ELSEVIER

Brain & Development xxx (2020) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Administration of nusinersen via paramedian approach for spinal muscular atrophy

Hideyuki Iwayama [a,*], Norimitsu Wakao [b], Hirokazu Kurahashi [a,c], Norika Kubota [d], Ayako Hattori [e], Toshiyuki Kumagai [c,f], Akihisa Okumura [a]

[a] *Department of Pediatrics, Aichi Medical University, Aichi, Japan*
[b] *Department of Orthopedics, Aichi Medical University, Aichi, Japan*
[c] *Department of Pediatric Neurology, Aichi Prefectural Colony Central Hospital, Aichi, Japan*
[d] *Department of Pediatrics, Matsue Medical Center, Shimane, Japan*
[e] *Department of Pediatrics and Neonatology, Nagoya City University, Aichi, Japan*
[f] *Kuma Home Medical Care Clinic, Aichi, Japan*

Received 28 April 2020; received in revised form 7 July 2020; accepted 21 July 2020

Abstract

Objective: To assess the success rate, procedure time, and adverse events of intrathecal administration of nusinersen via the paramedian approach in adolescents and adults with spinal muscular atrophy (SMA) associated with scoliosis.

Methods: Seven patients with genetically confirmed SMA (age, 12–40 years) were included. Intrathecal administration of nusinersen was performed via paramedian approach using fluoroscopy after determination of the largest interlaminal foramen among L2-L3, L3-L4, or L4-L5 by three-dimensional computed tomography. We measured the times for preparation, positioning, and puncture, and the total time of stay. Adverse effects of intrathecal administration were noted.

Results: Intrathecal administration via paramedian approach was successful for all 38 opportunities. The median total time of stay was 44.0 min (interquartile range, 37.3–50.0 min). The total time of stay was significantly longer in patients with SMA type 1 than in those with SMA type 2, but was not different according to the severity of scoliosis. Adverse effects included oxygen supplementation, headache, and back pain. Sedation was correlated with oxygen supplementation and headache.

Conclusions: Intrathecal administration of nusinersen via the paramedian approach had the advantages of a high success rate and short procedure time with fewer adverse events in SMA patients associated with scoliosis.
© 2020 The Japanese Society of Child Neurology. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Spinal muscular atrophy; Nusinersen; Intrathecal administration; Paramedian approach; Scoliosis

1. Introduction

Spinal muscular atrophy (SMA; OMIM# 253300) is caused by spinal motor neuron degeneration due to biallelic deletions of *SMN1*, which encodes survival motor neuron (SMN) protein [1]. The lack of SMN protein leads to muscular denervation and atrophy. The antisense oligonucleotide, nusinersen, alters splicing of *SMN2* pre-mRNA and increases the expression of stable SMN protein [2]. Repeated intrathecal administration of nusinersen improves survival and motor function in patients with SMA, even in adolescents and adults with SMA types 2 and 3 [3,4]. However, intrathecal adminis-

* Corresponding author at: 1-1, Yazako-Karimata, Nagakute, Aichi, 480-1195, Japan. Fax: +81-561-63-4835.
E-mail address: iwahide1976@gmail.com (H. Iwayama).

https://doi.org/10.1016/j.braindev.2020.07.014
0387-7604/© 2020 The Japanese Society of Child Neurology. Published by Elsevier B.V.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article in press as: Iwayama H et al. Administration of nusinersen via paramedian approach for spinal muscular atrophy. Brain Dev (2020), https://doi.org/10.1016/j.braindev.2020.07.014

tration is not always easy in older patients with joint contractures and/or severe scoliosis [4].

Intrathecal access in adolescents and adults with SMA can be achieved via different approaches [5-12]. Posterior midline (interspinous) or paramedian (interlaminar) approaches have been reported as the standard intrathecal administration routes. Lateral or prone position is required regardless of the way of approaches, which can cause pain and hypoxia due to hypoventilation. A short procedure time is preferable to reduce the stress of the patients. Indeed, our first intrathecal administration of nusinersen was performed via classical interspinous approach. It was very difficult and necessitated multiple attempts and long procedure time, resulting in unbearable burden of the patient. Then, we applied paramedian approach, which has made intrathecal administration much easier and reduced stress of the patients. There have been few studies regarding the success rates and required time of the procedure according to the procedure of intrathecal administration. We retrospectively analyzed the success rate, procedure time, and complications of intrathecal administration via the paramedian approach in adolescent and adult patients with SMA associated with mild-to-severe scoliosis.

2. Methods

2.1. Patients

We reviewed 38 consecutive opportunities of intrathecal nusinersen administration in 7 patients with SMA using radiograph-guided paramedian approach between November 2017 and March 2020. Five patients were referred to our hospital because intrathecal administration had been expected to be difficult. All patients had homozygous *SMN1* deletion. Two patients had 2 copies of *SMN2* and the other five had 3 copies of *SMN2* (Table 1). Three patients had very severe scoliosis with a Cobb angle (CA) >90° (Cases 1, 2, and 5) (Fig. 1A). No patient required spinal instrumentation due to scoliosis.

Nusinersen was intrathecally administered with 4 loading doses in a patient with SMA type 1, and 3 loading doses in 6 patients with SMA type 2. Maintenance administration was performed every 4 months in SMA type 1, and every 6 months in SMA type 2. Neuromuscular assessment was performed following previous studies [3,4,10], including Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Revised Upper Limb Module (RULM), and Hammersmith Functional Motor Scale-Expanded (HFMSE). Some of the items in CHOP INTEND, such as head/neck extension or spinal incurvation, could not be performed in these adult patients. Motor assessments were performed the day before each administration of nusinersen by the same occupational therapist and physical therapist.

This study was approved by the ethics committee of Aichi Medical University Hospital (19-H012). Informed consent was obtained from all patients.

2.2. Procedure

On admission, spinal plain radiography and three-dimensional computed tomography were performed to evaluate the severity of scoliosis and the width of the interlaminal foramen. Lumbar interlaminal foramen was visible in all patients, leading to application of paramedian approach (Fig. 1B). Four doses were administered by an orthopedic spine surgeon (NW) and the remaining 34 doses were administered by a pediatrician (HI). Imaging guidance (Ultimax-i X-ray; Canon Medical Systems, Tokyo, Japan) was utilized for needle placement. All procedures were performed under local anesthesia, and sedation was performed upon the patient's request.

The patients were placed in the prone position or left lateral decubitus position without their head flexed, depending on the patient's comfort. On the frontal spinal radiograph, the largest interlaminal foramen among L2-L3, L3-L4, or L4-L5 was chosen for the procedure. Using fluoroscopy, the skin was marked aiming for the spinous process and interlaminal foramen about 1.5 cm from the midline. After local anesthesia, a 21-gauge spinal needle was advanced with intermittent radiographic guidance into the interlaminal foramen (Fig. 1C). After the spinal needle was confirmed to be in the subarachnoid space, 5 mL of CSF was removed and 5 mL (12 mg) of nusinersen was slowly administered over 1–3 min in accordance with the standard protocol. All of the procedures from positioning to administration of nusinersen are shown in a movie (Supplemental File 1).

2.3. Evaluations

We evaluated the success rate, number of attempts, and procedure time. The times at the arrival at the radiographic fluoroscopy room (Time A), the beginning of fluoroscopy (Time B), the beginning of lumbar puncture (Time C), the beginning of administration of nusinersen (Time D), and the exit from the radiographic fluoroscopy room (Time E) were recorded. The times for preparation, positioning, puncture, and the total time of stay were calculated as Time (B minus (−) A), Time (C–B), Time (D–C), and Time (E–A), respectively. We also noted occurrence of major complications, including meningitis or hydrocephalus, and minor complications, including headache, back pain, nausea, and need for oxygen and/or sedation.

Please cite this article in press as: Iwayama H et al. Administration of nusinersen via paramedian approach for spinal muscular atrophy. Brain Dev (2020), https://doi.org/10.1016/j.braindev.2020.07.014

Table 1
Patient characteristics.

Case	Age (y)	Sex	Occupation	SMA type	*SMN2* copies	Number of opportunities	Electric Wheelchair	Scoliosis	Cobb Angle	G-tube	NIV	CHOP INTEND*2	RULM*2	HFMSE*2
1	19	M	University Student	2	2	7*1	+	Very severe	118	–	–	5/64 18/64	1/37 1/37	0/66 0/66
2	23	F	Office Worker	2	3	6	+	Very severe	109	–	–	24/64 24/64	18/37 18/37	2/66 2/66
3	26	F	Home Employment	2	3	6	+	Severe	76	–	–	31/64 31/64	20/37 21/37	3/66 3/66
4	20	M	University Student	2	3	6	+	Mild	20	–	During night	21/64 21/64	6/37 7/37	0/66 0/66
5	27	M	Company President	2	3	5	+	Very severe	113	+	During night	0/64 0/64	0/37 0/37	0/66 0/66
6	12	F	School Student	1	2	6	+	None	5	+	All day	0/64 0/64	0/37 0/37	0/66 0/66
7	40	M	Unemployed	2	3	3	+	Moderate	48	+	All day	0/64 0/64	0/37 0/37	0/66 0/66

SMA: spinal muscular atrophy, G-tube: gastrostomy tube, NIV: Non-invasive ventilation, CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, RULM: Revised Upper Limb Module, HFMSE: Hammersmith Functional Motor Scale-Expanded.
*1. The initial dose of Case 1 was not included in this study because interspinous route was applied.
*2. Upper, at baseline; Lower, at the last visit.

2.4. Statistical analysis

The time for each procedure were expressed as median (interquartile range (IQR)). We used the chi-square test and the Mann–Whitney *U* test to compare categorical and numerical variables, respectively. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [13], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

3. Results

3.1. Success rate and number of attempts for needle insertion

All doses of nusinersen (n = 38) were successfully administered via the paramedian approach (success rate, 100%). In 31 of 38 opportunities, nusinersen were successfully administered at first attempt (first-attempt success rate, 82%). In 7 opportunities, additional attempt of needle insertion was required. In one patient (Case 6 with SMA type 1), 2 and 3 attempts were required to deliver the second and the third opportunity, respectively.

3.2. Time for each procedure

The median total time of stay was 44.0 min (IQR, 37.3–50.0 min). The median times for preparation, positioning, and puncture were 10.2 min (IQR, 6.0–12.4 min), 7.0 min (IQR, 4.8–10.5 min), and 8.7 min (IQR, 7.5–14.0 min), respectively. We compared time for each procedure between 6 opportunities in SMA type 1 and 32 opportunities in SMA type 2 (Table 2). The times of positioning and puncture were not different. The time of preparation was relatively longer in SMA type 1 than in SMA type 2, whereas the difference was not significant ($p = 0.088$). The time of stay was significantly longer in SMA type 1 than in SMA type 2 ($p = 0.005$). The time of preparation, positioning, puncture, and total stay was not significantly different between patients with very severe scoliosis and those with mild to severe scoliosis (Table 2).

3.3. Adverse events

There were no major complications resulting in death or sequela. No patient required topical or general analgesia during intrathecal administration. No infection related to intrathecal injection was observed. Sedation was requested by Cases 1 and 2 for all but one opportu-

Please cite this article in press as: Iwayama H et al. Administration of nusinersen via paramedian approach for spinal muscular atrophy. Brain Dev (2020), https://doi.org/10.1016/j.braindev.2020.07.014

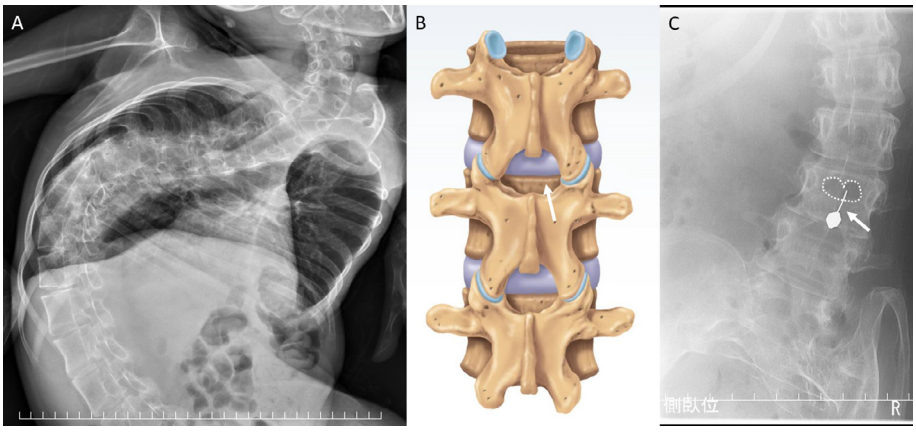

Fig. 1. Spinal radiograph shows severe scoliosis in patient 1 (A). The route of paramedian approach is illustrated by the arrow (B). Lumbar puncture at L2-L3 via paramedian approach on frontal view (C). The arrow indicates the spinal needle. The dotted line circles the interlaminal foramen.

Table 2
Procedure time.

	SMA Type 1 (N = 6)	SMA Type 2 (N = 32)	P value	Very severe scoliosis (N = 17)	None ~ severe scoliosis (N = 21)	P value
Time of preparation (min)	10.6 (10.1–13.2)	9.7 (5.0–12.1)	1.000	10.5 (7.6–12.5)	9.5 (5.0–12.0)	0.528
Time of positioning (min)	6.5 (4.6–9.2)	7.0 (4.9–10.8)	0.458	8.5 (5.0–11.8)	6.3 (4.6–8.0)	0.212
Time of puncture (min)	9.8 (9.1–15.2)	8.6 (7.4–13.9)	0.088	9.1 (7.7–15.3)	8.5 (6.8–11.6)	0.223
Total time of stay (min)	51.5 (49.3–53.8)	43.0 (34.8–48.0)	0.005	45.0 (40.0–50.0)	43.0 (33.0–50.0)	0.453

Values are shown as median (interquartile range).
SMA: spinal muscular atrophy

nity. Intravenous thiamylal (100–250 mg) was used for sedation. Oxygen supplementation was required only in 4 opportunities in Case 1, when SpO2 was <90%. Headache was observed after 3 opportunities in Case 1. Back pain was seen in at least one opportunity in all patients except Case 4. Nausea occurred after 1 opportunity in Case 2.

Sedation was significantly correlated with oxygen requirement ($p = 0.0082$) and the occurrence of headache ($p = 0.0047$), but not with back pain ($p = 0.931$) (Table 3). Time for puncture and multiple attempts were not correlated with these adverse events.

4. Discussion

This study showed that fluoroscopy-guided intrathecal administration via the paramedian approach was successful in patients with SMA associated with scoliosis. In patients with SMA, both scoliosis and lack of spinal flexibility can be a barrier for intrathecal nusinersen administration. In this study, all patients had spinal stiffness and 3 had very severe scoliosis with a CA >90°. For intrathecal administration, Bowens et al. [14] suggested that mild scoliosis should be managed with good positioning for neuraxial anesthesia. The paramedian approach with imaging guidance has been recommended for the management of moderate-to-severe scoliosis.

4.1. Success rate of intrathecal administration

A few studies have reported the first-attempt success rate, number of attempts, and procedure time [11]. These factors were important to reduce the patients' stress and radiation exposure. In our study, the first-attempt success rate was 82%, even though all 7 patients had scoliosis. In one series of 84 opportunities of nusinersen delivered via the interspinous approach (20 patients of 2–50 months of age with no scoliosis), the first-attempt success rate was 33% [12]. Wurster et al. compared between 36 opportunities of interspinous approach and 57 opportunities of paramedian approach, and showed that the first-attempt success rate was higher in paramedian approach than in interspinous approach (84% vs. 21%) [11]. Together with these findings, paramedian approach has an advantage of higher first-attempt success rate over interspinous approach in patients with SMA.

Please cite this article in press as: Iwayama H et al. Administration of nusinersen via paramedian approach for spinal muscular atrophy. Brain Dev (2020), https://doi.org/10.1016/j.braindev.2020.07.014

Table 3
Adverse events.

	Oxygen supplementation			Headache			Back pain		
	Yes (N = 4)	No (N = 34)	P value	Yes (N = 3)	No (N = 35)	P value	Yes (N = 10)	No (N = 28)	P value
Sedation	4 (100%)	7 (21%)	0.0082	3 (100%)	8 (23%)	0.0047	3 (30%)	8 (29%)	0.931
Time of preparation (min)*	8.7 (6.3–10.8)	10.2 (6.0–12.7)	0.634	10.5 (8.6–10.6)	10.1 (5.4– 12.7)	0.935	9.2 (6.5–12.0)	10.4 (5.0–12.2)	0.816
Time of positioning (min)*	10.0 (7.5–13.0)	6.7 (4.7–9.8)	0.199	8.3 (5.0–12.4)	6.9 (4.8–10.3)	0.849	7.5 (4.7–8.4)	6.8 (4.9–11.2)	0.690
Time of puncture (min)*	11.5 (7.6–16.5)	8.7 (7.2–13.3)	0.668	7.6 (7.6–13.6)	8.8 (7.3–13.9)	0.892	8.7 (7.1–13.3)	8.7 (7.7–14.3)	0.868
Total time of stay (min)*	45.0 (39.8–52.5)	44.0 (35.5–49.8)	0.583	40.0 (39.5–45.0)	45.0 (36.0–50.0)	0.828	40.0 (35.8–47.3)	45.0 (39.3–50.0)	0.344
Multiple attempts	1 (25%)	6 (18%)	0.719	0 (0%)	7 (20%)	0.391	3 (30%)	4 (14%)	0.271

*: Values are shown as median (interquartile range).

4.2. Time for the procedure

The median total time of stay was 44.0 min in this study, which is comparable to a previous report of paramedian approach with fluoroscopic guidance (38.0 min) and neural foramen approach (41.2 min) [7]. For the use of an implantable infusion port, a longer procedure time (1.1–2.0 h) has been reported [1]. Wurster et al. also reported that the procedure time for CT-guided intrathecal administration was longer than that of conventional intrathecal administration (42.2 min vs. 29.9 min) [11]. Of note, the procedure time in their study was from positioning of patients to successful administration of the drug, which is different from our study. Radiation exposure in fluoroscopy is lower than that in CT-guided injections [15]. On the basis of these results, fluoroscopy-guided intrathecal administration will result in shorter procedure time and less radiation exposure.

The time of stay was significantly longer in SMA type 1 than in SMA type 2. The patient with SMA type 1 had a ventilator, so it took time to move between bed and stretcher. After the administration of nusinersen, the patient with SMA type 1 needed a period of rest because of exhaustion. It is considered that these were the reasons why the stay time was longer in SMA type 1.

4.3. Adverse events

At present, the relation between adverse events and puncture time, number of attempts for needle insertion, and the use of sedation remains unclear. In this study, puncture time had no correlation with headache or back pain. The number of attempts was not related to the occurrence of adverse events. The use of sedatives was associated with requirement of oxygen supplementation and occurrence of headache, but was not associated with back pain. The patient who required oxygen supplementation had severe scoliosis and the deformity of the chest compromising respiration. It will be important to avoid sedation as much as possible in patients with severe scoliosis. Further study is needed to elucidate the relationship between adverse events and procedure of intrathecal administration of nusinersen.

4.4. Limitations of this study

Our study has several limitations. First, this is a retrospective and non-randomized evaluation of a method that has been used in only a few patients. Second, no control groups were used to compare the standard interspinous approach with the paramedian approach. However, we consider that the paramedian approach will be easy and safe once one get accustomed, because the target width of paramedian approach is much larger than that of interspinous approach. Third, our study was

Please cite this article in press as: Iwayama H et al. Administration of nusinersen via paramedian approach for spinal muscular atrophy. Brain Dev (2020), https://doi.org/10.1016/j.braindev.2020.07.014

based only on experience in a single center. A multicenter analysis confirming our results is needed before our conclusions can be generalized to broader populations of patients.

In summary, intrathecal administration of nusinersen via the paramedian approach had the advantages of a high success rate and short procedure time with fewer adverse events in SMA patients with scoliosis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the participants in this study, especially the patient in Case 1, for his brave decision to be the first patient to receive nusinersen in our institution. The research of HI was supported by Yoshiko & Seizo Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2020.07.014.

References

[1] Strauss KA, Carson VJ, Brigatti KW, Young M, Robinson DL, Hendrickson C, et al. Preliminary safety and tolerability of a novel subcutaneous intrathecal catheter system for repeated outpatient dosing of nusinersen to children and adults with spinal muscular atrophy. J Pediatr Orthop 2018;38:e610–7.

[2] Khorkova O, Wahlestedt C. Oligonucleotide therapies for disorders of the nervous system. Nat Biotechnol 2017;35:249–63.

[3] Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet 2016;388:3017–26.

[4] Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625–35.

[5] Weaver JJ, Natarajan N, Shaw DWW, Apkon SD, Koo KSH, Shivaram GM, et al. Transforaminal intrathecal delivery of nusinersen using cone-beam computed tomography for children with spinal muscular atrophy and extensive surgical instrumentation: early results of technical success and safety. Pediatr Radiol 2018;48:392–7.

[6] Ortiz CB, Kukreja KU, Lotze TE, Chau A. Ultrasound-guided cervical puncture for nusinersen administration in adolescents. Pediatr Radiol 2019;49:136–40.

[7] Mousa MA, Aria DJ, Schaefer CM, Kaye RD, Abruzzo TA, Bernes SM, et al. A comprehensive institutional overview of intrathecal nusinersen injections for spinal muscular atrophy. Pediatr Radiol 2018;48:1797–805.

[8] Veerapandiyan A, Pal R, D'Ambrosio S, Young I, Eichinger K, Collins E, et al. Cervical puncture to deliver nusinersen in patients with spinal muscular atrophy. Neurology 2018;91:e620–4.

[9] Nascene DR, Ozutemiz C, Estby H, McKinney AM, Rykken JB. Transforaminal intrathecal administration: an alternative technique in patients with challenging access. AJNR Am J Neuroradiol 2018;39:986–91.

[10] Stolte B, Totzeck A, Kizina K, Bolz S, Pietruck L, Monninghoff C, et al. Feasibility and safety of intrathecal treatment with nusinersen in adult patients with spinal muscular atrophy. Ther Adv Neurol Disord 2018;11:1756286418803246

[11] Wurster CD, Winter B, Wollinsky K, Ludolph AC, Uzelac Z, Witzel S, et al. Intrathecal administration of nusinersen in adolescent and adult SMA type 2 and 3 patients. J Neurol 2019;266:183–94.

[12] Pechmann A, Langer T, Wider S, Kirschner J. Single-center experience with intrathecal administration of Nusinersen in children with spinal muscular atrophy type 1. Eur J Paediatr Neurol 2018;22:122–7.

[13] Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452–8.

[14] Bowens C, Dobie KH, Devin CJ, Corey JM. An approach to neuraxial anaesthesia for the severely scoliotic spine. Br. J. Anaesth 2013;111:807–11.

[15] Dietrich TJ, Peterson CK, Zeimpekis KG, Bensler S, Sutter R, Pfirrmann CWA. Fluoroscopy-guided versus CT-guided lumbar steroid injections: comparison of radiation exposure and outcomes. Radiology 2019;290:752–9.