Posterior Spinal Correction and Fusion Surgery in Patients with Spinal Muscular Atrophy-Associated Scoliosis for Whom Treatment with Nusinersen Was Planned

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Abstract:

Introduction: Spinal muscular atrophy (SMA) is defined as a neuromuscular disorder induced by progressive weakness of the skeletal muscle and is usually accompanied by progressive spinal deformity including scoliosis. The newly developed Nusinersen, which is the first approved drug worldwide for SMA, requires accurate intrathecal injection, which is sometimes difficult in patients with severe spinal deformity.

Technical Note: For an accurate intrathecal approach in patients who have spinal fusion surgery to treat neuromuscular scoliosis, we have combined an L3 laminectomy with spinal correction and fusion surgery. Here, we review four cases of SMA in patients who underwent the additional L3 laminectomy during surgery to treat spinal scoliosis. A successful intrathecal approach was made using fluoroscopic guidance in all four patients, who were then administered with Nusinersen.

Conclusions: Our findings show that additional lumbar laminectomy during surgery for spinal scoliosis has effectively allowed for intrathecal injection of Nusinersen.

Keywords:

Neuromuscular scoliosis, Spinal muscular atrophy, Nusinersen

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Introduction

Spinal muscular atrophy (SMA) has been identified as a genetic disorder caused by a mutation in the survival motor neuron 1 gene (SMN1) affecting anterior horn cells in the spinal cord and inducing weakness in the skeletal muscle[1,2)]. Patients with SMA often show progressive muscle weakness and sometimes complain of difficulty in breathing, eating, and sitting. There are four types of SMA based on the age at symptoms onset and the highest physical achievement of activities of daily living. SMA Type 1, the most severe and the most common type, usually results in the early mortality or severe disability in survivors. Meanwhile, SMA Type 2 is usually diagnosed from 6 months to 2 years of age. Patients with SMA Type 2 are usually unable to walk, needing to use a wheelchair. They sometimes exhibit progressive neuromuscular scoliosis (NMS), which requires treatment[3)].

Newly developed Nusinersen (SPINRAZA®) is an antisense oligonucleotide, which helps in the production of fully functional SMN protein. It has been reported that Nusinersen treatment can prolong the survival of SMA Type 1 patients and significantly improves motor function in patients with SMA Type 2[4)]. To administer Nusinersen, an accurate intrathecal injection must be performed; however, there are concerns for this in patients with SMA because they usually show progressive NMS. Especially in SMA patients with severe spinal deformity, intrathecal injection is determined to be difficult after spinal fusion surgery. For accurate intrathecal injection of Nusinersen in patients who have spinal fusion surgery planned for NMS, we combined L3 laminectomy with spinal correction and fusion surgery from December 2017.

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The aims of the present report were to introduce our surgical technique and to elucidate the efficacy of this procedure for intrathecal injection of Nusinersen in patients with SMA.

Technical Note

We included four consecutive patients with SMA (3 boys and 1 girl; mean age: 11.5 years, range 11-12 years) who underwent posterior spinal corrective fusion surgery for NMS from December 2017 in the present study. We performed all surgeries under general anesthesia using motor evoked potentials in order to monitor spinal cord function. In all cases, we performed autotransfusion using preoperative storage and intraoperative collection during surgical procedure. We made a skin incision on the midline of the back, exposing widely the spinal structure from the upper thoracic spine to the L5 level or the sacrum. After removing the soft tissue, pedicle screw instrumentation was placed using computed tomography (CT)-based navigation. Hooks and sublaminar cables (Nesplon Cable System, Alfresa, Tokyo, Japan) were also installed. Fusion levels determined sitting balance and pelvic obliquity, and in all cases, were from T4 to L5 or the pelvis. Surgery to correct spinal deformity was performed by combining two techniques including rod rotation and a cantilever technique as previously reported[5]. We also performed a facetectomy and Ponte osteotomy depending on the spinal flexibility. Further, to facilitate intrathecal Nusinersen treatment, we performed an L3 laminectomy using an osteotome; then a transverse connector between two rods was placed at the level of the upper L3 laminectomy, which is used as a landmark for the intrathecal injection. Finally, we decorticated and placed local autograft bone mixed with bioresorbable bone graft. In particular, to obtain bone fusion at the laminectomy level, we performed thorough facet fusion surgery, including decortication of the bilateral L2-3 and L3-4 facet joints and placement of a large amount of local autograft material.

Clinical outcomes

To evaluate the clinical outcome, we reviewed the operation time, intraoperative blood loss, perioperative complications, duration of hospital stay, and preoperative and postoperative Cobb angle in all cases. Additionally, administration status including propriety and timing of Nusinersen intrathecal injection was reviewed. Further, the correction of Cobb angle was calculated using the following formula:

Correction (%) = (postoperative Cobb angle − preoperative Cobb angle)/preoperative Cobb angle

The results of surgery are summarized in Table 1. There was one determined perioperative complication of aspiration pneumonia, which was treated conservatively. At final follow-up performed 6 months to 2 years postoperatively, all four patients were successfully injected intrathecally with Nusinersen under fluoroscopic guidance at least once.

Table 1. Details of the Patients and Operative Parameters in the Study Group.

	Mean	Range
N	4	
Sex	M:3 F:1	
Age at operation (years)	11.5	11–12
Operation time (min)	318	241–400
Preoperative Cobb angle (degrees)	83.0	10–136
Postoperative Cobb angle (degrees)	37.8	6–66
Correction rate (%)	52.0	40.0–61.5
Hospital stay (days)	18	11–30
Complications	Aspiration pneumonia: 1	

Representative case presentation

Patient: A 12-year-old boy. When he was 2 years old, he was diagnosed with SMA due to motor retardation. When he turned 9, he showed symptoms of spinal scoliosis, which then progressed gradually. Subsequently, after turning 12, he was referred to our institution for treatment of spinal scoliosis. Further, treatment with Nusinersen was planned. The patient was determined to have sitting difficulty and back pain. An X-ray image of the spine from a frontal view of the boy sitting revealed severe spinal scoliosis with a Cobb angle of 115° (Fig. 1A). An X-ray image of the spine from a lateral view of the boy sitting revealed spinal kyphosis with lumbar lordosis (from first lumbar vertebra (L1) to sacrum) of −21°, thoracic kyphosis (from 5th thoracic vertebra (T5) to T12) of 65°, and thoracolumbar kyphosis of 50° (from T10 to L2) (Fig. 1B). In addition, an X-ray image of the spine with the boy supine under traction has revealed spinal scoliosis Cobb angle correction of 44% (Fig. 1C). Under general anesthesia, we corrected the spine using posterolateral fusion instrumented from T4 to the pelvis. Further, to allow an intrathecal approach for Nusinersen treatment, an L 3 laminectomy has to be performed using an osteotome. The operative time was 6 h 40 min, and the blood loss was 1176 mL. Postoperative X-ray imaging revealed good spinal correction with a Cobb angle of 52° and 55% correction (Fig. 2 A, B). Further, postoperative CT showed a successful L3 laminectomy (Fig. 2C). The patient was discharged from the intensive care unit 2 days after surgery and later started physical therapy 3 days after surgery. His difficulty sitting was improved gradually, and he was discharged home 19 days after surgery. Eight months after surgery, he was successfully treated with Nusinersen by intrathecal injection under fluoroscopic guidance (Fig. 3A, B). CT before the intrathecal injection showed a successful L3 laminectomy without a bone mass on the lamina (Fig. 3C, D). At the final follow-up 24 months after surgery, he had successfully received six intrathecal injections of Nusinersen.

Ethics approval

We obtained ethics approval from our Institutional Review Board (IRB) for this present study, which was conducted in

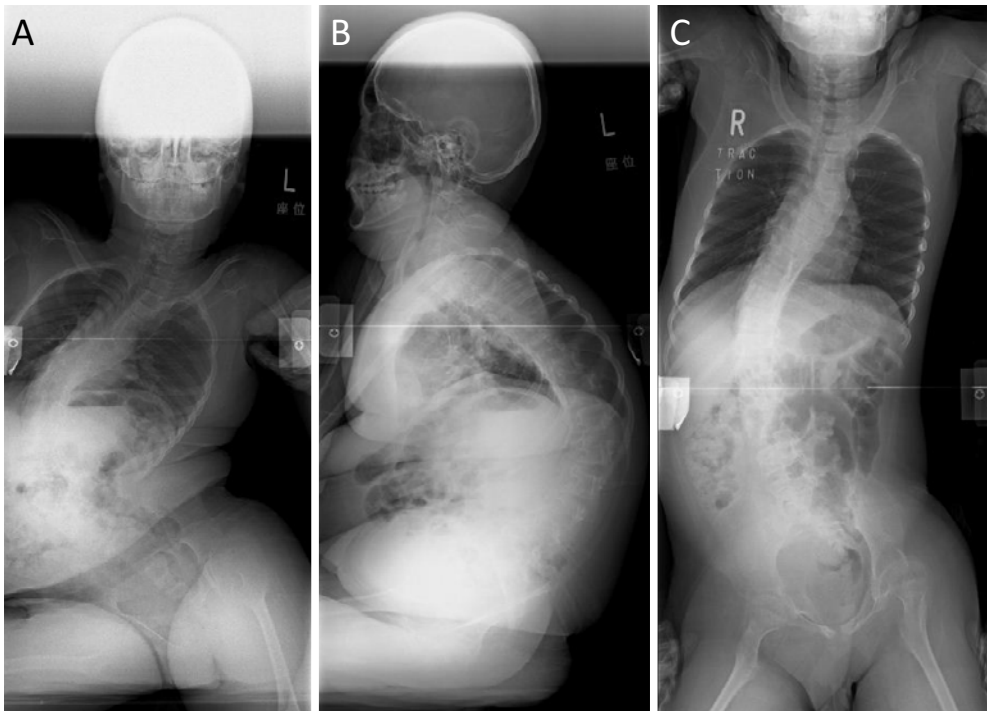

Figure 1. Preoperative X-ray images of a representative case of scoliosis secondary to spinal muscular atrophy (SMA). Frontal (A) and lateral view (B) with the 12-year-old patient sitting and frontal view while supine in traction (C). Preoperative Cobb angles were 115° while the boy was sitting and 60° while the patient was in traction and supine.

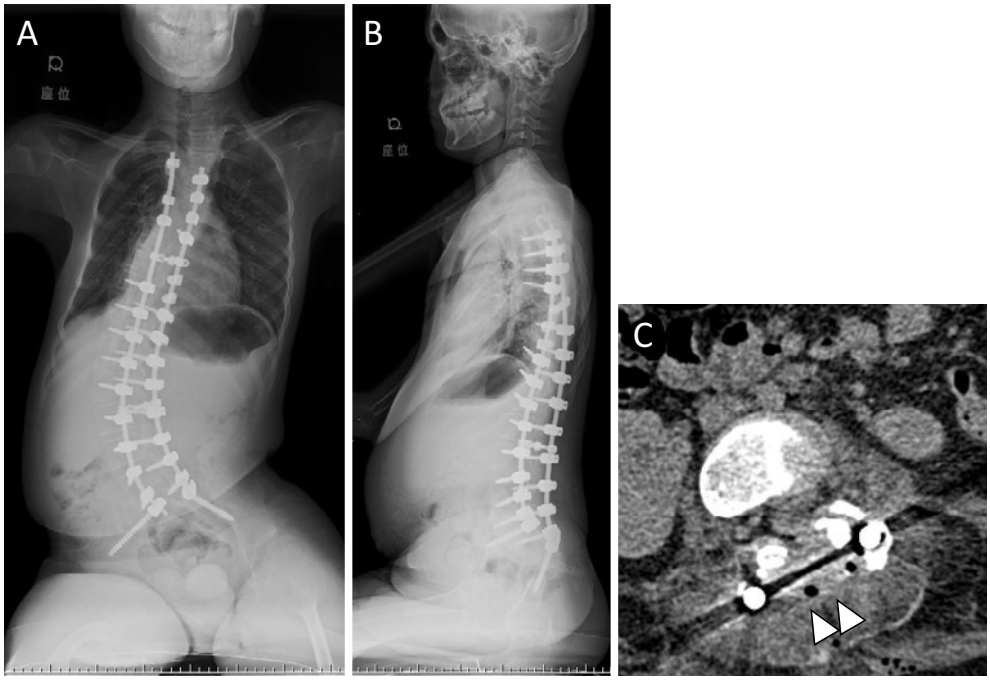

Figure 2. Postoperative X-ray image and CT image of representative case with scoliosis secondary to SMA. Frontal (A) and lateral view (B) X-ray images while the patient was sitting and axial CT image at the laminectomy site. Postoperative Cobb angle was 52° while sitting, and the Cobb angle correction was 55%. (C) Arrowheads indicate the laminectomy site at the L3 level.

accordance with the principles specified in the 1964 Declaration of Helsinki and its subsequent amendments.

Discussion

Nusinersen (SPINRAZA) is a newly developed drug and

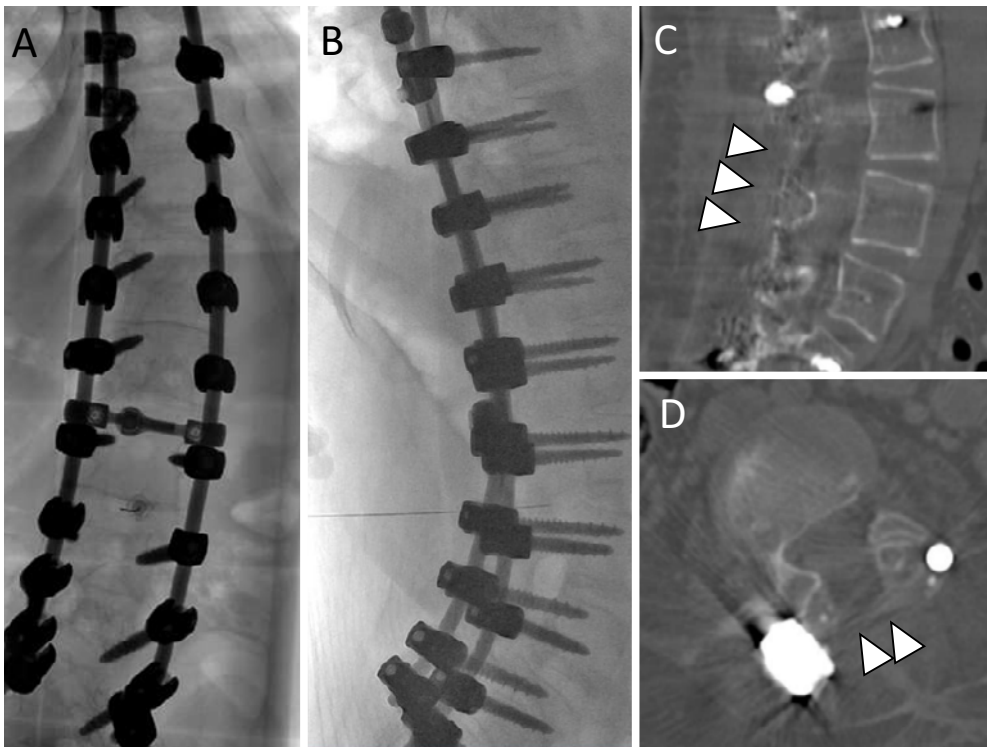

Figure 3. Fluoroscopic images and CT of the representative case during injection of Nusinersen. Frontal (A) and lateral (B) fluoroscopic views while the patient was prone and sagittal (C) and axial (D) CT views before Nusinersen injection. Intrathecal access was straightforward under fluoroscopic guidance.

the first for SMA to be approved worldwide, including in Japan in July 2017. Nusinersen treatment can expected to produce fully functional SMN protein and is observed to suppress the degeneration and loss of motor neurons. In a phase 3 safety and efficacy trial for infantile SMA, Nusinersen induced meaningful improvement of motor-milestone response and CHOP INTEND response measurements for motor function[6]. Although it remains unclear whether treatment-related improvement is expected in SMA patients with severe dysfunction including spinal deformity, Nusinersen is reportedly efficacious and safe, and it is expected to become the new standard treatment strategy for all types of SMA[4,7,8]. However, there are concerns for an accurate intrathecal injection of Nusinersen because of spinal deformity. Messina S et al. reported the injection procedure has failed at the first attempt in 24 of the 120 SMA patients because of severe spinal deformity including scoliosis and rotation[9]. Cartwright MS et al. also reported only 74% of patients with SMA and complicated spines were injected via lumbar puncture under fluoroscopic guidance, and others required alternative strategies for intrathecal injection of Nusinersen[10]. In some SMA patients with spinal deformity, the dural sac sometimes terminates at around the level of L 5, which is considered higher than normal[11]. Therefore, an intrathecal approach is considered difficult at L5/S1 level in patients with spinal deformity. For an accurate intrathecal approach, the intrathecal injection has been performed using a CT-guided transforaminal approach[4,12,13], videofluorangiography[4], and an intrathecal Ommaya reservoir approach[10], which was sometimes invasive for patients. Our surgical technique in this study seemed to be one of the good measures to approach intrathecally after spinal fusion surgery, less invasively. Further, Labianca et al. reported a technique using an additional L3-L4 laminotomy during spinal scoliosis surgery to allow a successful intrathecal approach, similar to the technique we used[14]. Compared with the technique used by Labianca et al., we performed an L3 laminectomy and placed a transverse connector between the two rods at the level of the upper L3 laminectomy, in order to provide a landmark for the intrathecal injection. Regarding the appropriate laminectomy level, there is concern regarding the typical rotation of the L3 vertebra. However, during the corrective surgery, we were generally able to place bilateral pedicle screws symmetrically at the lower vertebra because of the adequate thickness of the pedicle. During the lumbar puncture, the puncture site is easily detected with the frontal view under fluoroscopic guidance, even in rotated vertebra. Therefore, L3 laminectomy is recommended despite the presence of L3 rotation. Therefore, we believe that our technique might allow an easier intrathecal approach for Nusinersen treatment.

In terms of the duration from the surgery to the first injection of Nusinersen, a 2-month follow-up is needed in all cases, to confirm any leakage of Nusinersen. Although, suitable duration from the surgery to the first injection was still unclear, we should wait lumbar puncture until at least surgi-

cal wound was completely healed to prevent leakage of Nusinersen.

However, the suboccipital approach may also be a viable alternative in cases where lumbar puncture is difficult. However, this technique must be performed by a spinal surgeon or anesthesiologist, and many SMA patients find it difficult to visit well-equipped hospitals owing to distance. Therefore, the surgical technique described in this present study might have a great advantage because intrathecal injection can be accurately performed by doctors who were not specialist including spinal surgeon and anesthesiologist without any special equipment.

We conclude that the additional lumbar laminectomy during spinal scoliosis surgery effectively facilitates intrathecal injection of Nusinersen.

Conflicts of Interest: This research was supported in part by the Intramural Research Grant (29-3) for Neurological and Psychiatric Disorders of NCNP.

Ethical Approval: Ethical approval from the Institutional Review Board in Kitasato University has been obtained for this study, which was conducted in accordance with the ethical principles specified in the 1964 Declaration of Helsinki and its later amendments. The approval code is #B16-236.

Author Contributions: SM, MM, and WS conceived this study, performed surgery, and drafted the manuscript; AM administered with Nusinersen and helped to revise the manuscript; TI, GI, TN, ES, SI, AK, AK, YY, and YM performed surgery and participated in the design of the study; and KU, TA, and MT conceived the study and participated in its design and coordination. All authors have read and approved the final manuscript.

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