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Cervical Myelopathy in Patients With Athetoid Cerebral Palsy

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Study Design. Retrospective clinical study.

Objective. To report the surgical outcomes of patients with cervical myelopathy associated with athetoid cerebral palsy and to assess whether a halo vest is necessary for postoperative external immobilization.

Summary of Background Data. Although a halo vest has remained the first choice for postoperative external immobilization of patients with cervical myelopathy associated with cerebral palsy, simplification of this method has been attempted in recent years. Studies focusing on postoperative external immobilization are rare.

Methods. Since 2001, 20 patients underwent surgery with posterior instrumented fusion or posterior fixation and anterior decompression with fusion with a year or longer follow-up. Before 2004, all patients were given a halo vest for postoperative external immobilization. After 2004, halo vests were not used, and when abnormal involuntary neck movements were severe, an intramuscular injection of botulinum toxin was administered before and after surgery. Surgical outcomes, surgical methods and complications were compared between the group that used a halo vest and the group that did not use a halo vest.

Results. In the halo vest group, the average Japanese Orthopedic Association score was 6.9 points before surgery and 9.3 points at 1-year follow-up. The average recovery rate was 25.0%. In the group without halo vest use, the average Japanese Orthopedic Association score was 5.8 points before surgery and 9.9 points at 1-year follow-up. The average recovery rate was 35.7%. The group without halo vest use achieved outcomes equal to those achieved in the group with halo vest use. The frequency of complications was less without halo vest use than with halo vest use.

Conclusion. No inferiority in clinical outcomes was seen if postoperative halo vest use was omitted. Progress in surgical instrumentation and injection of botulinum toxin may explain this result.

Key words: cervical myelopathy, athetoid cerebral palsy, surgical outcomes, halo vest, botulinum, postoperative external immobilization, instrumentation. **Spine 2013;38:E151–E157**

Athetoid cerebral palsy (CP) can cause cervical spondylosis through involuntary movements, and cervical myelopathy can occur at a relatively young age.[1–4] Conservative therapy is not appropriate, and surgical treatment is often required.[5] Because of the additional problems of strong muscle tone and involuntary movements, the treatment of cervical myelopathy is more difficult than that of typical spondylotic myelopathy. Decompression without fusion is not recommended because of the repetitive cervical movement.[6] Patients with CP undergoing laminoplasty often show late neurological deterioration because of adjacent segment instability and progression of spondylosis of the upper cervical spine.[7] At surgery, therefore, rigid instrumented fixation using strong anchors such as pedicle screws at adequate levels is required. Although there are several reports concerning surgical outcomes,[1,2,5–21] studies that focus on postoperative external immobilization are rare. Here, we report the surgical outcomes of patients in our institute with cervical myelopathy associated with CP and compare the results obtained with and without the use of a halo vest for postoperative external immobilization.

MATERIALS AND METHODS

Patient Population

Patients who underwent posterior instrumented fusion were selected. To obtain a more homogeneous population, patients who underwent only posterior decompression were excluded. Since 2001, a total of 20 (14 males, 6 females) patients with cervical myelopathy with CP underwent posterior decompression with instrumented fusion or posterior fixation with anterior decompression with fusion in our hospital with a year

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TABLE 1. Summary of Clinical Data for the 20 Study Cases

	Halo Vest Group	Without Halo Vest Group
Total cases	10	10
Sex (n)		
Male	6	8
Female	4	2
Age at surgery (yr)*	50.6 (39–70)	58.6 (39–72)
Duration of symptoms (mo)*	61.7 (3–260)	61.1 (2–396)
Follow-up period (mo)*	91.9 (12–124)	29.9†(12–82)
Surgical Procedure		
PDF	9	9
PF + ADF	1	1

Values are expressed as the mean, with the range in parentheses.

†Statistically different from the data in halo vest group ($P < 0.01$).

PDF indicates posterior decompression with instrumented fusion; PF, posterior fixation; ADF, anterior decompression with fusion.

TABLE 2. Summary of Clinical Results for the 20 Study Cases

	Halo Vest Group (n = 10)	Without Halo Vest Group (n = 10)
JOA score (points)		
Before surgery*	6.9 (3.5–14.5)	5.8 (3.0–11.0)
A year follow-up*	9.3 (4.0–15.5)	9.9 (4.0–14.0)
Recovery rate (%)		
A year follow-up*	25.0 (13.0–44.4)	35.7 (7.1–66.7)
Fuji's classification at a year follow-up		
Excellent	2	3
Good	5	7
Fair	3	0
Poor	0	0

JOA indicates Japanese Orthopaedic Association (full score = 17 points).

Recovery rate = (Postoperative JOA score − preoperative JOA score)/(Full score (17)− preop. JOA score) × 100

Fuji's classification; Excellent, indicates improvement with the extent of patient's former level of activity; Good, improvement with a minimum decrease in activity; Fair, improvement with an incresed need for help; Poor, no improvement or worsening.

**Values are expressed as the mean, with the range in parentheses.*

No statistically difference between two groups.

or longer of follow-up. Their mean age at surgery was 54.6 years, and they were followed for an average of 61.4 months.

Before 2004, 9 patients were treated with posterior decompression with instrumented fusion, and 1 patient was treated with posterior fixation and anterior decompression with fusion. In these 10 patients, postoperative external immobilization was performed using a halo vest for 1 to 3 months. These 10 patients were defined as the " halo vest group" in this study.

After 2004, if abnormal involuntary neck movements in patients were severe, an intramuscular injection of botulinum toxin was given before and after surgery. We simplified the postoperative external immobilization treatment commencing with the botulinum toxin treatment. Nine patients were treated with posterior decompression with instrumented fusion, and 1 patient was treated with posterior fixation and anterior decompression with fusion. None of these 10 patients was treated with halo vest immobilization after surgery, and an intramuscular injection of botulinum toxin was given to 8 of them. These 10 patients were defined as the "without halo vest group" in this study. A summary of the clinical data for the 20 cases is shown in Table 1. A statistical difference in the length of the follow-up period was seen between the 2 groups, with a significantly longer duration of follow-up in the halo vest group. Among all 20 patients, there were 2 salvage surgeries.

Treatment of Cervical Myelopathy in Patients with CP

Essentially, laminoplasty was chosen for patients who had small involuntary movements and no instability. Posterior decompression with instrumented fusion was chosen for patients who had involuntary movements and evidence of instability. We made it a rule to add anterior decompression when the spinal decompression was considered inadequate after posterior decompression and fusion. Before 2004, halo vest immobilization was used routinely for any type of surgery for 1 to 3 months after surgery. After 2004, postoperative external immobilization was not used. Botulinum toxin treatment was initiated for patients who had large involuntary movements.

Clinical Assessment

The Japanese Orthopedic Association scoring system (JOA score) was used to evaluate patient neurological status before surgery and at a year's follow-up, and the Hirabayashi method[22] was used to calculate the recovery rate. Neurological status at a year's follow-up was also evaluated using the Fuji classification.[11] Details of the JOA scoring system and recovery rate are found in our previous report.[23] Postoperative external immobilization, surgical method, and preoperative and postoperative sagittal alignment of the cervical spine were examined in each patient. We examined sagittal alignment according to the report of Azuma *et al.*[15] Details regarding the surgical method, botulinum toxin treatment, and complications related to halo vest use and implants during the perioperative period are also provided.

Statistical Analysis

A Mann-Whitney *U* test was used to determine differences between the 2 groups. Significance was assessed at the $P < 0.05$ and $P < 0.01$ levels.

TABLE 3. Key Characteristics of the 20 Study Cases (Case 1–10, Halo Vest Group; Case 11–20, Without Halo Vest Group)

Case	Age (yr)/Sex	Duration of Halo Vest Use (d)	Injection of Botulinum Toxin	Surgical Method	Alignment of Cervical Spine		Nonunion
					Before Surgery	After Surgery	
1	55/M	90		PF+ADF	St	St	
2	42/F	65		PDF	St	St	
3	61/M	63		PDF	K	K	
4	70/M	60		PDF	K	St	
5	65/M	90		PDF	L	L	+
6	41/F	90		PDF	K	St	
7	39/M	60		PDF	L	L	
8	46/F	60		PDF	S	St	
9	48/F	3		PDF	L	K	+
10	39/M	32		PDF	St	St	
11	51/M		+	PDF	L	L	
12	72/M		+	PDF	S	K	
13	49/M		+	PDF	L	L	
14	46/M			PDF	L	St	
15	62/M		+	PDF	L	K	+
16	55/F		+	PF + ADF	S	S	
17	71/F			PDF	L	St	
18	73/M		+	PDF	K	St	
19	39/M		+	PDF	L	St	
20	68/M		+	PDF	L	L	

PF indicates posterior fixation; ADF, anterior decompression and fusion; PDF, posterior decompression with instrumented fusion; L, lordosis; K, kyphosis; S, S-shaped; St, straight.

RESULTS

Clinical results are summarized in Table 2. In the halo vest group, the average JOA score was 6.9 points before surgery and 9.3 points at 1-year follow-up. The average recovery rate was 25.0% at 1-year follow-up. In the group without halo vest use, the average JOA score was 5.8 points before surgery and 9.9 points at 1-year follow-up, and the average recovery rate was 35.7% at 1-year follow-up. According to the Fuji classification, the group without halo vest use obtained results equivalent to the group that used a halo vest. Key characteristics of the 20 study cases are shown in Table 3. Cases 1 to 10 were patients in the halo vest group, and cases 11 to 20 were patients without halo vest use. The mean duration of postoperative halo vest immobilization in the halo vest group was 61.3 days (range, 3–90 d). The patient who wore the vest for only 3 days (case 9) had difficulty swallowing, which was a complication of wearing the halo vest. After it was removed, this difficulty resolved. An intramuscular injection of botulinum toxin was administered to 8 patients in the group without halo vest use. Case 9 and 1 patient in the group without halo vest use (case 15) showed development of kyphosis at sagittal alignment of the cervical spine. Three cases, including cases 9 and 15, showed nonunion in the radiographical examination. These 3 cases resulted in implant failure.

Details of the instrumented methods are shown in Table 4. A plate-screw or plate-screw-hook system of instrumented fusion anchors was used initially. More recently a rod-screw system with pedicle and lateral mass screws was used. Notably, we commenced using polyaxial screws to increase the flexibility of the connection between rods from case 12 onward. Furthermore, a combination of sublamina wiring with ultra-high-molecular-weight polyethylene cable (Tekmilon tape; Alfresa Pharma, Osaka, Japan). A representative case from each group is shown in Figures 1 and 2 (cases 7 and 19).

Botulinum toxin treatment was used to decrease spasticity and involuntary movements. Details regarding botulinum toxin injections are shown in Table 5. Treatment during the preoperative period administered 1 to 3 times, depending on the grade of the involuntary movement in each patient. At treatment initiation, which varied from 14 to 126 days prior to surgery, the

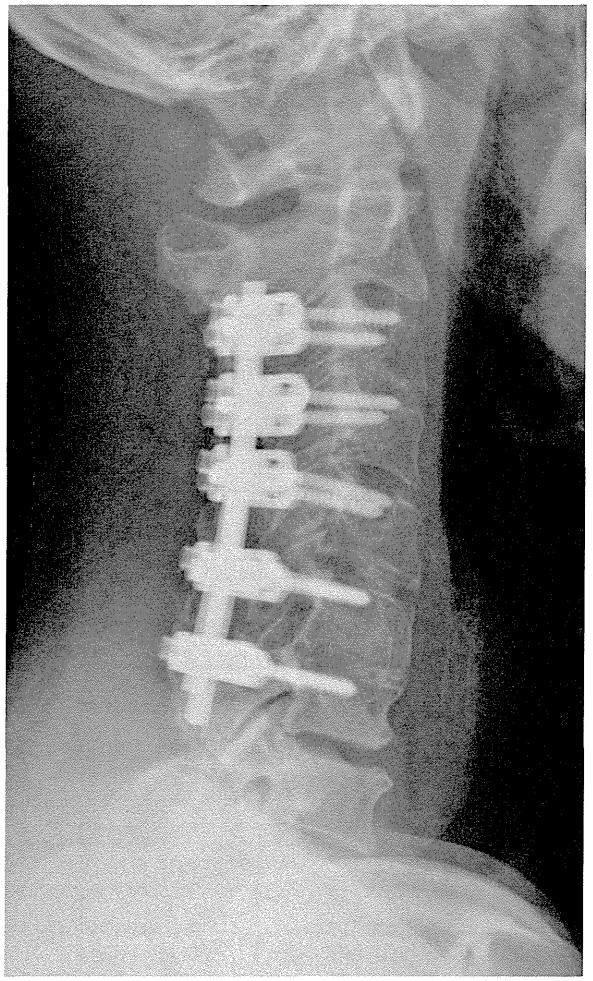

Figure 1. Postoperative lateral radiographical image in a neutral position, 7 years after posterior decompression at C5–C7 with instrumented fusion at C3–C7 using pedicle screws performed for a 39-year-old man who was diagnosed with cervical myelopathy because of athetoid CP (case 7). He was treated with a halo vest for postoperative external immobilization for 2 months.

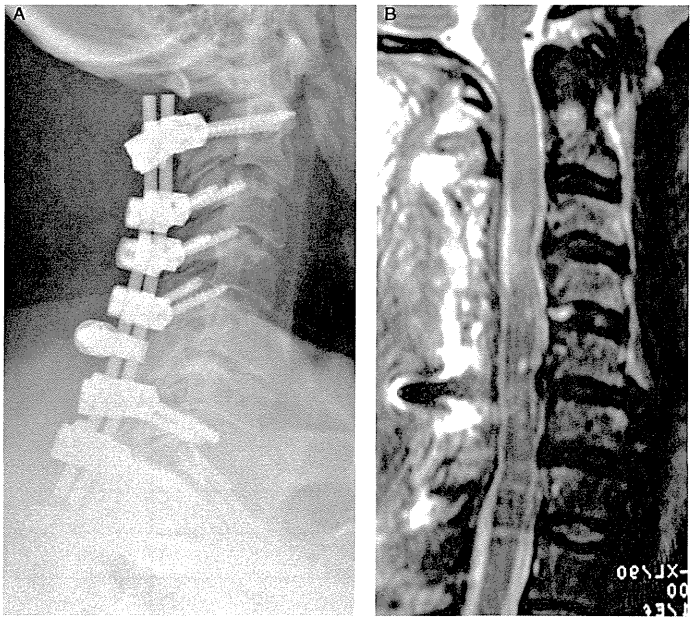

Figure 2. (**A**) Postoperative lateral radiographical image in a neutral position and (**B**) T-2 weighted midsagittal magnetic resonance (MR) image, 1 year after posterior decompression at C3–C7 with instrumented fusion at C2–Th1 using pedicle screws at C2, C7, and T1, and lateral mass screws at C3, C4, and C5 performed for a 39-year-old man diagnosed with cervical myelopathy because of athetoid CP (case 19). He was treated without a halo vest for postoperative external immobilization. An injection of botulinum toxin was given during the preoperative period.

initial dose was 60 to 100 units. The total amount administered varied from 60 to 385 units. The muscles into which the toxin was injected were the sternomastoid, trapezius, splenius capitis, platysma, iliocostalis thoracis, and scalenus muscles. The timing, dose, and site of administration were determined by the posture and muscle tone of the individual patients.

Surgical complications related to halo vest use and implants are shown in Table 6. Rod breakage (case 5) and loosening of a pedicle screw occurred (case 9) in patients in the halo vest group. Dislodgement of rods occurred in 1 patient (case 15) in the group without a halo vest. These patients disliked the cervical metallic sound and sense of incongruity that were caused by failed instrumentation. At the request of 2 patients in the halo vest group, we removed the internal fixation in the 22nd month and 18th month, respectively, after the primary surgery. As mentioned above, case 9 experienced difficulty in swallowing while wearing the halo vest. Infection of a halo vest pin occurred in another patient (case 3). One of the other complications related to surgery was postoperative radicular pain or motor weakness of the upper extremity. Postoperative radicular pain occurred in 1 patient in the halo vest group. We performed a second surgery for this case. Postoperative motor weakness in the upper extremity occurred in 1 patient in each group. We carefully observed these patients conservatively, and their muscle gradually recovered from weakness.

DISCUSSION

Postoperative Immobilization for Cervical Myelopathy Associated with CP

The findings of this study showed that there were no statistically significant differences in clinical outcomes between the halo vest group and the without halo vest group at 1-year follow-up after surgery. We examined previous reports of posterior decompression performed with instrumented fusion or posterior fixation and anterior spinal fusion for cervical myelopathy in patients with CP.[5,6,11–13,15–17,19–21] Although a halo vest has remained the first choice for postoperative external immobilization, simplification of this method has been attempted in recent years.[5,17,21] Onari *et al*[5] reported 8 cases that used a soft cervical collar for postoperative external immobilization. Jameson *et al*[21] reported 2 cases that used cervicothoracic orthosis. Duruflé *et al*[17] reported 1 case with no external immobilization in the postoperative period. Findings in this study indicated that a halo vest could be omitted for cases in which involuntary movements were controlled and rigid fixation was maintained. This seems to be beneficial in the context of the perioperative burden of wearing a halo vest.

TABLE 4. Details of the Instrumented Methods of the 20 Study Cases (Case 1–10, Halo Vest Group; Case 11–20, Without Halo Vest Group)

Case	Posterior Instrumented Fusion Levels	Type of Instrumentation	Type and Site of Anchors						Sublamina Wiring
			OS+ Occipital Wiring	TAS (C1/2, C3/4, C4/5, C5/6, C6/7)	PS (C2, C7, T1)	PS (C3, C4, C5, C6)	LMS (C3, C4, C5, C6)	Others	
1	C2–T1	Plate-screw		+	+				
2	O–C7	Rod-screw-hook	+	+					
3	O–C6	Rod-screw-hook	+	+					
4	C2–C7	Plate-screw		+	+		+		
5	O–C6	Rod-screw-hook	+	+					
6	C3–C7	Plate-screw			+		+		
7	C3–C7	Rod-screw			+	+			
8	C3–7	Rod-screw			+	+			
9	C3–T1	Rod-screw			+	+			
10	C3–C7	Rod-screw			+	+			
11	C3–C7	Rod-screw			+	+			
12	C2–C7	Rod-screw (P)			+		+		
13	C2–C7	Rod-screw (P)			+	+	+		C2, C7
14	C2–C7	Rod-screw (P)			+	+	+		C2, C7
15	C2–C7	Rod-screw (P)			+	+	+		C2, C7
16	C2–T4	Rod-screw (P)			+		+		C2, C3, T2, T3
17	C2–T1	Rod-screw (P)			+		+		C2, C7, T1
18	C1–T1	Rod-screw (P)			+		+	C1 LMS	
19	C2–T1	Rod-screw (P)			+		+		
20	C3–T1	Rod-screw (P)			+		+	C2 LS	C2

OS indicates occipital screw; TAS, transarticular screw; PS, pedicle screw; LMS, lateral mass screw; rod-screw (P), rod-screw (poly-axial screw); LS, lamina screw.

Posterior Instrumented Fusion for Cervical Myelopathy in Patients with CP

Surgical methods for cervical myelopathy in patients with CP can be classified generally into anterior decompression with fusion, posterior decompression with instrumented fusion, laminoplasty, and posterior fixation and anterior decompression with fusion. Each method has its merits and disadvantages. Choice of the surgical method varies among cases and institutes. The purposes of the surgery are spinal decompression and preservation of alignment by the fixation. Some authors have reported the clinical outcomes of posterior decompression with instrumented fusion for cervical myelopathy in patients with CP.[6,15–17,20,21] Fixation with a rod-wiring system,[16] C2 and C7 pedicle screws,[15] and C2 pedicle screws and C3 and C4 lateral mass screws have been reported.[6] Other reports have described details regarding the surgical outcomes of posterior fixation and anterior decompression with fus ion.[6,11–14,16,19,21] Posterior fixation with a rod or plate-wiring system,[11–14,19] plate-screw-wiring system,[16] and rod-screw system[6,21] have been reported. A rod or plate-wiring system has been the major technique for fixation in the past, but a rod-screw system has been the focus of much recent attention with the progress of this instrumentation. In Spine Division, Department of Orthopaedic Surgery, Chiba University Graduate School of Medicine, we obtain rigid fixation by using a C3–C6 pedicle screw system in addition to C2, C7, and T1 pedicle screws (Table 4). Recently, other notable techniques, including sublamina wiring and polyaxial screws, have been reported. Such new instrumentation and techniques contribute to the achievement of relatively good surgical outcomes.

Intramuscular Injection of Botulinum Toxin

Recently, the usefulness of the botulinum therapy has been reported.[6,21,24–29] Injection of botulinum toxin is widely used to decrease spasticity and involuntary movements associated with athetosis or dystonia. Wong *et al*[6] and Jameson *et al*[21]

TABLE 5. Injection of Botulinum Toxin

Case	Time of Injection Before Surgery (d)	Total Dose of Injection (Unit)	Muscle of Injection
11	21	60	SCM
12	14	60	SC
13	21 (1st)	100	SC, T
	7 (2nd)	125	SCM, SC, P
15	126 (1st)	100	P
	94 (2nd)	60	P
	8 (3rd)	225	SCM, SC, T
16	66 (1st)	100	SCM, SC
	38 (2nd)	100	P, ICT
18	51	100	SCM, S
19	27 (1st)	100	SC, T
	9 (2nd)	100	T, S
20	50 (1st)	100	SC
	23 (2nd)	150	SC

SCM indicates sternocleidomastoid; SC, indicates splenius capitis; T, trapezius; P, platysma; ICT, iliocostalis thoracis; S, scalenus.

reported cases of cervical myelopathy in patients with CP who received posterior fixation combined with an injection of botulinum toxin. In the current study, details of 8 cases with botulinum toxin use are reported (Tables 3 and 5). Although Lee *et al*[19] have indicated the possibility of serious complications associated with toxin injection, we have not experienced such complications to date. Our findings indicate that an injection of botulinum toxin may enable control of involuntary movement. This effect reinforces rigid cervical fixation even if a halo vest is not used.

Complications

Because of the large involuntary movements associated with CP, the number of postoperative complications is relatively high compared with typical cervical spondylotic myelopathy. Some of the complications are because of involuntary movements and surgery itself.[16, 20, 21] Others are the result of wearing a halo vest.[6,13,19] Dislodgement of rods[16,20,21] and loosening of screws[20] have been reported previously. Epstein *et al*[13] reported displacement of a halo vest 4 days after surgery because of severe involuntary movement. Wong *et al*[6] reported a case of loosening of a halo ring pin. Lee *et al*[19] reported a halo vest loosening and pin site infection of 4 out of 4 cases of anterior spinal fusion. Other important complications related to surgery are postoperative radicular pain and upper extremity motor weakness. Miyamoto *et al*[20] reported that 2 out of 19 patients developed C5 palsy. In this series, we experienced 2 cases of radicular pain and 1 case of motor weakness of the upper extremities in the early postoperative period. There is a risk that nerve-root irritation from foraminal stenosis will occur at a higher rate than in typical cervical spondylotic myelopathy.

TABLE 6. Surgical Complications Related to Halo Vest Use and Implants at the Postoperative Period

	Halo Vest Group (n = 10)	Without Halo Vest Group (n = 10)
Implant failure	2 (20.0%)	1 (10.0%)
Difficulty in swallowing after wearing a halo vest	1 (10.0%)	0 (0.0%)
Infection of halo vest's pin	1 (10.0%)	0 (0.0%)

Our results indicate that the frequency of complications was less in the group without halo vest use than in the group with halo vest use. We think that these findings are the result of the decrease in complications with the surgery itself because of the progress of instrumentation and the absence of complications because of halo vest omission.

Limitations and Conclusion

This study is limited by its retrospective nature relative to preoperative assessment of involuntary movements, and indeed, classification of CP is insensitive. We observed a statistical difference in the follow-up period between the 2 groups. Further, the surgical procedures and types of anchors were not homogeneous, nor was the use of botulinum toxin. Therefore the results should be interpreted with caution. Nevertheless, the data provide some useful new information. This study demonstrates that CP patients with cervical myelopathy can be adequately managed by botulinum injections into the neck muscles to reduce involuntary movements before posterior decompression with segmental screw fixation. There was a resultant improvement in neurological outcome. The addition of a postoperative halo vest does not improve clinical outcomes or reduce surgical complications, but poses additional risks of halo-related complications.

➢ Key Points

- ❑ The clinical outcomes of patients with cervical myelopathy associated with athetoid CP are reported. Results were compared between patients with and without halo vest use for postoperative external immobilization.
- ❑ At 1-year follow-up after surgery, no statistically significant differences in clinical outcomes were noted between the group that used a halo vest and the group that did not use a halo vest.
- ❑ Strong instrumented anchors and injection of botulinum toxin have enabled the reinforcement of rigid cervical fixation even if a halo vest is not used.

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ORIGINAL ARTICLE

Intravenous administration of granulocyte colony-stimulating factor for treating neuropathic pain associated with compression myelopathy: a phase I and IIa clinical trial

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Abstract
Objective To confirm the feasibility and safety of granulocyte colony-stimulating factor (G-CSF) for treating spinal neuropathic pain associated with compression myelopathy, we have initiated an open-label single-center prospective clinical trial.
Methods Between January 2009 and February 2011, 17 patients were accrued and were divided into two groups. One group included 7 patients who complained of pain associated with worsening symptoms of myelopathy (progressing myelopathy-related pain group). The other group included 10 patients who complained of pain that persisted after surgery for compression myelopathy (post-operative persistent pain group). All patients underwent intravenous administration of G-CSF (10 μg/kg/day) for 5 consecutive days. Pain severity was evaluated using a visual analog scale (VAS) before and after G-CSF administration.
Results In 14 of the 17 patients, pain was relieved within several days after G-CSF administration. Pain disappeared completely in 3 patients. In the progressing myelopathy-related pain group, the mean VAS score was 71.4/100 before G-CSF administration, and decreased to 35.9/100 at 1 week after G-CSF administration ($p < 0.05$). In the post-operative persistent pain group, the mean VAS score was 72.0/100 before G-CSF administration, and decreased to 51.7/100 at 1 week after G-CSF administration ($p < 0.05$). No severe adverse events occurred during or after G-CSF administration.
Conclusions The present results provide us with the possibility that G-CSF has a pain-relieving effect for neuropathic pain in patients with compression myelopathy.

Keywords Neuroprotective therapy · Granulocyte colony-stimulating factor · Myelopathy · Neuropathic pain · Clinical trial

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Introduction

Granulocyte colony-stimulating factor (G-CSF) is a cytokine that promotes survival, proliferation, and differentiation of cells in the neutrophil lineage [11, 16]. Furthermore, G-CSF can mobilize both immature and mature bone marrow cells into the peripheral blood. As a result, it is used clinically for patients with leukocytopenia and for donors of peripheral blood-derived hematopoietic stem cells for transplantation. Recent studies have indicated that G-CSF also has non-hematopoietic activity and can potentially be used for the treatment of neuronal injury, including stroke and neurodegenerative diseases [3, 5, 7, 18, 19]. We previously demonstrated that G-CSF promoted the restoration of damaged spinal cord tissue and the recovery of neural function in experimental spinal cord injury in both mice and rats [4, 6, 12]. In addition, we showed that G-CSF promoted the migration of bone marrow-derived cells into the damaged spinal cord, suppressed apoptosis of neuronal cells and oligodendrocytes, protected myelin, decreased inflammation, and promoted angiogenesis [4, 6, 12]. Based on these findings, we initiated a clinical trial that evaluated the safety and efficacy of neuroprotective therapy using G-CSF for patients with

Table 1 Patient data (progressing myelopathy-related pain group)

Case no.	Age (years)/gender	Diagnosis	Most stenotic level	Surgical procedure[a]	Time of surgery after G-CSF administration (weeks)
1	46/M	OPLL	T6–7	PDF (T2–11)	8
2	75/M	OPLL	C4–5	PDF (C2–7)	7
3	64/M	OPLL	C4–5	PDF (C2–7)	2
4	32/M	OPLL	T9–10	PDF (T7–12)	4
5	67/M	OLF	T11–12	PD (T10–12)	5
6	36/M	OPLL	T5–6	PDF (T2–10)	7
7	72/F	OPLL	T11–12	PDF (T6–L3)	23

OPLL ossification of posterior longitudinal ligament, *OLF* ossification of ligamentum flavum, *PDF* posterior decompression with instrumented fusion, *PD* posterior decompression

[a] Surgery after G-CSF administration

worsening symptoms of compression myelopathy [17]. In this clinical trial, we intravenously administered G-CSF (5 or 10 μg/kg/day) to 17 patients for 5 consecutive days. G-CSF administration suppressed progression of myelopathy in all patients, and no serious adverse events occurred during or after treatment [17].

During this trial, several cases unexpectedly experienced a dramatic reduction in neuropathic pain associated with thoracic myelopathy after G-CSF administration [22]. Such a pain-relieving effect of G-CSF was not specified as an endpoint of this trial. However, this effect has important implications for future clinical use of G-CSF for compression myelopathy. Thus, we initiated a new clinical trial to verify the feasibility and safety of using G-CSF for spinal neuropathic pain. In the present study, G-CSF was administered to patients who complained of pain associated with compression myelopathy, and the pain-relieving effect of G-CSF for spinal neuropathic pain was analyzed.

Materials and methods

We performed a phase I and IIa clinical trial evaluating G-CSF administration in patients who complained of neuropathic pain associated with compression myelopathy. The trial was initiated following the approval of the Institutional Review Board of our university. According to the inclusion criteria, patients of 20–85 years of age were recruited. Patients in the following categories were excluded: (1) those with intracranial pathologies (e.g., tumors, infection, or ischemia), (2) those with a history of major bleeding requiring blood transfusion or a history of leukopenia, thrombocytopenia, hepatic or renal dysfunction, severe heart failure, or splenomegaly, and (3) those with evidence of malignant disease within the last 5 years. We also excluded patients who were pregnant or nursing. Eligible patients gave informed consent for participation in the trial.

Granulocyte colony-stimulating factor (10 μg/kg/day) was intravenously administered for 5 consecutive days. This was an open-label study; thus, there was no control group. Spinal neuropathic pain of patients analyzed in the present clinical trial was classified into two categories: at-level pain and below-level pain [1]. At-level pain is characterized as pain located within two or three spinal segments below the neurological level of a spinal cord lesion. In contrast, below-level pain presents diffusely caudal to the level of a spinal cord lesion. The severity of pain was evaluated before and after G-CSF administration using a visual analogue scale (VAS) ranging from 0 to 100. We also evaluated severity of myelopathy using the Japanese Orthopaedic Association (JOA) score (cervical myelopathy scores range from 0 to 17, thoracic myelopathy scores range from 0 to 11) [9]. In the present study, two orthopedic spine surgeons specializing in cervical and thoracic spine surgery evaluated neurological status independently every month until 6 months after G-CSF administration, and calculated the mean data. Hematological data from treated patients were analyzed. Adverse events using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 3.0 were also evaluated.

Statistical analysis was performed using a Mann–Whitney U test. A p value less than 0.05 was considered statistically significant. Results are presented as mean ± SD.

Results

Patient data

Between January, 2009 and February, 2011, a total of 18 patients were enrolled in this trial. In one patient, however, fever developed 3 days after the initiation of G-CSF administration, and the administration was discontinued. This patient was excluded from the study. Thus, 17 patients

Table 2 Patient data (post-operative persistent pain group)

Case no.	Age (years)/gender	Diagnosis	Most stenotic level	Procedure of previous surgery[a]	Time of previous surgery before G-CSF administration (years)
8	58/M	OPLL	C5–6	PD (C3–6)	2
9	72/M	DH	T12–L1	PDF (T9–L3)	0.5
10	71/M	OPLL	C5–6	PD (C3–7)	3
11	78/M	OLF	T10–11	PDF (T10–12)	189
12	70/M	OPLL	C4–5	PD (C3–5)	30
13	70/F	OPLL	C5–6	PDF (C2–7)	1
14	81/F	OLF	T10–11	PD (T9–11)	5
15	69/M	CSM	C4–5	PDF (C4–5)	4
16	62/M	CSM	C5–6	PD (C3–7)	10
17	63/M	OPLL	C5–6	PDF (C3–7)	8

DH disc herniation, *CSM* cervical spondylotic myelopathy

[a] Surgery before G-CSF administration

Table 3 Neuropathic pain data

Case no.	Type of pain	VAS before G-CSF administration	Duration of pain
1	At-level	60	0.8
2	Below-level	50	3
3	At-level	50	0.3
4	At-level	80	4
5	At-level	90	0.2
6	At-level	100	0.2
7	At-level	70	5
8	At-level	50	1
9	Below-level	90	3
10	At-level	80	3
11	Below-level	60	19
12	At-level	60	27
13	At-level	60	1
14	Below-level	80	5
15	Below-level	80	4
16	Below-level	70	11
17	At-level	90	8

VAS visual analogue scale (0–100)

received G-CSF administration and were followed-up for ≥6 months (Tables 1, 2). These 17 patients were divided into two groups. One group included 7 patients (Cases 1–7) who complained of pain associated with worsening symptoms of myelopathy (progressing myelopathy-related pain group) (Table 1). The other group included 10 patients (Cases 8–17) who complained of pain that persisted after surgery for compression myelopathy (post-operative persistent pain group) (Table 2).

In the progressing myelopathy-related pain group, worsening of myelopathy occurred due to compression of the spinal cord by ossification of the posterior longitudinal ligament (OPLL) or ossification of the ligamentum flavum (OLF) (Table 1). The mean JOA score for cervical or thoracic myelopathy decreased ≥2 points or more during a recent 1-month period. Of the 7 patients in this group, 6 patients (Cases 1, 3, 4, 5, 6, and 7) complained of at-level pain and 1 patient (Case 2) complained of below-level pain (Table 3). The duration of pain was 0.2–5 years (mean, 1.9 years). In all 7 patients, surgery for myelopathy was performed 2–23 weeks after initial G-CSF administration (Table 1).

In the post-operative persistent pain group, pain caused by compression to the spinal cord persisted even after myelopathy surgery (Tables 2, 3). Of these 10 patients, 5 patients (Cases 8, 10, 12, 13, and 17) complained of at-level pain and 5 patients (Cases 9, 11, 14, 15, and 16) complained of below-level pain (Table 3). The duration of pain in all 10 patients in this group was 1–27 years (mean, 8.2 years), which was significantly longer than that of the progressing myelopathy-related pain group ($p < 0.01$).

VAS

In the progressing myelopathy-related pain group, a decrease in VAS score of >10 was obtained in all 7 patients within 1 week after initial G-CSF administration. In 1 patient (Case 4), pain completely disappeared. The mean VAS score immediately before G-CSF administration was 71.4, and it significantly decreased to 35.9 at 1 week after initial G-CSF administration ($p < 0.05$) (Fig. 1a). The pain-relieving effect of G-CSF was attenuated at 3 months after administration in 3 patients (Cases 2, 3, and 5), and the VAS score returned to the pre-administration level in 1 patient (Case 2). However, 3 and 6 months after G-CSF administration, mean VAS scores were still lower than those before G-CSF administration ($p < 0.05$) (Fig. 1a).

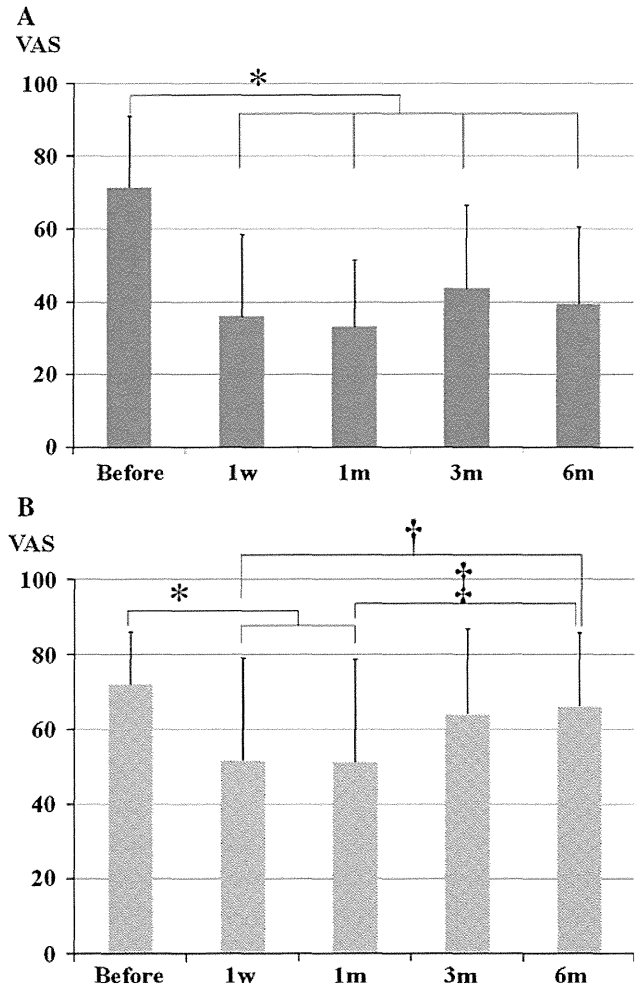

Fig. 1 Visual analogue scale before and after G-CSF administration in progressing myelopathy-related pain group (**a**) and post-operative persistent pain group (**b**). *VAS* visual analogue scale, *before* immediately before G-CSF administration, *1w* 1 week after initial G-CSF administration, *1 m* 1 month after initial G-CSF administration, *3 m* 3 months after initial G-CSF administration, *6 m* 6 months after initial G-CSF administration. $*p < 0.05$ compared with that before G-CSF administration. $^{\dagger}p < 0.05$ compared with that 1 week after G-CSF administration. $^{\ddagger}p < 0.05$ compared with that 1 month after G-CSF administration

Figure 2 shows the change of VAS before and after surgery in seven cases of the progressing myelopathy-related pain group. After surgery, VAS was not altered in four cases (Cases 1, 3, 4 and 6), increased in two cases (Cases 2 and 5), and decreased in one case (Case 7) (Fig. 2).

In the post-operative persistent pain group, a decrease in VAS score of $\geq$10 was obtained in seven out of ten patients within 10 week after initial G-CSF administration. In three patients (Cases 9, 14, and 16), G-CSF did not show any pain-relieving effect. The mean VAS score immediately before G-CSF administration was 72.0, and it significantly decreased to 51.7 at 1 week after initial G-CSF administration ($p < 0.05$) (Fig. 1b). The pain-relieving effect of

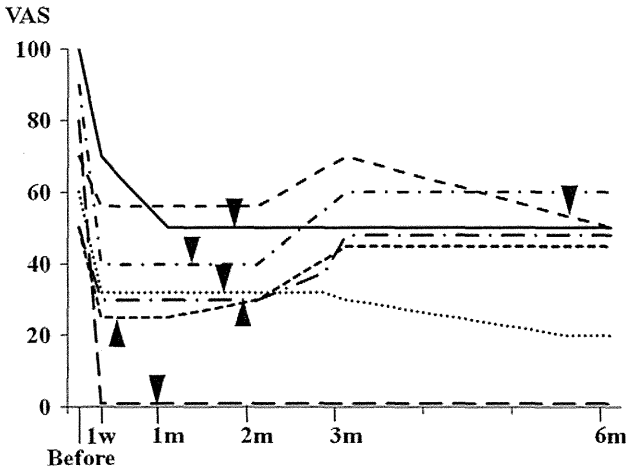

Fig. 2 Change of visual analogue scale after G-CSF administration in each case of progressing myelopathy-related pain group. *VAS* visual analogue scale, *before* immediately before G-CSF administration, *1 w* 1 week after initial G-CSF administration, *1 m* 1 month after initial G-CSF administration, *3 m* 3 months after initial G-CSF administration, *6 m* 6 months after initial G-CSF administration. *Arrowheads* indicate the time of surgery

G-CSF was attenuated at 3 months in 4 patients (Cases 11, 13, 15, and 17) and at 6 months in 1 patient (Case 12), and VAS scores returned to pre-administration levels in 4 patients (Cases 11, 13, 15, and 17). The mean VAS score increased to 64.0 at 3 months after G-CSF administration (Fig. 1b).

JOA score

In all 7 patients in the progressing myelopathy-related pain group, the JOA score increased after G-CSF administration. The mean JOA recovery rate at 1 and 6 months after G-CSF administration was 32.3 and 54.2 %, respectively (Table 4).

In the post-operative persistent pain group, an increase in JOA score was observed in only 3 patients (Cases 8, 10, and 11). Three patients (Cases 9, 14, and 16), in whom no pain-relieving effect was observed after G-CSF administration, also did not show any increase in JOA score. The mean JOA recovery rate at 1 month and 6 months after G-CSF administration was 7.3 and 7.3 %, respectively (Table 4). Thus, the neurological improvement after administration of G-CSF in the post-operative persistent pain group was inferior to that in the progressing myelopathy-related pain group (Table 4).

Blood data

White blood cell count dramatically increased the day after G-CSF administration; during G-CSF administration, it increased to 31.2 ± 8.3 ($\times 10^3/mm^3$) (Table 5). G-CSF mobilized cells of the neutrophil lineage, but lymphocytes

Table 4 Recovery rate of JOA score after G-CSF administration

Group	Time after G-CSF administration	
	1 month	6 months
Progressing myelopathy-related pain group	32.3 ± 27.7* (0–70.6)	54.2 ± 21.2** (28.6–81.8)
Post-operative persistent pain group	7.3 ± 12.2 (0–28.6)	7.3 ± 12.2 (0–28.6)

Data are expressed as the mean ± standard deviation, with the range in parentheses. Recovery rate = (post-operative JOA score − preoperative JOA score/full score − preoperative JOA score) × 100 (%)

JOA score Japanese Orthopaedic Association score (cervical myelopathy 1–17 points, thoracic myelopathy 0–11 points)

* $p < 0.05$ compared with that of the post-operative persistent pain group

** $p < 0.01$ compared with that of the post-operative persistent pain group

Table 5 Blood data before and after G-CSF administration

	Normal range	Before	Peak value after G-CSF administration[a]	*p*
WBC ($\times 10^3/mm^3$)	4.0–9.0	6.2 ± 2.0 (3.3–12.5)	31.2 ± 8.3 (19.2–47.3)	<0.01
Neutrophil ($\times 10^3/mm^3$)	1.8–5.0	3.6 ± 1.2 (2.0–6.6)	25.8 ± 5.4 (16.6–34.1)	<0.01
Lymphocyte ($\times 10^3/mm^3$)	1.0–4.1	2.0 ± 1.0 (0.9–5.4)	2.1 ± 1.1 (0.7–5.9)	0.25
Monocyte ($\times 10^3/mm^3$)	0.1–0.6	0.4 ± 0.1 (0.2–0.6)	1.2 ± 0.9 (0.3–3.4)	<0.01
CRP ($\times 10^3/mm^3$)	<0.5	0.1 ± 0.1 (0.0–0.4)	0.3 ± 0.4 (0.0–1.3)	<0.01

WBC white blood cell, *CRP* C-reactive protein

[a] Peak value within 7 days after initiating G-CSF administration

were not affected. G-CSF also caused an increase of monocytes. C-reactive protein levels slightly increased, but this did not appear to be related to any clinical events.

Adverse events

In this series, no patient experienced bone pain or hepatic dysfunction after G-CSF administration. No other severe adverse events occurred during or after G-CSF administration.

Case presentation

Case 6 (progressing myelopathy-related pain group)

A 36-year-old man was admitted to our hospital complaining of progressive motor weakness of his lower extremities and gait disturbance. On admission, his JOA score for thoracic myelopathy was 3/11 points. He also showed spontaneous severe back pain (at-level pain). Magnetic resonance (MR) and computed tomography (CT) images showed beak-type OPLL and OLF that compressed his spinal cord anteriorly and posteriorly at T5–6 (Fig. 3a, b). Beginning on the day of admission, he received G-CSF. Six days after initial G-CSF administration, he felt relief of his back pain. His pain VAS score was 100 before G-CSF administration, and it decreased to 70 1 week after initial treatment. At 1 month after initial administration, his VAS score further decreased to 50. He also felt improved muscle strength of his legs, and his JOA score increased to 3.5 points. At 7 weeks after G-CSF administration, he underwent surgery for spinal cord decompression using a posterior approach and T2–T10 posterior instrumented fusion. At 6 months after G-CSF administration, he showed recovery from myelopathy (JOA score = 8 points) and his VAS score was 50.

Case 11 (post-operative persistent pain group)

A 78-year-old man was admitted to our hospital complaining of motor weakness of his lower extremities and gait disturbance. Nineteen years prior, he had undergone T10–12 laminectomy for thoracic myelopathy due to OLF. After surgery, pain persisted in his lower extremities. On admission, his JOA score was 4/11 points. In addition to myelopathy symptoms, he complained of spontaneous severe bilateral pain at the level of his thigh and leg (below-level pain). MR images showed that his spinal cord was decompressed, but was atrophic at T10–11 (Fig. 4a, b). Beginning on the day of admission, he received G-CSF. One day after initial G-CSF administration, he felt pain relief in his bilateral thigh and leg. His VAS score for pain was 60 before G-CSF administration. At 1 week after initial administration, the VAS score was reduced to zero and his pain was diminished. His myelopathy also improved,

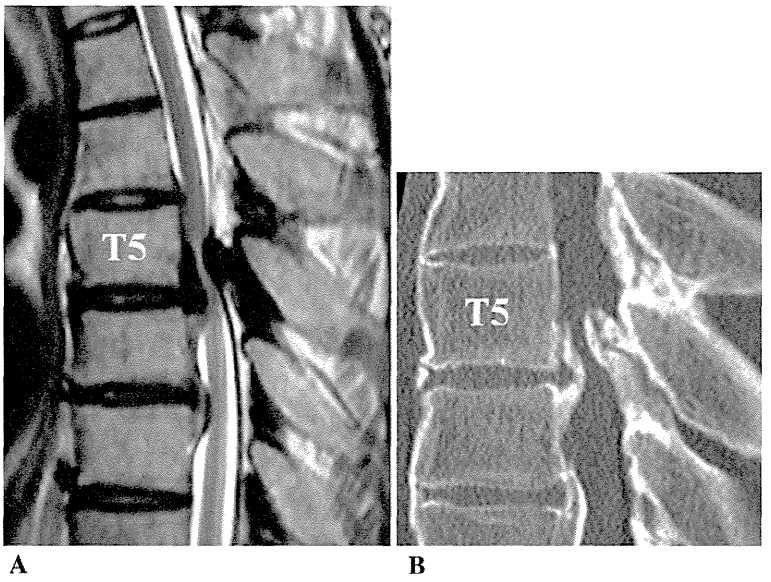

Fig. 3 Case 6. T2-weighted midsagittal MR image (**a**) and CT midsagittal reconstruction plane (**b**) showing anterior and posterior compression of the spinal cord by beak-type OPLL and OLF at T5–T6

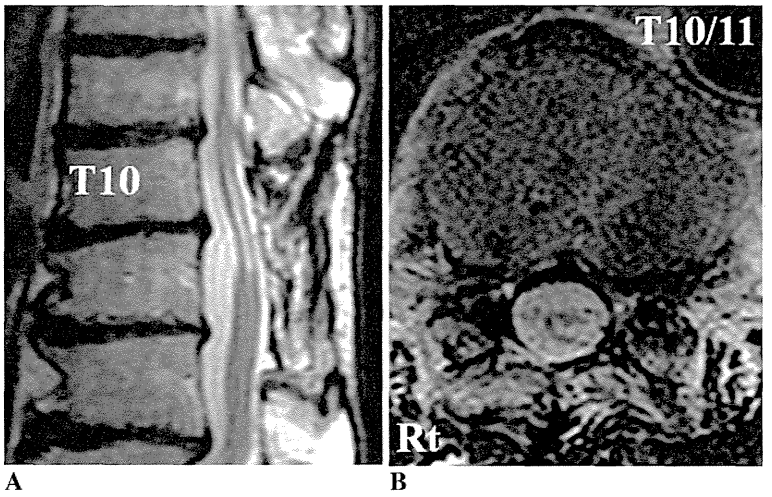

Fig. 4 Case 11. T2-weighted MR midsagittal image (**a**) and axial image at T10–T11 (**b**) showing that the spinal cord was decompressed but was atrophic at T10–T11

and his JOA score increased to 6/11 points 1 month after G-CSF administration. At 3 months after administration, however, he felt recurrence of his pain and his VAS score returned to 60.

Discussion

Neuropathic pain has been defined as a type of pain arising as a direct consequence of a lesion affecting parts of the somatosensory system, such as the brain, spinal cord, and peripheral nerves [1, 10, 21]. Among numerous diseases of the spinal cord, neuropathic pain following spinal cord injury (SCI) has been studied most extensively [10, 21]. Baastrup and Finnerup [1] reviewed pharmacological management of neuropathic pain following SCI. Based on the data from several randomized controlled trials, these investigators suggested that pregabalin, gabapentin, and tricyclic antidepressants (TCAs) are optimal first-line treatments for neuropathic pain associated with SCI. Furthermore, they considered that serotonin–norepinephrine reuptake inhibitors (SNRIs) are second-line choices, and that tramadol, opioids, and lamotrigine are third-line options. However, these researchers concluded that such oral pharmacological intervention is often inadequate, commonly resulting in a reduction of only 20–30 % in pain intensity. Thus, no established cure for spinal neuropathic pain currently exists.

The present study is the first to report the results of a clinical trial that evaluated the therapeutic effect of G-CSF on neuropathic pain associated with compression myelopathy. G-CSF was administered to two distinct groups of spinal neuropathic pain patients: the progressing myelopathy-related pain group and the post-operative persistent pain group. In the 7 patients in the progressing myelopathy-related pain group, G-CSF administration reduced

neuropathic pain within several days in all patients. The mean VAS score was 71.4/100 before G-CSF administration, and it significantly decreased to 35.9/100 at 1 week after administration, indicating that the severity of pain decreased to 50 % of the pre-administration level. In all 7 patients, surgery for compression myelopathy was performed ≥2 weeks after initial G-CSF administration. Thus, the pain-relieving effect of G-CSF occurred prior to surgery. We suggest that the pain reduction observed within 1 week of administration in these seven cases was caused by the pharmacological effect of G-CSF and not by surgery.

To the best of our knowledge, no report has fully determined the effect of surgery itself on spinal neuropathic pain associated with compression myelopathy. In the present study, all seven patients in the progressing myelopathy-related pain group underwent surgery ≥2 weeks after the initial G-CSF administration. At the time of surgery, pain reduction had already been achieved in all the patients receiving G-CSF. After surgery, further decreases of pain were not obtained. These findings suggest the possibility that surgery itself does not have pain-relieving effects exceeding G-CSF. However, there are several limitations to this hypothesis. In this study, surgeries were performed a rather long time after myelopathy worsening. In addition, the number of patients analyzed in the present study was too small for definitive conclusions. Further studies with a larger number of patients will be required. We will determine the effect of much earlier times of surgery on the reduction of neuropathic pain due to compression myelopathy.

In the present study, we employed only one pain measure, VAS, to evaluate the severity of pain before and after the G-CSF administration. A number of pain measures have been reported for evaluating the intensity and quality of pain in patients with spinal neuropathic pain [2, 8, 14, 20]. Previous clinical trials analyzing the effect of amitriptyline [2, 14], gabapentin [8, 14], and pregabalin [20] on neuropathic pain associated with SCI employed multiple pain measures in addition to VAS, such as the McGill Pain Questionnaire (MPQ) and the Center for Epidemiologic Studies Depression Scale (CESD). They combined several pain measures based on the characteristics of each tool, and adequately evaluated the efficacy of the drugs for neuropathic pain. Since our present study was a phase I and IIa clinical trial, we utilized only VAS. In the subsequent phase IIb clinical trial of G-CSF neuroprotective therapy, we are planning to employ multiple pain measures in addition to VAS to evaluate the details of the effect of G-CSF on spinal neuropathic pain.

In the 10 patients in the post-operative persistent pain group, G-CSF administration did not have a pain-relieving effect in 3 patients. Since no improvement of myelopathy was observed in these 3 patients, we speculate that the pain-relieving and neuroprotective effects with respect to improvement of motor and sensory deficits of G-CSF are correlated. However, a pain-relieving effect was observed in the other 7 patients within 1 week after initial G-CSF administration. The mean VAS score of all 10 patients in the post-operative persistent pain group was 72.0/100 prior to G-CSF administration, and it significantly decreased to 51.7/100 at 1 week after administration. This indicates that the severity of pain decreased to 72 % of the pre-administration level. Based on this finding, we suggest that G-CSF may have a certain pain-relieving effect in patients who complain of post-operative persistent pain, although this effect is not as pronounced as that for patients with worsening symptoms of compression myelopathy.

Of the 17 patients analyzed in the present study, a pain-relieving effect associated with G-CSF was detected in 14 patients. However, recurrence of pain occurred in 8 out of these 14 patients during the follow-up period. Notably, pain returned to pre-administration levels in 5 patients. The recurrence of pain was detected at 3 months after G-CSF administration in 7 patients and at 6 months after G-CSF administration in 1 patient. This finding suggests that the pain-relieving effect by G-CSF only lasts for at most 3–4 months. Therefore, when the clinical utility of G-CSF for spinal neuropathic pain is evaluated in the future, administration every 3–4 months should be considered.

Previous studies reported the presence of placebo effects in patients suffering from neuropathic pain, although the duration of the placebo effect was not fully established [13]. In the present study, the pain-relieving effect of G-CSF continued for 3–4 months. Because the study design was open label, we cannot deny the contribution of the placebo effect of injection for reducing the spinal neuropathic pain. To verify the pharmaceutical pain-relieving effect of G-CSF on spinal neuropathic pain, a subsequent clinical trial with double-blind placebo-controlled study design will be necessary.

To the best of our knowledge, no reports of experimental studies of G-CSF administration in an animal model of spinal neuropathic pain have been published. In our studies using animal models of compression-induced and contusive SCI, intravenously administered G-CSF resulted in functional recovery by (1) promoting the migration of bone marrow-derived cells into the damaged spinal cord, (2) directly suppressing the neural apoptosis that occurs via G-CSF receptors at the injured spinal cord, and (3) decreasing the expression of inflammatory cytokines such as IL-1β and TNF-α [4, 6, 12]. Ro et al. [15] administered G-CSF to animal models of peripheral neuropathic pain, and demonstrated that G-CSF increased the number of opioid-contained polymorphonuclear cells and relieved neuropathic pain. We suggest that such mechanisms may

participate in the pain-relieving effect of G-CSF on spinal neuropathic pain, although further studies are required to fully clarify all of the underlying mechanisms.

To date, no effective therapies for spinal neuropathic pain have been established. To the best of our knowledge, this is the first report showing the possibility of a therapeutic effect of G-CSF on neuropathic pain associated with compression myelopathy. The biggest limitation of the present study was that this was an open-label study, so no comparison with a control group was performed. We cannot deny the possibility that a placebo effect of injection and surgical intervention contributed to pain relief. Based on the experience of the present findings, however, we intend to advance to a further clinical trial to verify the feasibility of using G-CSF for relief of spinal neuropathic pain. This will be a multi-center, double-blind, controlled clinical trial; the control group will receive placebo injection. If the efficacy and safety of G-CSF treatment for spinal neuropathic pain is confirmed and clinical use of G-CSF therapy is approved, a novel and effective approach for the treatment of this disorder will be available.

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Conflict of interest No funds were received in support of this study.

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Case report

Granulocyte colony-stimulating factor reduced neuropathic pain associated with thoracic compression myelopathy: Report of two cases

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Context: A clinical trial was conducted to evaluate the safety and efficacy of neuroprotective therapy using granulocyte colony-stimulating factor (G-CSF) for patients with worsening symptoms of compression myelopathy. During this trial, we found that neuropathic pain associated with thoracic myelopathy was dramatically reduced after G-CSF administration in two cases.

Findings: A 32-year-old man with compression of the spinal cord at levels T7–T10 complained of spastic gait associated with spontaneous severe pain from his back to his chest. G-CSF 10 μg/kg/day was administered for 5 consecutive days; his pain was reduced 1 day after the initial G-CSF administration. One month after administration, he underwent spinal fusion surgery for decompression of the spinal cord. Six months after G-CSF administration, he showed recovery from myelopathy and no recurrence of pain. A 68-year-old man with spastic gait and bilateral thigh pain caused by ossified ligamentum flavum at T11–T12 was treated with G-CSF 10 μg/kg/day for 5 days; his pain was reduced 1 day after initial administration. One month later, he underwent a T10–T12 laminectomy. Three months after G-CSF administration, his thigh pain began to attenuate. At 6 months after administration, he showed recovery from myelopathy, and his pain was still improved compared with that before administration.

Conclusion: G-CSF may have a therapeutic effect on spinal neuropathic pain.

Keywords: Myelopathy, Spinal cord compression, Neuroprotective therapy, Granulocyte colony-stimulating factor, Thoracic myelopathy, Neuropathic pain, Spasticity, Clinical trial

Introduction

Granulocyte colony-stimulating factor (G-CSF) is a cytokine that promotes survival, proliferation, and differentiation of cells in the neutrophil lineage.[1] Recent studies have indicated that G-CSF also has non-hematopoietic functions and can potentially be used for the treatment of neuronal injury, including stroke and neurodegenerative diseases.[2] We previously demonstrated that G-CSF promoted the restoration of damaged spinal cord tissue and the recovery of neural function in experimental spinal cord injury (SCI) in both mice and rats.[3–5] On the basis of these findings, we initiated a clinical trial to evaluate the safety and efficacy of neuroprotective therapy using G-CSF for patients with worsening symptoms of compression myelopathy.[6] In phases I and IIa of the clinical trial, we recruited patients 20–75 years of age, in whom Japanese Orthopaedic Association (JOA) score for cervical and thoracic myelopathy decreased 2 points or more during a recent 1-month period.[6] In the first step of this trial, G-CSF 5 μg/kg/day was intravenously administered for 5 consecutive days in five patients. We then administered G-CSF 10 μg/kg/day for 5 consecutive days in 10 patients. No serious adverse events occurred during or after treatment, and all patients showed neurological improvement, although G-CSF 10 μg/kg/day resulted in better neurological recovery. Thus, we suggested that intravenous administration of G-CSF at a dosage of 10 μg/kg/day for 5 days is an appropriate protocol for G-CSF neuroprotective therapy.[6]

During this trial, we encountered an unexpected finding – two patients in whom neuropathic pain associated with thoracic myelopathy was dramatically reduced after G-CSF administration. Such a pain-relieving effect of G-CSF had not been included as an endpoint in this

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trial. However, the effect is a significant feature with implications for future clinical use of G-CSF for compression myelopathy.

Case reports

Case 1

A 32-year-old man was admitted to our hospital complaining of progressive motor weakness of his lower extremities and gait disturbance. On admission, his JOA score for thoracic myelopathy (motor function: 0–4 points, sensory function: 0–4 points, bladder function: 0–3 points, total possible score = 11 points)[7] was 4 points. He also showed spontaneous severe pain developing from his back to his chest.

Four years prior to this admission, he suffered from thoracic myelopathy because of postvertebral osseous spurs that compressed his spinal cord anteriorly at T7–T10 (Figs. 1A and B). He underwent surgical treatment for T7–T10 anterior decompression with spinal fusion. Before his first surgery, he had complained of gait disturbance and spontaneous pain from his back to his chest. After the surgery, his symptoms of myelopathy and pain were relieved. Three years after the surgery, however, his symptoms began to deteriorate.

Reconstruction images from a computed tomography (CT) myelogram showed that the grafted bone at the T7–T8, T8–T9, and T9–T10 intervertebral disc levels was absorbed, and spine fusion was not obtained (Fig. 1C). The CT images showed regrowth of osseous spurs that compressed his spinal cord anteriorly at T7–T8 and T9–T10 (Figs. 1C and D, arrows) and newly developed ossified ligamentum flavum (OLF) that compressed his spinal cord posteriorly at T9–T10 (Figs. 1C and D, arrowheads).

From the day of admission, he underwent administration of G-CSF (10 μg/kg/day) for 5 consecutive days. One day after the initial G-CSF administration, he felt relief of his back and chest pain. Visual analog scale (VAS) score of his pain was 80 mm before G-CSF administration, and it decreased to 50 mm 1 day after the initial G-CSF administration. At 1 week after the initial administration, his VAS score became 0 mm, and his pain was diminished. He also felt improved muscle strength of his legs, and his JOA score was increased to 6 points at 1 month after the administration.

According to the protocol for G-CSF neuroprotective therapy for worsening symptoms of compression myelopathy, we followed the patients without surgical treatment for 1 month after G-CSF administration.[6] At 1 month after the administration, he underwent surgery for decompression of the spinal cord using a posterior approach and T4–T12 posterior instrumented fusion. At 6 months after the administration, his recovery from myelopathy was maintained (JOA score = 6 points) with no recurrence of pain.

Case 2

A 68-year-old man was admitted to our hospital with a complaint of motor weakness of his lower extremities and gait disturbance. On admission, JOA score was 4 points. In addition to the symptoms of myelopathy, he complained of spontaneous severe bilateral pain at the level of his thigh.

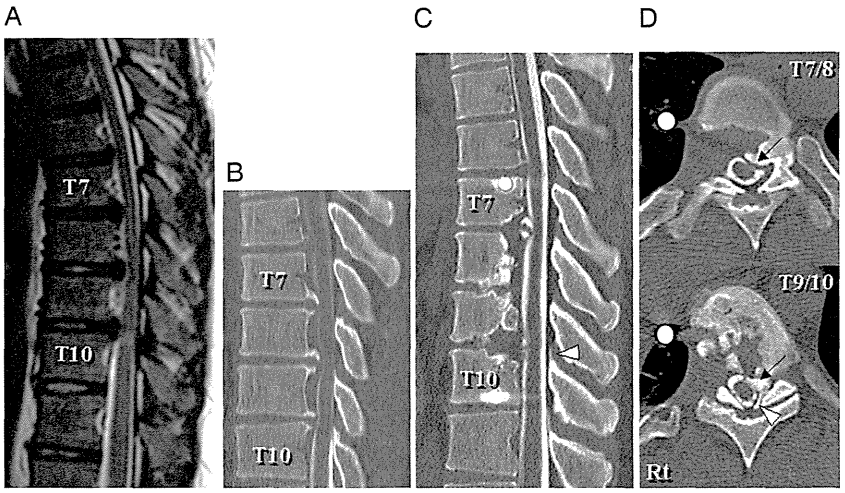

Figure 1 Case 1: T2-weighted midsagittal magnetic resonance image (A) and CT myelogram midsagittal reconstruction plane (B) 4 years prior to this admission showing anterior compression of the spinal cord by postvertebral osseous spurs at T7–T10. CT myelogram midsagittal reconstruction plane (C) and axial planes at T7–T8 and T9–T10 (D) on admission showing re-growth of the osseous spurs that compressed the spinal cord anteriorly at T7–T8 and T9–T10 (C, D, arrows) and a newly developed ossified ligamentum flavum (OLF) that compressed the spinal cord posteriorly at T9–T10 (C, D, arrowheads).

From 10 years earlier, his gait had become progressively unstable. Beginning 2 months previously, his gait disturbance progressed rapidly, and he could not walk without canes on admission. He had also felt severe bilateral thigh pain for the previous 2 months.

Sagittal magnetic resonance and reconstruction CT images showed that his spinal cord was severely compressed posteriorly by an OLF at T10–T11 (Figs. 2A–C).

From the day of admission, he underwent administration of G-CSF (10 μg/kg/day) for 5 consecutive days. One day after the initial G-CSF administration, he felt relief of his pain at his bilateral thigh. His VAS score for pain was 90 mm before the G-CSF administration, and it decreased to 40 mm 1 day after the initial G-CSF administration. His myelopathy also improved, and his JOA score became 6.5 points 1 month after G-CSF administration.

At 1 month after the administration, he underwent surgery for T10–T12 laminectomy. At 3 months after the administration, his pain recurred and the VAS score increased to 60 mm. After that, however, further aggravation of his pain did not occur, and the VAS score was 60 mm 6 months after the administration. The recovery from myelopathy was also maintained, and the JOA score was 6.5 points 6 months after G-CSF administration.

Discussion

Neuropathic pain has been defined as a type of pain arising from the direct consequence of a lesion affecting the somatosensory system such as in the brain, spinal cord, or peripheral nerves.[8,9] Among numerous diseases of the spinal cord, neuropathic pain following SCI has been studied most commonly. Previous studies have classified neuropathic pain from spinal cord lesions into two types: at-level pain and below-level pain.[1] At-level pain is characterized as pain located within two or three spinal segments below the neurological level of the spinal cord lesion. In contrast, below-level pain presents diffusely caudal to the level of the spinal cord lesion.

In case 1, the patient complained of spontaneous severe pain developing from his back to his chest. We suggest that his pain is a typical at-level pain originating from the spinal cord lesions at vertebral levels T7–T10. In case 2, the patient complained of spontaneous severe bilateral thigh pain corresponding to dermatome levels L2–L3. In this patient, the spinal cord was compressed by a T11–T12 OLF. Anatomically, the spinal cord level compressed by a T11–T12 OLF is considered to be the upper portion of the epiconus, where multiple spinal cord segments (usually L2–L5) are densely located.[10] Thus, we suggest that the thigh pain of this patient is also at-level pain. In the present two cases, G-CSF administration resulted not only in recovery from myelopathy, but also in reduction of neuropathic pain. In case 1, the VAS score was 80 mm before G-CSF administration, and it became 0 mm at 1 week after administration. In case 2, the pre-administration VAS score was 90 mm, and it decreased to 40 mm 1 day after G-CSF administration. In both cases, decompression surgery was performed 1 month after G-CSF administration. Thus, we suggest that the pain reduction observed in the present two cases during the 1 month after G-CSF administration was caused by the pharmacological effect of G-CSF and not by surgery. After surgery, however, the VAS score of both

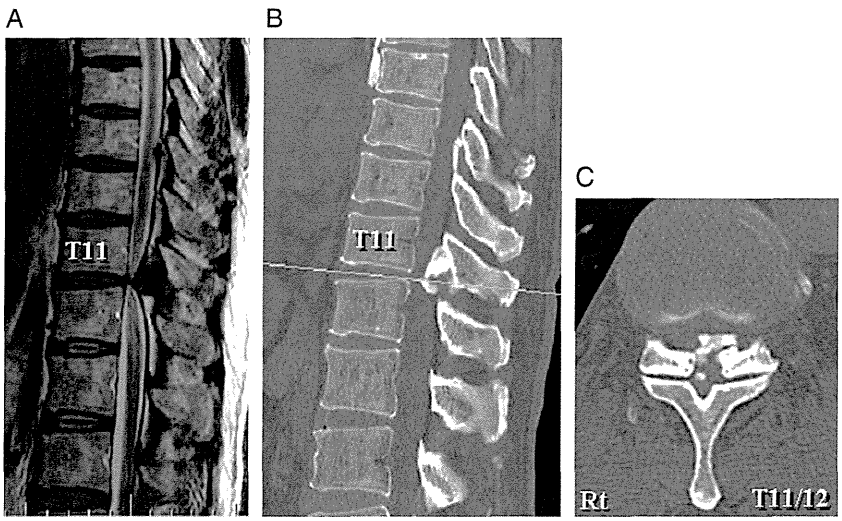

Figure 2 Case 2: T2-weighted midsagittal magnetic resonance image (A) and CT midsagittal reconstruction plane (B) and CT axial plane at T11–T12 (C) showing posterior compression of the spinal cord by an OLF at T11–T12.

cases did not necessarily reflect the neuroprotective effect of G-CSF. Despite the confounding factor of surgery, the present findings suggest that G-CSF may have a therapeutic effect on neuropathic pain in patients with thoracic compression myelopathy.

To the best of our knowledge, no reports of experimental studies of G-CSF administration in an animal model of spinal neuropathic pain have been published. In our studies using animal models of compression-induced and contusive SCI, intravenously administered G-CSF resulted in functional recovery by (1) promoting the migration of bone marrow-derived cells into the damaged spinal cord, (2) directly suppressing the neural apoptosis that occurs via G-CSF receptors at the injured spinal cord, and (3) decreasing the expression of inflammatory cytokines such as IL-1β and TNF-α.[3–5] Ro *et al.*[9] administered G-CSF to animal models of peripheral neuropathic pain, and demonstrated that G-CSF increased the number of opioid-contained polymorphonuclear cells and relieved neuropathic pain. We suggest that such mechanisms may participate in the pain-relieving effect of G-CSF on spinal neuropathic pain, although further studies are required to fully clarify all of the underlying mechanisms.

Among numerous diseases of the spinal cord, neuropathic pain following SCI has been studied most extensively.[8] Investigators have suggested that pregabalin, gabapentin, and tricyclic antidepressants are optimal first-line treatments for neuropathic pain associated with SCI. Furthermore, serotonin–norepinephrine reuptake inhibitors are considered to be second-line choices, and tramadol, opioids, and lamotrigine are used as third-line options. However, these researchers concluded that such oral pharmacological intervention is often inadequate, commonly resulting in a reduction of only 20–30% in pain intensity.[8] To date, therefore, no effective therapies for spinal neuropathic pain have been established.

Conclusion

To the best of our knowledge, this is the first report showing the therapeutic effect of G-CSF on neuropathic pain associated with compression myelopathy. We cannot deny the possibility that the placebo effect of injection and the surgical intervention contributed to the pain relief. On the basis of the experience of the present cases, however, we intend to advance to a clinical trial to verify the feasibility of using G-CSF for relief of spinal neuropathic pain. If the efficacy and safety of G-CSF treatment for spinal neuropathic pain is confirmed and clinical use of G-CSF therapy is approved, a novel and effective approach for the treatment of this disorder will be available.

Acknowledgement

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ORIGINAL ARTICLE

Three-dimensional evaluation of volume change in ossification of the posterior longitudinal ligament of the cervical spine using computed tomography

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Abstract
Background Two-dimensional imaging is not adequate for evaluating ossification of the posterior longitudinal ligament (OPLL). This study was designed to evaluate the accuracy of a novel computed tomography (CT)-based three-dimensional (3D) analysis method that we had devised to measure volume changes in OPLL.
Subjects and methods Twenty OPLL patients (12 male and 8 female; mean age 63.6 years) who were being followed conservatively were examined twice with an interval of at least 1 year between the two scans. The mean interval was 22 (range 12–45) months. A 3D model was created with DICOM data from CT images, using the MIMICS® software to calculate the volume. The mean ossification volume was determined from two measurements. Since ossification size varies widely, evaluation of change in volume is generally affected by the original size. Therefore, the change in ossification volume between the first and second CT examinations was calculated as the annual rate of progression.
Results The type of OPLL was classified as continuous in 3 patients, segmented in 3, and mixed in 14. The mean ossification volume was 1,831.68 mm^3 at the first examination and 1,928.31 mm^3 at the second, showing a significant mean increase in ossification volume. The mean annual rate of lesion increase was 3.33 % (range 0.08–7.79 %).
Conclusion The 3D method used allowed detailed OPLL classification and quantification of change in the ossified volume. Thus, this method appears to be very useful for quantitative evaluation of OPLL with only minimal measurement error.

Keywords OPLL · 3D analysis · CT · Ossification

Introduction

Ossification of the posterior longitudinal ligament (OPLL) of the cervical spine is one of the main causes of myeloradiculopathy in Asian populations, especially in Japan [1–4]. Accurate determination of the size of OPLL and the nature of its growth in terms of length and thickness is important because these factors crucially relate to spinal canal stenosis and can cause myelopathy [5]. Evaluating the size and growth of OPLL is important to determine the timing of the operation and the risk factors for rapid progression of OPLL. Previous attempts have already been made to measure the size of OPLL [6–10]. However, these methods involved two-dimensional imaging. Recent technical improvements in computed tomography (CT)-based three-dimensional (3D) imaging analysis have made accurate 3D measurement of OPLL possible [5, 11]. Previous studies on lung cancer growth found that evaluation of the growth of lung cancer using a 3D measurement method was more reliable than using a 2D method [12–15]. The present study was designed to evaluate the accuracy of a novel CT-based method of 3D analysis we had previously devised, to measure changes in the volume of OPLL.

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