimulation evoked significantly greater Bic amplitudes than monophasic stimulation. It is also possible that the significant difference in Bic amplitudes was caused by the large derivation rate and stable amplitude of Bic potentials despite unstable amplitudes in Del due to stimulation artifacts and in ADM and FHB due to spinal cord impairment. We plan to increase the number of cases to perform more detailed studies. However, thus far, the findings suggest that biphasic stimulation results in similar or superior potentials in the target muscles compared with monophasic stimulation for which the polarity needs to be reversed to obtain TCE-MEP from both sides.

The warning criteria used under monophasic stimulation are controversial. Hsu *et al*[17] set the warning threshold during spinal cord surgery to 50% or more of the amplitude lasting for at least 1 minute, and achieved a sensitivity of 100% and specificity of 97% in 172 patients.[17] In another study of 52 patients with cervical compression myelopathy, Kim *et al*[18] set the warning threshold at an amplitude decrease of 80% or more and reported 100% sensitivity and 90% specificity. Furthermore, Sakaki *et al*[16] operated on 350 patients with cervical compression myelopathy using different warning thresholds based on the spinal tracts and segments (30% of control segmental potentials and disappearance of the tract potentials) and found a sensitivity and specificity of 100% and 83.7%, respectively.

We used different warning criteria in the monophasic and biphasic groups at our institution. Warning criteria need to be as similar as possible to compare the sensitivity and specificity of the 2 stimulation methods properly. We therefore established hypothetical warning criteria in examination 2 to analyze the changes in TCE-MEP waveforms retrospectively. We disregarded changes in TCE-SCEP waveforms in both groups and determined the sensitivity and specificity based on the presence/absence of postoperative paralysis with the assumptions that warnings were given because of TCE-MEP amplitudes for segmental potentials had decreased to less than 30% of the control value and waveforms of spinal tract potentials had disappeared. Because this was a retrospective analysis, we excluded cases in which the surgeon responded promptly and in which the TCE-MEP waveforms recovered after decreasing or disappearing temporarily. Although this may not be the most appropriate way to compare 2 stimulation methods, we think the present findings are valuable because this study was conducted at a single institution by the same research group. The analysis showed that sensitivity and specificity would have been 100% and 96.7% under monophasic stimulation and 100% and 97.8% under biphasic stimulation, respectively. Thus, both methods were shown to be equally effective.

To elucidate TCE-MEP–related complications, MacDonald[19] investigated 15,000 cases reported in various studies and found 5 cases of seizures, 29 of injury to the teeth and gums, 1 of mandibular fracture, 5 of arrhythmia, 1 of intraoperative awakening, and 1 of burn injury at the site of stimulation. Schwartz *et al*[20] observed 26 cases (0.14%) of TCE-MEP–related complications in 18,862 patients. In examination 2 of this study in which 100 patients were stimulated using one of the methods, there were no such complications. Although the number of patients may not be large, this study demonstrates that the safety of stimulation is similar for both methods.

CONCLUSION

Compared with monophasic stimulation, single biphasic TCE stimulation can elicit MEPs on both sides during intraoperative neurophysiological monitoring, reducing measurement time by half. This also reduces the time surgeons spend standing by as well as overall operation time. Our findings clearly show that, compared with monophasic stimulation, biphasic stimulation produces similar sensitivity, specificity, safety, the same or higher derivation rates, and similar or superior potentials and convenience, and thus promises to be an effective method of transcranial stimulation.

➢ Key Points

- ❑ Both biphasic and monophasic stimulation were performed in 31 patients with cervical compression myelopathy to compare the transcranial electrical motor evoked potentials (TCE-MEPs) of recorded muscles. Deviation rates and amplitudes elicited by biphasic stimulation were either the same or higher than those obtained by monophasic stimulation.
- ❑ TCE-MEP monitoring in 100 patients with cervical compression myelopathy undergoing biphasic stimulation had similar sensitivity and specificity compared with another 100 patients with cervical compression myelopathy undergoing monophasic stimulation. None of the patients in either group experienced complications related to stimulation.
- ❑ Biphasic stimulation was comparable with monophasic stimulation in terms of deviation rate, sensitivity, specificity, and safety, suggesting that it is an effective method for TCE-MEP monitoring during cervical spine surgery.

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ORIGINAL ARTICLE

New classification system for ossification of the posterior longitudinal ligament using CT images

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Abstract
Background Ossification of the posterior longitudinal ligament (OPLL) is most frequently seen in the cervical spine. The types of cervical OPLL are classified into continuous, mixed, segmental, and other based on plain lateral X-ray. Computed tomography (CT) imaging is often used in clinical practice for evaluating ossified lesions as it can detect their precise location, size, and shape. However, to date, no CT classification of OPLL lesions has been proposed.
Methods One hundred and forty-four patients diagnosed with cervical OPLL by plain radiograph were included in this study. Sagittal and axial CT images of the cervical spine were obtained. We propose three classification systems: A, B, and axial. Classification A comprises two lesion types: bridge and nonbridge. Classification B requires examiners to describe all vertebral and intervertebral levels where OPLL exits in the cervical spine. Axial classification comprises central and lateral lesions identified on axial CT images. Seven observers evaluated CT images using this classification system, and intra- and interrater reliability were examined.
Results Averaged Fleiss' kappa coefficient of interrater agreement was 0.43 ± 0.26 among the seven observers, averaged intrarater reliability for the existence of OPLL was 72.4 ± 8.8 % [95 % confidence interval (CI) 67.5–76.8]. Fifty-four patients (37.5 %) had the bridge type and 90 the nonbridge type according to Classification A; 102 (70.8 %) had central and 42 (29.2 %) lateral OPLL in the axial classification. Four representative cases defined according to the three classification types are reported here.
Conclusion Subcommittee members of the Investigation Committee on the Ossification of the Spinal Ligaments of the Japanese Ministry of Public Health and Welfare propose three new classification systems of cervical OPLL based on CT imaging: A, B, and axial.

Study group of subcommittee members of the Investigation Committee on the Ossification of the Spinal Ligaments of the Japanese Ministry of Public Health and Welfare.

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Introduction

Ossification of the posterior longitudinal ligament (OPLL) is characterized by the replacement of ligamentous tissue by ectopic new bone [1]. OPLL often causes narrowing of the spinal canal and has been recognized as one of the causes of myelopathy and/or radiculopathy [2]. The disease was first reported in Japan in 1960 [1]. Since then, numerous cases of OPLL have been reported, and its existence in the general Japanese population is reported to be 1.9–4.3 % among people >30 years [3]. Although the pathogenesis of OPLL has not been fully elucidated, a genetic background factor related to systemic ossification could be involved [4].

A radiological study revealed that OPLL is frequently observed in the cervical spine [5] and are classified as continuous, mixed, segmental, and other types based on plain lateral X-ray of the cervical spine according to the classification established by the Investigation Committee on the Ossification of Spinal Ligaments of the Japanese Ministry of Public Health and Welfare in 1981 [6]. This classification [6] is very simple and easy to use; however, X-ray-based classification has the following potential limitations:

1. Explicit definition of each type is unclear
2. Agreement ratio between examiners has not been confirmed
3. Precise evaluation of the ossified lesion at each vertebral and intervertebral level is not sufficiently expressed
4. Data collection regarding lesion location might be difficult using X-ray classification

Computed tomography (CT) imaging is often used in clinical practice to evaluate OPLL lesions and can detect the precise location, size, and shape of ossified lesions. Thus, several members of the investigation committee were selected to develop new classifications for cervical OPLL using CT imaging. The purpose of this study was to introduce the new classification system and assess its classification adequacy.

Materials and methods

One hundred and forty-four patients diagnosed with cervical OPLL by plain radiograph were entered into this study. All patients were treated and followed in one university hospital. There were 90 men and 54 women, with an average age of 67.5 years (range 36–86 years). Informed consent was obtained from each patient before enrollment, and the study was approved by the Institutional Review Board of the university hospital. Forty-six patients had a history of cervical laminoplasty, which is a posterior decompression surgery in the cervical spine. Patients who had anterior decompression surgery (ADS) for OPLL treatment were excluded, because ADS might affect OPLL configuration. Lateral radiographs [6] were obtained in all patients; accordingly, 35 were classified with continuous, 66 with mixed, 41 with segmental, and two with other OPLL types. Sagittal and axial multidetector CT images (SOMATOME Sensation 64 Cardiac, SIEMENS Co., Erlangen, Germany) were also obtained. Specific CT parameters were 1 tube rotation/s, 17.28 mm/s table-feed speed, 160 mA, and 120 kV. Image reconstructions were made using a CT console (Wizard, SIEMENS, Co.) at a 1-mm interval from the 0.75-mm scan-slice data. A technique was used to determine the threshold for bone-density measurement. Images were constructed using the bone-window setting (width 1,500, center 200); OPLL lesion classifications were established and then evaluated. Classification analysis was independently performed by seven senior spine surgeons. Classification system details are described below.

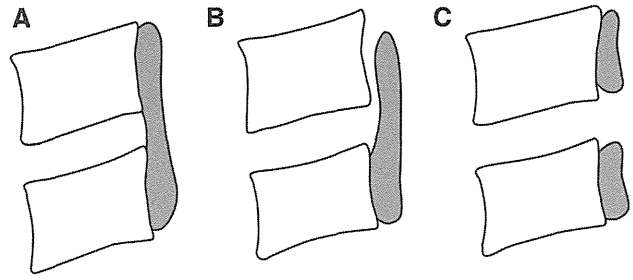

Fig. 1 Typical bridge (**a**) and nonbridge (**b**, **c**) lesions. *Gray areas* ossification of the posterior longitudinal ligament (OPLL) lesions

Classification A

In classification A, ossified lesions were divided into two types: bridge and nonbridge, based on presence or absence of a bony bridge between vertebral bodies on sagittal CT images (Fig. 1). Bony bridge is defined as an OPLL connection to the adjacent posterior margins of vertebral bodies at two or more levels. The observers evaluated the ossification using all of the sagittal CT images. When an ossified lesion connected to the adjacent posterior margin of a vertebral body, even if a small ossification and not necessarily the most extended ossification, it was classified as a bridge type. The number of connected vertebral bodies is included in the classification.

Classification B

This classification requires the examiners to describe all vertebral and intervertebral levels where OPLL >2 mm in

width exist in the cervical spine. Then, connection or disconnection of OPLL is expressed as follows:

① A dot (".") is applied when the OPLL lesion is disconnected, similar to the segmental type in the X-ray classification.
② A slash ("/") is applied when the OPLL lesion is beyond the intervertebral level, without any bridge formation to the adjacent vertebral body.
③ A bar ("-") is applied when the OPLL lesion is beyond the intervertebral level, with bridge formation to the adjacent vertebral body.
④ A circle ("○") is applied at the level of the vertebral body when the OPLL lesion is not attached to the vertebral body (level number is circled). This means that if the OPLL lesion is fused with the vertebral body, the circle is not applied at the level of the vertebral body.

Axial classification

The ossified lesion is divided into two types, central and lateral, on axial CT images at the level where the ossification most significantly occupies the spinal canal. If the posterior prominence of the OPLL is located in the middle third of the spinal canal, it is defined as central; the lateral type is subdivided into left- and right-side types.

Interrater and intrarater reliability and agreement

To evaluate the adequacy of classification A, inter- and intrarater reliability measures were determined with Fleiss' kappa coefficient using a dedicated MATLAB (Mathworks, Paris, France) program. Kappa values of 0.00–0.20 were considered as being slight agreement, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect [7, 8]. As classification B is a complex process, we did not calculate its inter- and intrarater agreement ratio. Likewise, we did not calculate the agreement ratio of the axial image classification.

Results

Interrater and intrarater reliability and agreement in classification A

Averaged Fleiss' kappa coefficient of interrater agreement was 0.43 ± 0.26 among the seven observers. The averaged intrarater reliability for the existence of OPLL was 72.4 ± 8.8 % [95 % confidence interval (CI) 67.5–76.8].

Table 1 Classification A

Ossification of posterior longitudinal ligament (OPLL) lesions	No. of patients
Bridge type	54
2-level	28
3-level	4
4-level	5
4 continuous levels	2
2 + 2 levels	3
>5-level	17
5 continuous levels	3
2 + 3 levels	5
3 + 2 levels	2
7 continuous levels	4
2 + 5 levels	1
8 continuous levels	1
4 + 4 levels	1
Nonbridge type	90

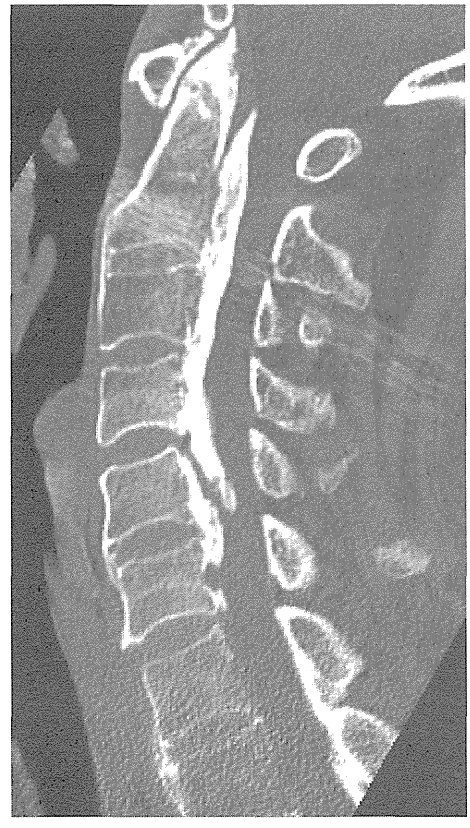

Fig. 2 Typical case with bridge formation in two separate areas. 63-year-old man with three-level bridge at C2–4 and two-level bridge at C5–6 (3 + 2)

Analysis of OPLL type according to classification A and axial classification in 144 patients

Classification A

Fifty-four patients (37.5 %) had a bridge formation between vertebral bodies on the sagittal plane. Bridge formation occurred from vertebral bodies 2–8: in 28 patients at two levels, four patients at three levels, five patients at four levels, and 17 patients at more than five levels (Table 1). Twelve patients had bridge formation in two separate areas, shown as 2 + 2 (2-level bridge + 2-level bridge), 2 + 3, 4 + 4 and 2 + 5 (Table 1 and Fig. 2). Ninety patients had nonbridge OPLL.

Axial classification

One hundred and two patients (70.8 %) had central-type OPLL, and 42 (29.2 %) had the lateral type.

Case presentation

Case 1

The patient, a 59-year-old man, had mixed type OPLL according to X-ray of the cervical spine (Fig. 3a). He had the bridge type according to classification A, as OPLL was seen from C5–7 and was connected to vertebral bodies (Fig. 3b). In classification B, the OPLL lesion was expressed as "C③/4, 5–7". The spinal canal was the narrowest at C4. Ossification was classified as the central type on axial image at C4 (Fig. 3c).

Case 2

A 74-year-old had a C3–7 laminoplasty 5 years earlier. His OPLL was classified as continuous based on cervical X-ray (Fig. 4a). According to classification A, he had bridge type OPLL from C3 to T2 (Fig. 4b). OPLL lesions were expressed as "C3–7" according to classification B and left lateral type at C5–6 according to axial classification (Fig. 4c).

Case 3

A 69-year-old woman with OPLL considered as the segmental type according to X-ray (Fig. 5a). She had the nonbridge type at C4 and C5 and was classified as "C4.5.6" according to classification B (Fig. 5b). She had the central type in axial classification at C5, where the OPLL was the most pronounced (Fig. 5c).

Case 4

A 66-year-old man had mixed OPLL according to cervical X-ray (Fig. 6a), bridge type in classification A, expressed as "C②/3–4/5/6" in classification B (Fig. 6b) and as central type in axial classification at C3 level (Fig. 6c).

Discussion

Lateral X-ray examination is the gold standard by which to determine the existence of OPLL in the cervical spine and by which most physicians establish the diagnosis. OPLL classification by lateral X-ray, proposed by the Investigation Committee on OPLL of the Japanese Ministry of Public Health and Welfare in 1981, has widely been used

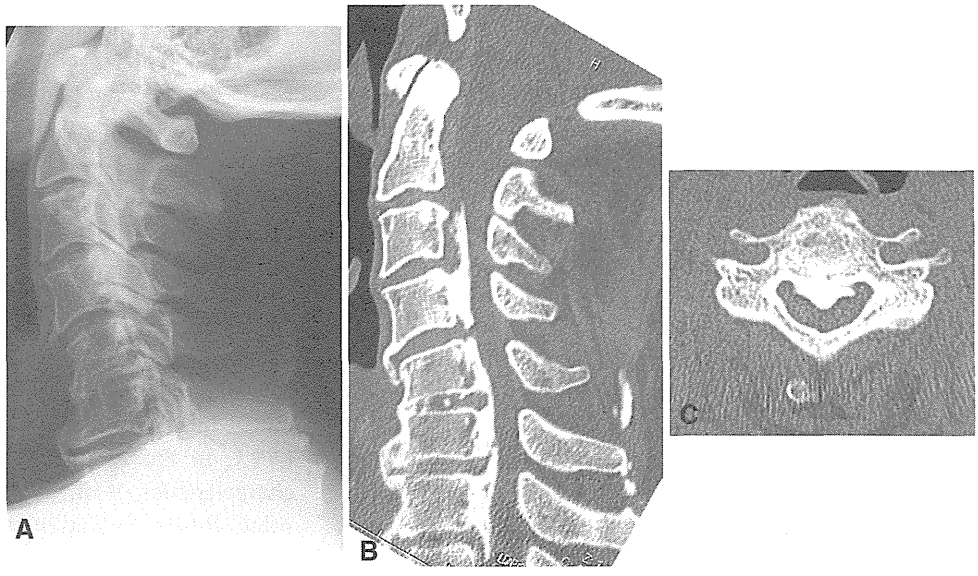

Fig. 3 A 59-year-old man. Lateral cervical X-ray (**a**), midsagittal computed tomography (CT) image (**b**), and axial CT image at C4 (**c**)

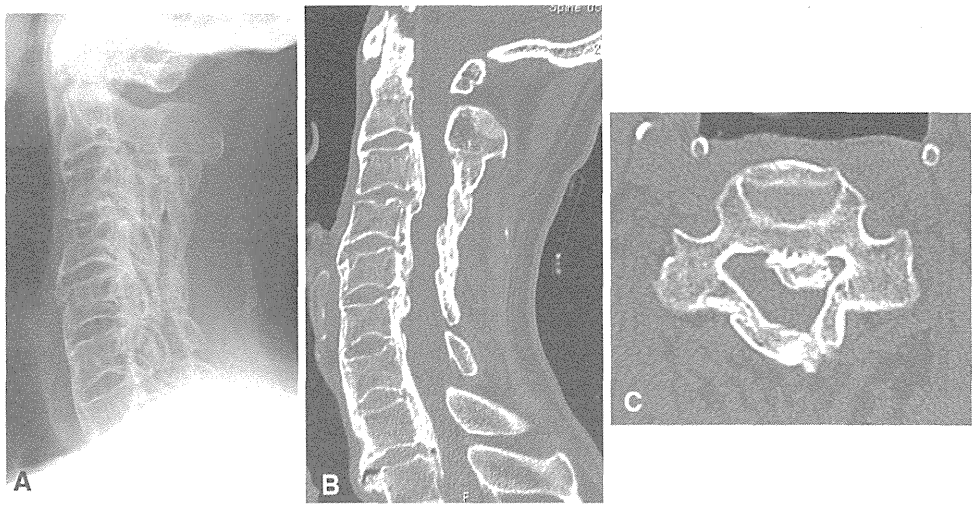

Fig. 4 A 74-year-old man. Lateral cervical X-ray (**a**), midsagittal computed tomography (CT) image (**b**), and axial CT image at C5–6 level (**c**)

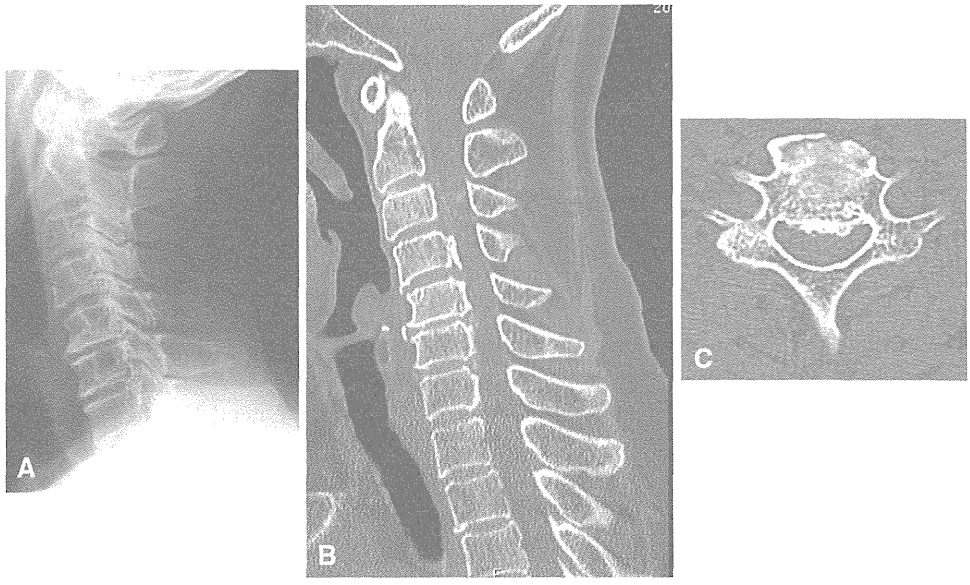

Fig. 5 A 69-year-old woman. Lateral cervical X-ray (**a**), midsagittal computed tomography (CT) (**b**), and axial CT at C5 level (**c**)

[6] and is useful for assessing OPLL characteristics because it is easy to identify ossified lesions and is beneficial for predicting OPLL progression and the occurrence of cervical myelopathy. However, the lateral X-ray does not provide details of lesions themselves. A recent study has shown that CT imaging is necessary for precise detection of such lesions [9]. In fact, CT has become a standard tool for evaluating such ossified lesions, and most spine surgeons obtain CT imaging before surgical intervention in patients with OPLL. Therefore, we decided to develop a new classification system of OPLL based on CT imaging.

In classification A, we noted bridge formation of ossified lesions to the vertebral body for the following two reasons: (1) The absence of bridge formation is directly related to segmental motion of vertebrae, which is lost at the level where the bridge is formed [10]. On the other hand, the segment adjacent to the bridge formation might have greater motion, which results in adjacent segmental instability. It has been reported that segmental motion is a factor causing neurological impairment, such as cervical myelopathy [11]. In their long-term follow-up study, Matsunaga et al. [11] stated that range of motion (ROM) was significantly larger in patients with than those without myelopathy. They emphasized the importance of cervical motion that might lead to the development of neurological compromise. (2) Bridge formation may be related to the extension of ossified lesions along the entire spine. Matsunaga et al. also demonstrated that bridge formation in OPLL in the cervical spine is strongly related to multiple OPLL in the entire spine [9] and might represent the characteristics of diffuse ossification in PLL in the entire spine. Bridge formation can be precisely evaluated by CT imaging, but it is difficult to assess the finding using lateral

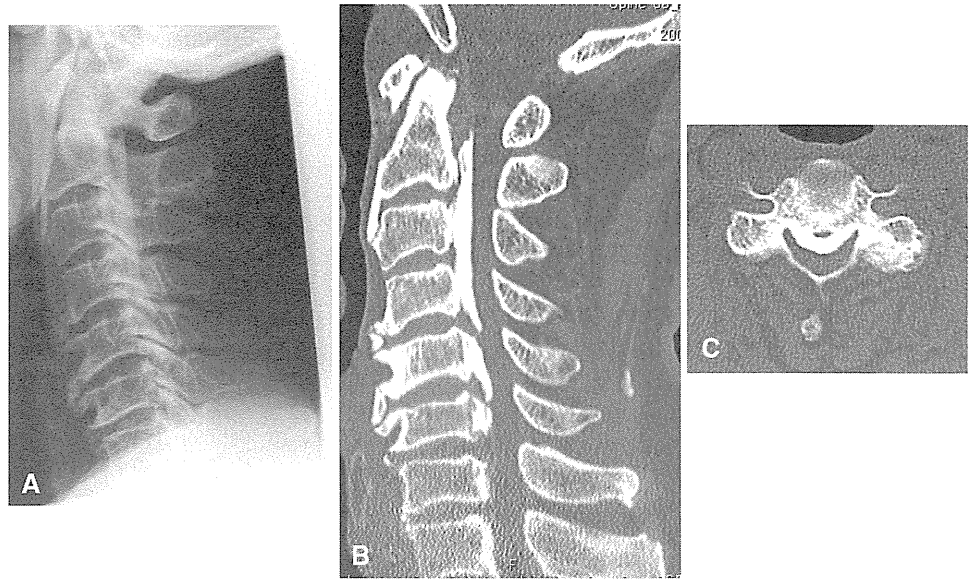

Fig. 6 A 66-year-old man. Lateral cervical X-ray (**a**), midsagittal computed tomography (CT) image (**b**), and axial CT image at C3 (**c**)

X-ray alone. In classification A, the interrater agreement ratio was 0.43 among the seven examiners, indicating moderate agreement. Interrater agreement ratio was not high but seems to be acceptable according to evaluation among the seven examiners. This low ratio might be due to examiners' unfamiliarity with evaluating ossified lesions on CT images. In particular, it is difficult to judge the bony bridge on a CT image if the small ossification connects to the adjacent vertebrae. It might be important to check segmental motion in order to evaluate connection or disconnection between adjacent vertebrae. When the examiners become familiar with the evaluation technique using CT images, the agreement ratio might increase. The averaged intrarater reliability was 72.4 %, which indicates substantial agreement. Therefore, we believe that this classification system is very easy to use and has the potential benefit for evaluating characteristics of cervical OPLL lesions.

CT provides an excellent axial view of the spinal canal, yielding valuable information on the area and median or paramedian location of ossification. In axial-image classification, we selected the level where OPLL most frequently occurs in the spinal canal. Information regarding the ratio of ossified lesions to the spinal canal is very important, because previous report indicate that patients with $\geq$60 % of the cervical spinal canal/stenosis by OPLL had cervical myelopathy [12, 13]. Laterality of the ossified lesion can be evaluated using this classification. Patients with cervical myelopathy due to OPLL sometimes have a predominant side of neurological impairment [12]. However, data of patients' clinical symptoms were not included in the study reported here. The relationship between the axial classification and clinical symptoms will be an important research theme for future studies.

For classification B, we evaluated ossified lesions at all vertebral and intervertebral levels and checked for and described their connection or disconnection and whether or not lesions are attached to the upper or lower border of the vertebral body. This classification provides a precise means of identifying the existence of OPLL lesions and, if they are present, describes their characteristics. However, this classification is somewhat complex, and we believe it may not be appropriate for daily clinical use but, rather, may be useful for precise data collection in future studies.

This study has several limitations. First, we did not check the dynamic factor or cervical spine alignment using CT images. CT was taken with the patient in a supine position without performing flexion and extension analysis. Thus, segmental motion could not be detected. Second, we did not evaluate the relationship between OPLL types and clinical symptoms. In the axial image, the occupied ratio against the spinal canal can be easily detected. It might be interesting to determine how laterality is related to the predominant side of the neurological deficit; however, we have no MRI information regarding spinal cord compression due to OPLL. The relationship of OPLL lesions and/or dynamic factors to clinical symptoms is a theme for future study. Thirdl, the agreement ratio for both types of classification A is moderate, although we consider it acceptable for use. Classification B is a highly complicated procedure, and we thus did not analyze intra- or interobserver agreement ratio. Despite these several study limitations, CT classification provides precise evaluation of OPLL lesions and might also be useful to help determine the appropriate operative procedure. For example, fusion surgery is not necessary at a level where there is bridge formation, because there is no segment motion at that level. This might be the advantage of CT classification over X-ray classification.

In conclusion, we, the subcommittee members of the Investigation Committee on the Ossification of the Spinal Ligaments of the Japanese Ministry of Public Health and Welfare, propose three new classification systems for cervical OPLL based on CT imaging: classification A, classification B, and the axial image classification. It is our hope that these classifications will be recognized as useful clinical assessment tools for evaluating OPLL lesions.

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Conflict of interest The authors declare that they have no conflict of interest.

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Preoperative Predictors of Patient Satisfaction with Outcome after Cervical Laminoplasty

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Abstract

Study design Prospective cohort study.

Objective The purpose of the present study was to identify the predictors of patient satisfaction with outcome after cervical laminoplasty for compressive cervical myelopathy.

Methods A cohort of 143 patients with compressive myelopathy who underwent cervical double-door laminoplasty between 2008 and 2011 was studied prospectively. The principal outcome was patient satisfaction with outcome at 1 year after surgery. Patient satisfaction was graded on an ordinal scale from 1 to 7. Subjective health-related quality of life (QOL) and objective disease-specific outcome was measured by Short Form-36 (SF-36) and the Japanese Orthopaedic Association (JOA) score, respectively, before surgery and at 1-year follow-up. We evaluated the association between patient satisfaction at 1-year follow-up and various baseline parameters, including patient demographics, duration of symptoms, comorbidities, imaging findings, JOA score, and SF-36 scores.

Results A total of 116 patients completed subjective and objective follow-up for a minimum of 1 year. Of 116 patients, 95 patients (81.9%) were satisfied with the outcome ("satisfied a little" or more). The unsatisfied group ("neutral" or less) showed significantly lower baseline SF-36 scores in bodily pain (BP), general health perceptions (GH), and vitality (VT) domains compared with the satisfied group. At the 1-year follow-up, SF-36 scores showed significant differences between the groups in all eight domains, whereas the JOA score showed no significant difference.

Conclusions Lower baseline QOL measured by SF-36 scores, specifically in BP, GH, and VT domains, are associated with lower satisfaction with outcome after cervical laminoplasty.

Keywords
- cervical spine
- myelopathy
- laminoplasty
- outcome
- patient satisfaction

Introduction

Over the past decade, there has been increasing interest in the use of patient-based measures of medical care. Patient-based measures include generic measures, disease-specific measures, and measures of patient satisfaction. Measuring patient satisfaction has a variety of clinical and economic implications. For example, it can be used for validating the quality of care, developing patient care models, and facilitating quality improvement.[1–3] Despite several potential benefits to both clinicians and patients, measurement of patient satisfaction has not been used effectively in clinical settings.

The assessment of outcome after cervical spine surgery has historically involved objective disease-specific scales, such as

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the Nurick score,[4] the European myelopathy scale,[5] the myelopathy disability index,[6] and the Japanese Orthopaedic Association (JOA) score.[7] Because these scales evaluate only physician-based outcomes, limited information is available regarding patient-based outcomes, including patient satisfaction, after cervical spine surgery. Identification of factors that determine patient satisfaction after surgery would be useful for improving the quality of care. Moreover, identifying predictors of patient satisfaction after surgery is of primary concern for surgeons.

The purpose of the present study was to identify the preoperative predictors of patient satisfaction with outcome after cervical laminoplasty for compressive cervical myelopathy.

Materials and Methods

Study Population

A cohort of 143 patients with compressive myelopathy who underwent cervical double-door laminoplasty between 2008 and 2011 was studied prospectively. The research protocol was approved by the Institutional Review Board of the authors' institute. The diagnosis of myelopathy was confirmed both by thorough neurologic examination and by imaging studies showing spinal cord compression, which is generally associated with an intramedullary high-intensity area on T2-weighted magnetic resonance imaging (MRI). Exclusion criteria included concurrent lumbar spine surgery, traumatic spinal cord injury, and other disorders that might impair motor function such as cerebral infarction, rheumatoid arthritis, or cerebral palsy. Based on these criteria, 20 patients were excluded. Of the remaining 123 patients, 116 patients completed the objective and subjective follow-up evaluations done at a minimum of 1 year (mean 35 ± 13 months; range: 14 to 55 months) after surgery. Six patients were lost to follow-up, and one patient died due to a malignant tumor. In addition to patient characteristics, the duration of symptoms and the severity of comorbidity were investigated. The severity of comorbidity was graded by the Cumulative Illness Rating Scale (CIRS).[8] The procedure for double-door laminoplasty has been described in detail elsewhere.[9]

Imaging Parameters

Preoperative cervical alignment was measured as the C2/7 angle on a lateral radiograph taken in the neutral position. The range of motion between C2 and C7 was also measured on flexion-extension radiographs. All but one patient with a pacemaker underwent MRI before surgery. Preoperative MRI was analyzed using the following two parameters: transverse area of the spinal cord at the levels of maximal compression and intramedullary signal intensity (SI) changes on T2-weighted images. SI changes were classified as type 0 if no intramedullary high SI on T2-weighted images was noted, type 1 if a predominantly (>50%) faint and fuzzy border of high SI was noted, or type 2 if a predominantly (>50%) intense and well-defined border of high SI was noted.[10] The classification of SI changes was performed independently by two blinded readers (A.K. and E.T.). If they disagreed with each other's reading, a third reader (A.S.) was consulted as a tiebreaker.

Subjective and Objective Outcomes

The principal outcome was patient satisfaction with outcome evaluated at the time of 1-year follow-up. This was assessed with the use of a paper questionnaire that asked the patient, "How satisfied are you with the outcome?" Patient satisfaction was graded on an ordinal scale from 1 to 7 (1, "very dissatisfied"; 2, "dissatisfied"; 3, "dissatisfied a little"; 4, "neutral"; 5, "satisfied a little"; 6, "satisfied"; and 7, "very satisfied"). The response was then dichotomized into two categories: satisfied and unsatisfied. The satisfied group comprised patients with grade 5 satisfaction ("satisfied a little") or more, and the unsatisfied group comprised patients with grade 4 satisfaction ("neutral") or less. Subjective health-related quality of life (QOL) and objective disease-specific function was measured by Short Form-36 (SF-36) and JOA scores, respectively, before surgery and at 1-year follow-up.

Statistical Analysis

Group data are presented as means ± standard deviations. Within-group comparisons were performed using the Wilcoxon signed rank test for paired samples, and between-group comparisons were made using the Mann-Whitney *U* test (except for the type of intramedullary SI on MRI, which was analyzed by the chi-square test). All data was analyzed using statistical software (SPSS version 17, SPSS Inc., Chicago, Illinois, United States).

Results

Patient Characteristics

Patients comprised 78 men and 38 women (mean age, 63 years; age range: 20 to 88 years). The follow-up rate was 95.1%. Patient characteristics, duration of symptoms, the severity of comorbidity measured by CIRS, and the levels of maximal compression are summarized in ►**Table 1**.

Objective and Subjective Outcomes

Of the 116 patients, 95 (81.9%) were satisfied with the outcome ("satisfied a little" or more; ►**Fig. 1**). These 95 patients were categorized into the satisfied group, and the remaining 21 patients ("neutral" or less) were categorized into the unsatisfied group. At the 1-year follow-up, the mean SF-36 scores improved significantly compared with baseline scores in all eight domains (►**Fig. 2**). The SF-36 general health perceptions (GH) domain showed the smallest postoperative change in the mean value (3.6 ± 15.8) among the eight domains. The median JOA score also improved significantly from a preoperative score of 11 to a postoperative score of 14 ($p < 0.0001$, Wilcoxon signed rank test).

Comparisons between the Satisfied and Unsatisfied Groups

To identify parameters for predicting patient satisfaction with outcome after surgery, various baseline data, including

Table 1 Patient characteristics ($n = 116$)

Characteristics	
Age (y)	63.3 ± 12.7
Gender (M/F)	78/38
Etiology of myelopathy	
Spondylosis	77 (66%)
OPLL	39 (34%)
Duration of symptom (mo)	34.3 ± 47.2
CIRS	6.9 ± 3.1
Level of the maximum compression	
C2–C3	2
C3–C4	39
C4–C5	48
C5–C6	26
C6–C7	1

Abbreviations: CIRS, Cumulative Illness Rating Scale; OPLL, ossification of posterior longitudinal ligament.
Note: Data are reported as numbers (%) or mean ± standard deviation.

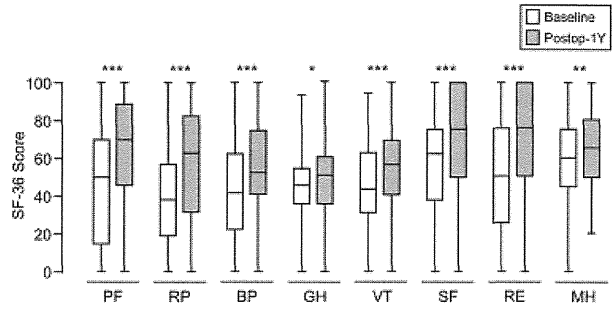

Fig. 2 Postoperative changes in SF-36 scores. White bars indicate baseline values and gray bars indicate 1-year follow-up values. SF-36 scores increase significantly compared with baseline values in all eight domains. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; the Wilcoxon signed rank test. Abbreviations: BP, bodily pain; GH, general health perceptions; MH, mental health; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; SF-36, MOS 36-Item Short-Form Health Survey; VT, vitality.

patient demographics, imaging findings, and preoperative subjective and objective outcomes, were compared between the satisfied and unsatisfied groups (►**Table 2**). The mean age and the severity of comorbidity evaluated by CIRS were higher in the unsatisfied group than in the satisfied group (67.4 versus 62.4, and 7.8 versus 6.7, respectively), although the difference was not significant. The ratio of type 2 SI, which is reportedly associated with poor functional outcome, was also higher in the unsatisfied group than in the satisfied group (0.43 versus 0.35); however, the difference was not significant. On the other hand, the unsatisfied group had significantly lower SF-36 scores in bodily pain (BP), GH, and vitality (VT) domains than the satisfied group.

Comparisons of postoperative outcomes between the satisfied and unsatisfied groups are summarized in ►**Table 3**. At the 1-year follow-up, the unsatisfied group showed a lower mean JOA score than the satisfied group (13.2 versus 14.2), but the difference was not significant. When postoperative JOA scores were analyzed separately for the six function categories (motor functions of upper and lower limbs; sensory functions of upper limbs, lower limbs, and torso; and bladder function), only sensory function of upper limbs showed a significant difference between the satisfied and the unsatisfied groups (1.3 ± 0.5 versus 1.0 ± 0.6, $p = 0.010$, Mann-Whitney U test). In contrast, the satisfied group showed significantly higher SF-36 scores than the unsatisfied group in all eight domains. With regard to JOA score improvement, 55 patients showed good score improvement after surgery (>50%). Although the ratio of patients with good improvement was higher in the satisfied group than the unsatisfied group, there was no statistically significant difference between the groups (49/95 versus 6/21, $p = 0.090$, Fischer exact test).

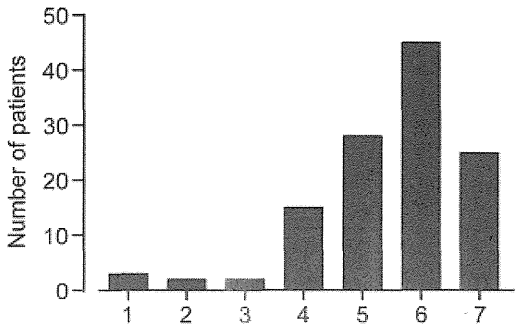

Fig. 1 The distribution of grades for patient satisfaction with outcome evaluated at 1-year follow-up.

Three patients (two in the satisfied group and one in the unsatisfied group) experienced C5 palsy, which recovered spontaneously within 3 months after surgery. Six patients (five in the satisfied group and one in the unsatisfied group) had cerebrospinal fluid leakage, which also recovered spontaneously within 2 weeks after surgery. The incidence of these complications did not differ significantly between the two groups ($p > 0.99$ and $p = 0.44$, respectively, Fisher exact test).

Discussion

This prospective study evaluated various patient parameters and baseline functional outcomes as predictors of postoperative patient satisfaction. The key finding of this study was that lower preoperative QOL measured by SF-36 scores, specifically in the BP, GH, and VT domains, was associated with lower postoperative satisfaction. Another finding was that patient satisfaction was closely associated with the current state of patient-based outcome rather than that of physician-based functional outcome. These results highlight the

Table 2 Comparison of patient demographics and baseline outcomes between satisfied and unsatisfied groups

Parameters	Satisfied group	Unsatisfied group	*p* value
Age at the operation (y)	62.4 ± 12.6	67.4 ± 12.7	0.071
Gender (M/F)	62/33	16/5	0.334
Ratio of OPLL patients	0.35 (33/95)	0.29 (6/21)	0.588
Duration of symptom (mo)	34.5 ± 49.5	33.8 ± 34.9	0.412
CIRS	6.7 ± 3.2	7.8 ± 2.2	0.052
Radiograph			
C2/7 angle (degree)	12.4 ± 10.0	10.1 ± 10.7	0.257
Range of motion (degree)	35.8 ± 12.7	36.2 ± 10.0	0.917
MRI			
Narrowest canal area (mm^3)	62.4 ± 16.4	66.5 ± 12.7	0.158
Ratio of type 2 intramedullary SI	0.35 (33/94)	0.43 (9/21)	0.505
JOA score	11.0 ± 2.7	11.5 ± 1.6	0.628
SF-36			
Physical functioning	46.5 ± 28.3	38.8 ± 27.4	0.323
Role-physical	39.2 ± 28.6	39.6 ± 34.1	0.880
Bodily pain	47.7 ± 26.3	33.5 ± 18.3	0.031[a]
General health perceptions	46.2 ± 17.5	35.5 ± 14.1	0.018[a]
Vitality	45.4 ± 21.3	35.2 ± 13.9	0.027[a]
Social functioning	57.6 ± 27.8	61.7 ± 31.8	0.511
Role-emotional	47.8 ± 31.8	53.3 ± 37.4	0.581
Mental health	58.7 ± 21.1	48.8 ± 23.0	0.094

Abbreviations: CIRS, Cumulative Illness Rating Scale; JOA, Japanese Orthopaedic Association; OPLL, ossification of posterior longitudinal ligament; SF-36, MOS 36-Item Short-Form Health Survey; SI, signal intensity.
Note: Unless otherwise indicated, values are expressed as the mean ± standard deviation.
[a]Statistically significant ($p < 0.05$, Mann-Whitney *U* test or chi-square test).

importance of patient-based outcome as a determinant of patient satisfaction after cervical spine surgery.

Predictors of patient satisfaction have been reported almost exclusively in patients undergoing lumbar spine surgery. Soroceanu et al examined the relationship between preoperative expectations, satisfaction, and functional outcomes in patients undergoing lumbar and cervical spine surgery.[11] They identified preoperative expectations as a predictor of patient satisfaction

Table 3 Comparison of postoperative outcomes between satisfied and unsatisfied groups

Parameters	Satisfied group	Unsatisfied group	*p* value
JOA score	14.2 ± 2.1	13.2 ± 2.1	0.052
SF-36			
Physical functioning	69.4 ± 24.9	49.5 ± 27.7	0.003[a]
Role-physical	64.3 ± 28.9	33.8 ± 28.3	<0.001[a]
Bodily pain	59.7 ± 22.5	41.8 ± 25.2	0.001[a]
General health perceptions	51.0 ± 19.9	33.5 ± 16.2	<0.001[a]
Vitality	57.6 ± 19.5	42.2 ± 22.5	0.007[a]
Social functioning	77.8 ± 24.1	61.3 ± 22.3	0.003[a]
Role-emotional	72.4 ± 29.8	37.1 ± 32.2	<0.001[a]
Mental health	68.2 ± 19.5	53.3 ± 16.6	0.002[a]

Abbreviations: JOA, Japanese Orthopaedic Association; SF-36, MOS 36-Item Short-Form Health Survey.
Note: Values are expressed as the mean ± standard deviation.
[a]Statistically significant ($p < 0.05$, Mann-Whitney *U* test).

after surgery; however, the result was obtained from a mixed patient group, the majority of whom underwent lumbar spine surgery. To the best of our knowledge, no research has been reported in the current literature examining predictors of satisfaction exclusively in patients undergoing cervical spine surgery.

Predictors of patient satisfaction after lumbar spine surgery include patients' assessments of their own health, comorbidity, and the degree of expectations for surgery.[11–13] Katz et al demonstrated that a powerful predictor of satisfaction was patients' rating of their own health, which was derived from a simple question: "How would you rate your health?"[12] This result is similar to the present result that patients who were not satisfied with their outcome had significantly lower preoperative general health perception as measured by the SF-36 GH domain. Moreover, Yee et al found that the SF-36 GH domain predicted patients with a high expectation for surgery and that patients with high expectation showed greater functional recovery after surgery.[13] These results are similar to the present result in cervical spine surgery that satisfied patients showed significantly higher preoperative scores in the SF-36 GH and VT domains. Although the underlying common mechanism remains to be elucidated, poor health perceptions and low vitality may play a role in magnifying the perception of residual symptoms after surgery, leading to lower satisfaction with outcome.

Several studies have shown predictors of functional outcome after surgical treatment of cervical spondylotic myelopathy.[14–16] These include age, duration of symptoms, preoperative neurologic function, and SI change of the spinal cord on MRI. In the present study, none of these factors differed significantly between the satisfied and unsatisfied groups. These results suggest that patient dissatisfaction does not stem solely from a poor functional outcome, and that traditional objective measures are insufficient for predicting patient satisfaction. Because the vast majority of studies have used physician-based outcome for the analysis of predictors, further detailed studies are needed to identify predictors of patient-based outcome after cervical spine surgery.

This study has several important limitations. First, this study did not evaluate the influence of patient expectation for surgery. Patient expectation has been suggested as a predictor of patient satisfaction after lumbar spine surgery.[13] Thus, future studies should include patient expectation as a candidate predictive factor. Second, because this study focused on preoperative predictors of patient satisfaction, we have limited information on perioperative complications such as axial pain, which might affect patient satisfaction. Detailed prospective studies on bodily pain would be valuable, because unsatisfied patients showed significantly lower SF-36 BP scores than satisfied patients, both at baseline and at 1-year follow-up. Finally, the small number of patients in the unsatisfied group suggests increased possibility of type II statistical error. A larger patient cohort is required to allow more accurate comparisons between the groups.

Predictors of poor surgical outcome are useful if they can be modified and if modification of the factors improves outcomes. It is unclear whether general health perceptions are modifiable before surgery; however, given the smallest postoperative change in SF-36, it might be difficult to gain a dramatic change in general health perception by short-term interventions before surgery. Careful preoperative explanation of the course and outcome is recommended for patients with poor baseline general health perceptions because low fulfillment of expectations is associated with low patient satisfaction after spine surgery.[11] In particular, it may be important to convey information about the possibility of persistent numbness and pain in the extremities even after complete decompression of the spinal cord, because the unsatisfied group showed significantly deteriorated sensory function in the upper extremities.

It remains to be elucidated how much surgeons should pay attention to patient satisfaction and whether surgeons should alter the decision-making process to please patients rather than adhere to evidence-based medicine. Lyu et al recently demonstrated that patient satisfaction is not related to standard process-of-care measures that have long been used to increase surgical quality.[17] Moreover, patient satisfaction may be driven by the patients' feelings and emotions at the moment of surveillance rather than the assessment of the entire experience.[18] Given the limited availability of universal and standardized instruments in measuring patient satisfaction, it may be too early to treat patients solely on the basis of patient satisfaction. Further study is required before patient satisfaction is widely applied to surgeons as a quality indicator.

Disclosures

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

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ORIGINAL ARTICLE

Neuroprotective therapy with granulocyte colony-stimulating factor in acute spinal cord injury: a comparison with high-dose methylprednisolone as a historical control

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Abstract
Purpose We performed a phase I/IIa clinical trial and confirmed the safety and feasibility of granulocyte colony-stimulating factor (G-CSF) as neuroprotective therapy in patients with acute spinal cord injury (SCI). In this study, we retrospectively analyzed the clinical outcome in SCI patients treated with G-CSF and compared these results to a historical cohort of SCI patients treated with high-dose methylprednisolone sodium succinate (MPSS).
Methods In the G-CSF group ($n = 28$), patients were treated from August 2009 to July 2012 within 48 h of the injury, and G-CSF (10 μg/kg/day) was administered intravenously for five consecutive days. In the MPSS group ($n = 34$), patients underwent high-dose MPSS therapy from August 2003 to July 2005 following the NASCIS II protocol. We evaluated the ASIA motor score and the AIS grade elevation between the time of treatment and 3-month follow-up and adverse events.
Results The ΔASIA motor score was significantly higher in the G-CSF group than in the MPSS group ($p < 0.01$). When we compared AIS grade elevation in patients with AIS grades B/C incomplete paralysis, 17.9 % of patients in the G-CSF group had an AIS grade elevation of two steps compared to 0 % of patients in the MPSS group ($p < 0.05$), and the incidence of pneumonia was significantly higher in the MPSS group (42.9 %) compared to the G-CSF group (8.3 %) ($p < 0.05$).
Conclusions These results suggest that G-CSF administration is safe and effective, but a prospective randomized controlled clinical trial is needed to compare the efficacy of MPSS versus G-CSF treatment in patients with SCI.

Keywords Spinal cord injury · Neuroprotective therapy · G-CSF · High-dose methylprednisolone · Clinical trial

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Introduction

Acute spinal cord injury (SCI) is characterized by two pathological phases known as primary and secondary injury [1]. Primary injury occurs when the tissue is destroyed by direct mechanical trauma. Secondary injury occurs when the spinal cord reacts to the primary injury. Neurons and glial cells that were left intact by the initial trauma undergo apoptosis during the secondary phase of injury. Multiple factors exacerbate the secondary phase of injury, including vascular changes, increased concentrations of free radicals and free fatty acids, ionic mechanisms of axonal injury, glutamate excitotoxicity and immune and inflammatory reactions [2]. Secondary injury is, therefore, a rich target for drug therapy [3]. According to the NASCIS II protocol, high-dose methylprednisolone sodium succinate (MPSS) is the standard treatment for attenuation of

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secondary injury after acute SCI [4]. In recent years, MPSS therapy for acute SCI became controversial. Cochran review shows the efficacy of MPSS therapy for SCI [5]. In contrast, the updated guidelines for the management of acute cervical spine and spinal cord injury released by American Association of Neurological Surgeons and Congress of Neurological Surgeons Guidelines Committee described MPSS therapy for SCI as "not recommend" [6]. Hence, new drug therapies for the treatment of secondary injury after acute SCI are needed.

Granulocyte colony-stimulating factor (G-CSF) is a clinically important cytokine that is commonly used to treat neutropenia [7]. Granulocyte colony-stimulating factor also has non-hematopoietic functions and has been suggested as a treatment for neuronal injury [8]. We have previously reported that G-CSF promotes functional recovery in a rodent model of SCI [9–12]. Based on these results, we performed a preliminary phase I/IIa clinical trial and confirmed the safety and feasibility of G-CSF as neuroprotective therapy in patients with acute SCI [13]. The next step is to verify the efficacy of G-CSF compared to standard high-dose MPSS therapy. Toward this end, we retrospectively analyzed the clinical outcome and the incidence of drug-related adverse events in SCI patients treated with G-CSF and compared these results to a historical cohort of SCI patients treated with MPSS.

Methods

Study design

The study was designed as a retrospective comparative analysis using an historical cohort control.

Patient population

Between August 2009 and July 2012, all patients with complete or incomplete C3-C7 cervical SCI who presented to Chiba University Hospital within 48 h of injury were recruited into the study. Exclusion criteria included the following: (1) age younger than 16 years or greater than 85 years, (2) treatment with high-dose MPSS therapy after the SCI event, (3) splenomegaly or altered mental status, (4) history of leukemia, thrombosis or embolism, (5) current treatment of myocardial infarction or angina, and (6) evidence of malignant disease within the last 5 years. Pregnant patients were also excluded. Written informed consent was obtained from all patients prior to G-CSF treatment (G-CSF group).

Patients with acute cervical SCI who received high-dose MPSS therapy following the NASCIS II protocol between August 2003 and July 2005 served as an historical control (MPSS group). Patients were selected based on the same exclusion criteria outlined above. A larger number of patients with complete paralysis (American Spinal Injury Association impairment scale: AIS grade A) were observed in the MPSS group compared to the G-CSF group. No other significant differences in patient background were observed between the two groups, including patient age, sex, injury level and AIS grade (Chi square test).

Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Boards of both participating institutions. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on harmonization good clinical practice guidelines.

Treatment

G-CSF group

Patients were treated with i.v. Granulocyte colony-stimulating factor (dissolved in normal saline) at a dose of 10 μg/kg/day (administered over 1 h) for five consecutive days. Granulocyte colony-stimulating factor dose regimen was determined by the previous preliminary clinical trial of G-CSF neuroprotective therapy for acute SCI, of which study design was single armed with dose escalation [13].

MPSS group

Methylprednisolone sodium succinate was administered according to the NASCIS II protocol within 8 h after injury. Methylprednisolone sodium succinate was first administered as a bolus dose of 30 mg/kg MPSS. After a 45-min withdrawal period, 5.4 mg/kg was administered intravenously over the next 23 h.

Patients in each group received similar surgical, rehabilitation and nursing care.

Efficacy assessments

Neurologic function was assessed with the American spinal injury association (ASIA) motor and sensory scores immediately upon study entry and after 3 months of follow-up. The primary outcome was the change in ASIA motor score between the time of treatment and 3 months following treatment. The initial analysis included all patients, including those with AIS grade A paralysis. However, because these patients have complete paralysis and typically demonstrate little significant neurological

recovery, a second comparison was performed in which patients with AIS grade A were excluded.

Assessment of adverse events

Adverse events were evaluated retrospectively by review of patient records and compared between treatment groups. Pneumonia was defined as respiratory distress accompanied by an infiltrating shadow on plain radiogram, positive sputum cultures and an elevated white blood cell count (WBC) or C-reactive protein. Urinary tract infection was defined as fever and elevated WBC in the context of positive urinary cultures. Notably, G-CSF treatment alone increases WBC, hence these criteria were excluded from the diagnosis of pneumonia and urinary tract infection in the G-CSF group. Gastric ulcers were defined as obvious ulcers of any stage observed by upper gastrointestinal fiber examination. Other adverse events were determined by review of patient records. The severity of each adverse event was assessed according to the Japanese version of the common terminology criteria for adverse events (CTCAE), version 4.0. The initial analysis of adverse events was performed on all patients, including those with AIS grade A. However, because these patients have complete paralysis which might increase the incidence of pneumonia and urinary tract infections, a second analysis was performed in which patients with severe incomplete paresis AIS grades B and C.

Statistical analysis

The ASIA motor score and the ΔASIA motor score were analyzed by the Mann–Whitney's U test. The extent of AIS grade elevation between the time of treatment and 3-month follow-up and the number of adverse events were compared between treatment groups using Fisher's exact test. A $p < 0.05$ was considered significant.

Results

Patient background data are shown in Table 1. No statistically significant differences in age, sex, mechanism of injury or injured vertebral level were observed between the groups. No statistically significant difference was observed in the baseline ASIA motor scores between the G-CSF and control groups (59.0 ± 29.6 and 50.3 ± 33.0, respectively). The ΔASIA motor score was significantly higher in the G-CSF group than in the MPSS group (27.7 ± 19.8 and 12.0 ± 11.0, respectively, $p < 0.01$) when all patients were included in the analysis.

The difference in patient background data between the groups, the MPSS group contained significantly larger number of AIS A patients who generally show poor neurological recovery, must influence the neurological outcome. Therefore, we excluded patients with AIS A complete paralysis and compared ΔASIA motor score in patients with severe incomplete paresis AIS grades B and C between both groups (12 patients in the G-CSF group and 14 patients in the MPSS group). Repeatedly, the ΔASIA motor score was also significantly higher in the G-CSF compared to the MPSS group (44.4 ± 17.2 and 17.4 ± 13.6, respectively, Fig. 1a, $p \leq 0.01$).

Next, the change in the AIS grade between the time of treatment and 3 months after treatment was compared between groups (Fig. 1b). We found that 67.9 % of patients in the G-CSF group had an AIS grade elevation of more than one step compared to 50.0 % of patients in the MPSS group, a difference that was not statistically significant. It is widely known that patients with AIS grade A complete paralysis demonstrate very little AIS grade elevation following injury. The MPSS group included more patients with AIS grade A paralysis, hence these results might underestimate the grade elevation in this group. To exclude the bias of patient background difference, we compared AIS grade change between both groups in AIS B/C patients, excluding AIS A complete paralysis patients and AIS D minor injury patients. We found that 91.7 % of patients in the G-CSF group had an

Table 1 Patient background data

	G-CSF	MPSS
Number	28	34
Male	21	27
Female	7	7
Age cause of injury	57.5 (38–72)	60.5 (18–85)
Over-turning	11	11
Falling	7	11
Road trauma	6	11
Falling Object	1	0
Sports	3	1
AIS		
A	2	9
B	4	3
C	8	11
D	14	11
Level of injury		
C2/3	0	3
C3/4	10	13
C4/5	9	5
C5/6	7	8
C6/7	2	4
Unclear case		1

The MPSS group contained significantly larger number of AIS A patients, whereas no statistically significant differences in age, sex, mechanism of injury, injured vertebral level or baseline ASIA motor score were observed between the groups

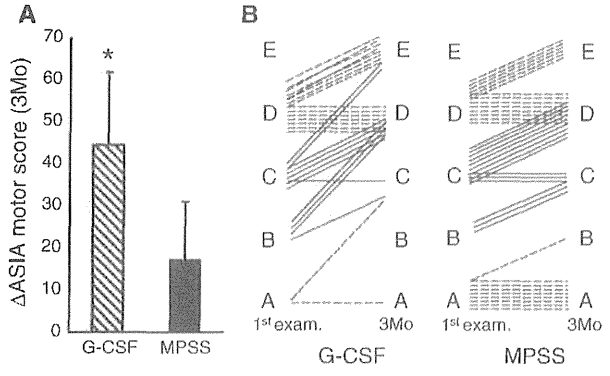

Fig. 1 Neurological recovery. The difference in patient background data between the groups, the MPSS group contained significantly larger number of AIS A patients who generally show poor neurological recovery, must influence the neurological outcome. Therefore, we excluded patients with AIS A complete paralysis and compared ΔASIA motor score in patients with severe incomplete paresis AIS grades B and C between both groups [12 patients in the G-CSF group and 14 patients in the MPSS group, (**a**)]. The ΔASIA motor score was also significantly higher in the G-CSF compared to the MPSS group [44.4 ± 17.2 and 17.4 ± 13.6, respectively, (**a**), $p < 0.01$]. Next, the change in the AIS grade between the baseline and 3 months after treatment was compared between groups (**b**). To exclude the bias of patient background difference, we compared AIS grade change between both groups in AIS B/C patients (*solid lines*), excluding AIS A complete paralysis patients and AIS D minor injury patients (*dashed line*). We found that 91.7 % of patients in the G-CSF group had an AIS grade elevation of more than one step compared to 78.6 % of patients in the MPSS group, a difference that was not statistically significant. However, we observed that 17.9 % of patients in the G-CSF group had an AIS grade elevation of two steps compared to 0 % of patients in the MPSS group ($p < 0.05$)

AIS grade elevation of more than one step compared to 78.6 % of patients in the MPSS group, a difference that was not statistically significant. However, we observed that 17.9 % of patients in the G-CSF group had an AIS grade elevation of two steps compared to 0 % of patients in the MPSS group ($p \leq 0.05$).

Finally, we compared the incidence of adverse events between treatment groups. The incidence of pneumonia was significantly higher in the MPSS group (44.1 %) compared to the G-CSF group (3.6 %). It has been shown that the severity of paralysis positively correlates with the incidence of pneumonia in patients with SCI. Hence, the fact that the MPSS group contained more patients with AIS grade A complete paralysis might have contributed to the higher incidence of pneumonia observed in the MPSS group. To exclude this bias, we analyzed the incidence of pneumonia in patients with AIS grades B/C incomplete paralysis. Again, we observed a significant difference in the incidence of pneumonia between treatment groups (42.9 % in the MPSS group and 8.3 % in the G-CSF group, Table 2, $p < 0.05$).

No significant difference in the incidence of urinary tract infections was observed between groups (35.7 % in the MPSS group and 16.7 % in the G-CSF group).

Table 2 Incidence of adverse events in AIS B/C incomplete paralysis patients

	G-CSF ($n = 12$)	MPSS ($n = 14$)	p-value
Pneumonia	1 (8.3 %)	6 (42.9 %)	$p < 0.05$
Urinary tract infection	2 (16.7 %)	5 (35.7 %)	$p = 0.17$
Gastric ulcer	0 (0 %)	2 (14.3 %)	$p = 0.27$

The difference in patient background data between the groups, the MPSS group contained significantly larger number of AIS A patients who can be easily affected with pneumonia, must influence the incidence of pneumonia. Therefore, we compared the incidence of pneumonia in incomplete paralysis patients of both groups, the result showed significant difference between G-CSF and MPSS groups

The incidence of gastric ulcers tended to be higher in the MPSS group compared to the G-CSF group (14.7 and 0 %, respectively, $p = 0.051$). When patients with AIS grade A and D were excluded from the analysis, no significant difference was observed between treatment groups.

Discussion

In the present study, the G-CSF group showed better neurological recovery compared to the MPSS group. Moreover, the incidence of severe adverse events is less frequent in patients treated with G-CSF than in patients treated with MPSS.

The MPSS group contained significantly larger number of AIS A patients who generally show poor neurological recovery, must influence the neurological outcome. Therefore, we assessed neurological outcome in severe incomplete paralysis patients (excluding AIS A and D patients) between both groups. Repeatedly, the G-CSF group showed better neurological recovery compared to the MPSS group, suggesting the superior neuroprotective potential of G-CSF treatment in SCI.

We observed that the incidence of pneumonia was significantly higher in patients treated with MPSS than in patients treated with G-CSF. The difference in patient background data between the groups, the MPSS group contained significantly larger number of AIS A patients who can be easily affected with pneumonia, must influence the incidence of pneumonia. Therefore, we compared the incidence of pneumonia in severe incomplete paralysis patients of both groups, the result repeatedly showed significant difference between G-CSF and MPSS groups (Table 2).

Methylprednisolone sodium succinate is a widely recognized immunosuppressant. In addition, spinal cord injury itself can induce systemic immunosuppression [14]. Hence, the immunosuppressive effects of SCI and MPSS may function in an additive or synergistic manner, increasing