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Considerations for repetitive intrathecal procedures in longterm nusinersen treatment for non-ambulatory spinal muscular atrophy

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Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder characterized by progressive motor function loss and skeletal muscular atrophy. Nusinersen, an antisense oligonucleotide, is the first FDA-approved therapy to achieve a significant milestone in SMA management. However, its high molecular weight requires intrathecal administration, posing challenges for clinical implementation. This study aimed to identify factors associated with postprocedural pain following repeated CT-guided transforaminal nusinersen injection in non-ambulatory patients with SMA. This single-center retrospective study evaluated 34 patients who underwent a total of 290 procedures. Postprocedural pain occurred in 49.3% of cases. Factors influencing postprocedural pain included needle angle with vertical and horizontal lines, prophylactic pain control, and number of CT scans (p < 0.05). In patients experiencing postprocedural pain, the needle angle with vertical and horizontal lines emerged as significant variables, with a beta coefficient (standard error) of 0.034 (0.011) (p < 0.05). Needle angle was an important predictor of postprocedural pain.

Keywords Spinal muscular atrophy, Nusinersen, CT-guided transforaminal injection, Prognosis, Pain

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder that affects approximately 1 in 10,000 live births^{1–3}. SMA is a leading cause of infant mortality worldwide⁴. SMA is an autosomal recessive disorder due to biallelic mutations in the *SMN1* gene in chromosome 5q13, which encodes the survival motor neuron protein⁵. SMA has been categorized into three primary types that manifest in childhood (types I-III) and two rarer types (antenatal type 0 and adult-onset type IV). This classification system is primarily determined by the age of onset and the best motor function achieved⁶. Infants with type I SMA cannot sit, with the disease manifesting at 0 to 6 months of age; those with type II disease cannot walk and are diagnosed at 6 to 18 months of age; and those with type III disease can walk but manifest symptoms after 18 months of age.

The *SMN2* gene is a centromeric copy of the *SMN1* gene, but differs by a C-to-T substitution in exon 7. This single nucleotide change causes exon 7 to be skipped during *SMN2* pre-mRNA splicing, resulting in the production of a mostly nonfunctional SMN protein. Only 10–15% of the *SMN2* transcripts produce a full-length, functional protein. In patients with SMA, an inverse correlation between *SMN2* copy number and the severity of the phenotype has been established. Increasing the full-length SMN protein level by modifying the *SMN2* function is the main target of SMA treatment. Nusinersen (Spinraza*; Biogen Inc, Boston, MA) achieved a significant milestone as the first drug to successfully complete randomized, sham-controlled clinical trials in early-infantile and late-infantile onset SMA, leading to its Food and Drug Administration approval in 2016. It is a splice-switching antisense oligonucleotide that facilitates the incorporation of exon-7 into the *SMN2* gene

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transcript, thereby augmenting the quantity of biologically active SMN protein⁷⁻¹⁰. Nusinersen is a diseasemodifying drug that reduces patient mortality rates, lowers the need for permanent ventilator support, and improves bulbar and motor function¹¹.

Owing to its high molecular weight, nusinersen cannot traverse the blood-brain barrier, necessitating intrathecal injections¹². Various methods have been employed for intrathecal injection, including blind lumbar puncture, ultrasound-guided injection, fluoroscopy-guided injection, and computed tomography (CT)-guided injection. In patients with intermediate- and late-onset SMA (types II–IV), scoliosis frequently develops because of neuromuscular weakness, often requiring spinal instrumentation to prevent the progression of deformities¹³. Intrathecal drug delivery can pose challenges in these patients and conventional lumbar puncture techniques are often insufficient to achieve intrathecal access.

CT-guided transforaminal injection has been reported to be an effective method for drug delivery in patients with severe scoliosis or in those who have undergone fusion surgery¹⁴. However, nusinersen treatment requires short-term four loading doses therapy and periodic maintenance therapy¹⁵, necessitating multiple invasive procedures. Along with radiation exposure, various side effects have been reported, including post-lumbar puncture headaches, radiculopathy, and pain at the lumbar puncture site. Patients with SMA often complain of chronic and persistent pain and fatigue; however, its exact cause remains unclear¹⁶. Some researchers argue that an imbalance in the body and increased muscle tension may be contributing factors¹⁷. Regardless of the underlying reasons, repeated procedures and secondary pain resulting from such interventions can be burdensome for patients who consistently experience pain and fatigue. Therefore, factors associated with postprocedural pain should be determined, as identifying potential avenues to mitigate such pain is crucial. Thus, we hypothesized that aspects directly related to the procedure, such as needle angle, needle insertion depth, and needle tip position, could be associated with postprocedural pain in patients.

Therefore, our study aimed to identify the factors associated with postprocedural pain following repeated CT-guided nusinersen therapy in non-ambulatory patients with SMA.

Results

Patient and procedure data

Our research involved 34 patients who underwent a total of 290 CT-guided transforaminal injections, with an equal distribution of 17 men and 17 women, and an average age of 21.8 ± 9.3 years (Tables 1 and 2). The median follow-up period for the entire cohort was 33.1 months, with an interquartile range (IQR) of 20.4 to 42.6 months. Most patients (88.2%) were diagnosed with type II SMA. The mean *SMN2* copy number in all patients included in this study was 3. The baseline Expanded Hammersmith Functional Motor Scale (HFMSE), Hammersmith Infant Neurological Examination (HINE), and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores were 3.7 ± 6.6 , 5.7 ± 4.2 , and 21.1 ± 12.4 , respectively (Table 1). Of the 34 patients, 30 experienced at least mild pain, 17 with moderate to severe pain, 17 with headaches after at least one procedure, 9 with radicular pain, and 2 with nausea and fever. Of the 290 procedures conducted, 49.3% had postprocedural pain and 13.8%with moderate-to-severe pain. Specific discomforts included headache (11.0%, 32 of 290), radicular pain (6.2%, 18 of 290), nausea (0.7%, 2 of 290), and fever (1.0%, 3 of 290). The average radiation dose was 207.2 ± 120.5 mGy, with an average of 3.9 ± 2.2 CT scans performed per procedure. The mean procedural duration was 23.5 ± 9.1 min (Table 2).

	Total	SMA type 1	SMA type 2	SMA type 3
Men:Women (n)	17 (50):17 (50)	1 (50):1 (50)	15 (50):15 (50)	1 (50):1 (50)
Age at onset of symptoms (month), mean ± SD	11.6 ± 5.4	2.4 ± 1.0	11.5 ± 4.1	24.4 ± 0.0
Age at diagnosis (year), mean±SD	5.0 ± 7.2	1.2±1.1	5.4 ± 7.7	3.3 ± 0.7
Age at initiation of therapy (year), mean \pm SD	21.8±9.3	9.7±4.5	22.8 ± 9.5	23.5 ± 2.7
Spondylodesis (n)	22 (64.7)	0 (0)	20 (66.7)	2 (100)
Age at surgery (year), mean ± SD	13.9±4.9	N/A	14.2 ± 5.3	13.6 ± 0.5
SMA type (n)	34 (100)	2 (5.9)	30 (88.2)	2 (5.9)
BMI (kg/cm ²), mean ± SD	16.5 ± 4.4	14.7 ± 1.0	16.5 ± 4.6	19.0 ± 0.0
HFMSE (points), mean ± SD	3.7 ± 6.6	0.0 ± 0.0	4.2 ± 6.9	0.0 ± 0.0
HINE (points), mean ± SD	5.7 ± 4.2	0.0 ± 0.0	6.3 ± 4.1	2.5 ± 3.5
CHOP-INTEND (points), mean ± SD	21.1 ± 12.4	5.0 ± 4.2	21.9±12.2	15.0 ± 7.1
CT-guided injection / Total procedure (n)	290 / 402 (72.1)	7 / 36 (19.4)	265 / 346 (76.6)	20 / 20 (100)
CT-guided injection per patient (n), mean ± SD	8.6±4.1	3.5 ± 3.5	8.8 ± 4.0	10.0 ± 4.2
Blind lumbar puncture per patient (n), mean \pm SD	3.2 ± 5.3	14.5 ± 3.5	2.7 ± 4.7	0.0 ± 0.0
Follow-up period (month), mean ± SD	33.1±15.5	58.8 ± 0.5	31.8 ± 14.6	26.9 ± 17.5

Table 1. Patient demographic characteristics at baseline. Data in parentheses are percentages (%).Abbreviations: SMA, spinal muscular atrophy; SD, standard deviation; N/A, not applicable; BMI, body massindex; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE, Hammersmith Infant NeurologicalExamination; CHOP-INTEND, Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders;CT, computed tomography.

Spinal level		
L2/3	1 (3.4)	
L3/4	116 (40.0)	
L4/5	142 (49.0)	
L5/S1	31 (10.7)	
Laterality		
Right	154 (53.1)	
Left	136 (46.9)	
Performer experience (year)		
<1	234 (80.7)	
>1	56 (19.3)	
Needle length (mm)	7.4 ± 2.4	
Needle angle with vertical line (°)	16.1 ± 18.1	
Needle angle with vertical & horizontal line (°)	13.5±13.2	
Needle angle with skin (°)	9.6±8.1	
Intrathecal needle advance (mm)	9.8±6.7	
Needle location in foramen		
Anterior	72 (24.5)	
Middle	35 (12.0)	
Posterior	183 (63.1)	
Prophylactic pain control	187 (64.5)	
Pain		
None	147 (50.7)	
Mild	103 (35.5)	
Moderate to severe	40 (13.8)	
Headache	32 (11.0)	
Radicular pain	18 (6.2)	
Fever	3 (1.0)	
Nausea	2 (0.7)	
Radiation dose (mGy)	207.2 ± 120.5	
Number of CT scans	3.9±2.2	
Procedure time (min)	23.5+9.1	

Table 2. Details of CT-guided transforaminal injection procedure. Abbreviation: CT, computed tomography.

 Data in parentheses are percentages (%).

Factors affecting post-procedural pain

In the multivariate analysis of postprocedural pain (Table 3), the only factor significantly associated with the presence of post-procedural pain was the pre-procedure HFMSE score (odds ratio [OR], 0.998; 95% confidence interval [CI], 0.988–0.998; p = 0.0101). In the subgroup analysis conducted on patients experiencing postprocedural pain, the needle angle with vertical (V) and horizontal (H) lines and the presence of prophylactic pain control emerged as significant variables in the multivariable analysis. The coefficients (standard error [SE]) of these variables were 0.034 (0.011) and 1.013 (0.290), respectively (p < 0.05, both).

Factors affecting radiation dose

In the multivariate analysis of radiation dose (Table 4), significant correlations were observed with injection age, CT-guided injection number, performer experience, needle length, needle angle with V and H lines, and CT scan number (all p < 0.05). The respective coefficients (SE) for these variables were 3.730 (1.147), -8.070 (1.571), -25.637 (10.113), 0.802 (0.317), 1.037 (0.397), and 34.140 (1.995), respectively.

Factors affecting procedure time

In the multivariate analysis of procedure time (Table 4), significant correlations were observed between needle angles with V and H lines and CT scan number (all p < 0.05). The coefficients (SE) of these variables were 4.341 (2.190) and 120.754 (13.142), respectively.

Discussion

Recent real-world studies on nusinersen treatment in adult and older pediatric SMA patients have shown favorable efficacy and safety profiles. However, in long-term follow-up data for non-ambulatory patients, the factors contributing to discomfort from intrathecal injections remain inadequately investigated.

Our main procedural finding was the association between postprocedural pain and the planned needle angle during the procedure. This may be because using the ground or the operator's body axis as a reference line

		Pain (presence or ab	Pain (only patients with pain, 143 procedures)				
		Univariate	Univariate		Multivariate		
Variable		OR (95% CI)	<i>p</i> -value	Beta (SE)	<i>p</i> -value	Beta (SE)	<i>p</i> -value
Sex	Man (ref: women)	0.818 (0.456-1.467)	0.5009	-0.521 (0.406)	0.2015		
BMI (kg/m ²)		1.010 (0.994–1.026)	0.2192	0.005 (0.047)	0.9087		
Injection age (year)		1.002 (0.995-1.009)	0.5309	0.040 (0.026)	0.1336		
Spondylodesis	pondylodesis Done (ref: none)		0.4603	-0.109 (0.462)	0.8143		
CT-guided injection number		0.998 (0.982-1.015)	0.8304	0.022 (0.040)	0.5835		
Cainal laval	L4/5 (ref: L2/3&L3/4)	0.844 (0.494–1.442)	0.5338	0.194 (0.358)	0.5881		
Spinal level	L5/S1 (ref: L2/3&L3/4)	0.756 (0.312-1.834)	0.5362	-0.857 (0.593)	0.151		
Laterality	Left (ref: right)	1.315 (0.739–2.341)	0.3517	-0.341 (0.419)	0.4179		
Performer experience	>1 year (ref: <1 year)	0.662 (0.387-1.134)	0.1332	0.026 (0.365)	0.944		
Needle length (mm)		1.000 (0.997-1.003)	0.9074	-0.000 (0.008)	0.9949		
Needle angle with vertical line (°)		1.002 (0.998-1.006)	0.4092	0.020 (0.009)	0.03		
Needle angle with vertical and horizontal line (°)		1.002 (0.997-1.008)	0.3622	0.043 (0.011)	0.0002	0.034 (0.011)	0.0027
Needle angle with skin (°)		1.002 (0.995-1.008)	0.6311	0.010 (0.020)	0.6316		
Intrathecal needle advance (1	mm)	0.996 (0.991-1.002)	0.2118	-0.059 (0.036)	0.036) 0.1034		
	Middle (ref: anterior)	1.662 (0.661-4.180)	0.2799	-0.118 (0.466)	0.8009		
Needle location in loramen	Posterior (ref: anterior)	1.479 (0.833-2.624)	0.1814	-0.173 (0.344)	0.6167		
Prophylactic pain control	Done (ref: none)	0.745 (0.436-1.275)	0.2832	1.173 (0.303)	0.0002	1.013 (0.290)	0.0007
CT scan number		1.022 (0.997-1.047)	0.086	0.179 (0.055)	0.0017	0.114 (0.061)	0.0654
Procedure time (s)		1.000 (1.000-1.000)	0.3485	0.001 (0.000)	0.0064	0.000 (0.000)	0.5101
Pre_procedure_HFMSE		0.993 (0.988-0.998)	0.0101	-0.047 (0.026)	0.0712		
Pre_procedureHINE		0.998 (0.981-1.015)	0.7899	-0.095 (0.044)	0.0319	-0.074 (0.040)	0.0684
Pre_procedure_CHOPINTEND*		1.000 (0.994-1.006)	0.944	-0.030 (0.015)	0.0405	-0.023 (0.012)	0.0689

Table 3. Factors affecting the presence and severity of post-procedural pain. Abbreviations: OR, odds ratio; SE, standard error; ref, reference; BMI, body mass index; CT, computed tomography; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE, Hammersmith Infant Neurological Examination; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. *Average scores of both sides.

enables quicker, more accurate procedures, reducing the need for multiple insertions or trajectory adjustments. Prophylactic pain control was considerably linked to higher pain severity, maybe because patients who experienced pain in previous procedures were more likely to receive prophylactic interventions. The only factor significantly associated with the presence of post-procedural pain was the pre-procedure HFMSE score (OR, 0.998; 95% CI, 0.988–0.998; p=0.0101). Higher baseline motor function was related to a reduced likelihood of experiencing pain. The higher the HFMSE scores, the better muscle strength and motor function, which suggests that patients with greater physical function may have increased resilience to invasive procedures, reducing pain perception¹⁸. In addition, higher motor function may reduce anxiety and boost confidence during procedures, further lowering pain reports¹⁹.

This study highlights key factors influencing radiation dose and procedure time during CT-guided injections. In the multivariate analysis of radiation dose, several variables were significantly correlated, including injection age, CT-guided injection number, performer experience, needle length, needle angle with vertical and horizontal lines, and the number of CT scans. These factors demonstrated significant associations, with injection age and needle-related parameters playing critical roles in determining radiation exposure.

Furthermore, older patients tended to receive higher radiation doses, likely due to their larger body size. Similarly, needle length, which reflects the distance to the thecal sac, follows the same rationale. These two factors were considered more important than body mass index (BMI) in influencing radiation exposure. Additionally, performer experience was inversely correlated with radiation dose, suggesting that more experienced practitioners perform procedures more efficiently, reducing exposure and the need for additional imaging. The finding that more CT-guided injections were associated with lower radiation doses supports this, likely due to the cumulative expertise gained. Needle angle with vertical and horizontal lines was also a key predictor of radiation dose. Adjusting the needle trajectory requires additional imaging to ensure precision, thereby increasing radiation exposure. The significant correlation between the number of CT scans and radiation dose underscores the importance of precise procedural planning to minimize scans. Regarding procedure time, needle angles and the number of CT scans were associated with longer procedures, likely due to the need for more intricate adjustments. Therefore, careful planning is crucial to increase the chances of success on the first attempt, reducing procedure time and radiation exposure.

These findings emphasize the importance of modifiable procedural factors, particularly needle positioning, which impacts postprocedural pain, radiation exposure, and procedure time. Thus, to improve safety, we optimize needle placement to minimize repeated adjustments and imaging, which can considerably enhance the safety and efficiency of CT-guided injection procedures.

Radiation dose			mGy)			Procedure time (sec)			
		Univariate		Multivariate		Univariate		Multivariate	
Variable		Beta (SE)	<i>p</i> -value	Beta (SE)	<i>p</i> -value	Beta (SE)	<i>p</i> -value	Beta (SE)	<i>p</i> -value
Sex	Man (ref: women)	18.297 (25.865)	0.48			52.534 (74.172)	0.4794		
BMI (kg/m ²)		9.117 (2.145)	<.0001	2.520 (1.878)	0.1808	10.833 (8.034)	0.1787		
Injection age (year)		3.052 (1.423)	0.0329	3.730 (1.147)	0.0013	-2.017 (4.912)	0.6818		
Spondylodesis	Done (ref: none)	-3.949 (27.321)	0.8852			-75.186 (86.503)	0.3856		
CT-guided injection number		-12.170 (1.757)	<.0001	-8.070 (1.571)	<.0001	-14.985 (9.241)	0.1062		
Curta al Lanal	L4/5 (ref: L2/3&L3/4)	-18.820 (17.742)	0.2898			17.875 (73.478)	0.808		
Spillar level	L5/S1 (ref: L2/3&L3/4)	-34.294 (28.890)	0.2363			-11.676 (119.753)	0.9224		
Laterality	Left (ref: right)	10.405 (26.127)	0.6908			-59.354 (74.036)	0.4235		
Performer experience	>1 year (ref: <1 year)	-55.704 (16.198)	0.0007	-25.637 (10.113)	0.0119	-82.042 (81.368)	0.3143		
Needle length (mm)		1.590 (0.397)	<.0001	0.802 (0.317)	0.012	2.719 (1.470)	0.0655		
Needle angle with vertical line (°)		1.115 (0.468)	0.0178			4.403 (1.862)	0.0188		
Needle angle with vertical and horizontal line (°)		2.406 (0.595)	<.0001	1.037 (0.397)	0.0095	6.258 (2.552)	0.0149	4.341 (2.190)	0.0485
Needle angle with skin (°)		0.137 (1.033)	0.895			6.236 (4.238)	0.1424		
Intrathecal needle advance (mm)		0.315 (1.056)	0.766			-2.507 (4.990)	0.6158		
Needle location in foramen	Middle (ref: anterior)	18.961 (22.205)	0.394	-6.598 (14.035)	0.6387	22.404 (112.839)	0.8428		
	Posterior (ref: anterior)	62.659 (15.759)	<.0001	17.373 (10.397)	0.096	39.938 (77.365)	0.6062		
Prophylactic pain control	Done (ref: none)	-14.439 (15.194)	0.3429			30.172 (69.746)	0.6657		
CT scan number		39.155 (2.209)	<.0001	34.140 (1.995)	<.0001	123.442 (13.152)	<.0001	120.754 (13.142)	<.0001
Pre_procedure_HFMSE		-2.788 (1.421)	0.0509			4.567 (4.408)	0.3011		
Pre_procedureHINE		-5.570 (2.602)	0.0333	0.197 (1.735)	0.9096	1.202 (8.448)	0.887		
Pre_procedure_CHOPINTEND_average*		-3.167 (0.859)	0.0003	-0.230 (0.627)	0.7142	-0.553 (2.814)	0.8443		

Table 4. Factors affecting radiation dose and scan time. Abbreviations: SE, standard error; ref, reference; BMI,body mass index; CT, computed tomography; HFMSE, Hammersmith Functional Motor Scale Expanded;HINE, Hammersmith Infant Neurological Examination; CHOP-INTEND, Children's Hospital of PhiladelphiaInfant Test of Neuromuscular Disorders. *Average scores of both sides.

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Our study had limitations. First, beyond clinical scores, factors, such as feeding tubes, respiratory support, and tracheostomy have a significant impact on a patient's quality of life. Unfortunately, the limited number of patients with these factors prevented us from conducting related analyses. Second, post-lumbar puncture headache is also a significant cause of patient discomfort. It is known that the rapid removal of excessive cerebrospinal fluid (CSF) can influence the occurrence of this headache²⁰. We analyzed the variables within our patient group to identify the factors contributing to post-lumbar puncture headache; however, no significant variables were found, likely due to the small sample size relative to the number of procedures. Third, pain was assessed in the immediate postprocedural period, and the potential for long-term pain or chronic discomfort remains unknown, warranting further investigation. Fourth, further studies are needed to determine whether these procedure-related factors apply to broader patient populations, such as those with less severe forms of the disease or other neuromuscular disorders. Finally, as this was a retrospective study, causality may not have been established, and potential confounding variables, such as patient psychological factors influencing pain perception, may not have been fully accounted for.

In conclusion, in patients with severe non-ambulatory SMA, the needle angle during the procedure was identified as a significant factor influencing post-procedural pain. Our findings may guide clinicians and spark further studies on treatment protocols to improve treatment response and post-procedural adverse events in patients with SMA requiring frequent intrathecal injections.

Methods

Ethical declarations

This retrospective single-center study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, (approval number 3–2023-0339), and all the procedures adhered to the ethical standards outlined in the Declaration of Helsinki. The need for informed consent was waived because the data was fully de-identified to safeguard patient confidentiality.

Patient selection and data acquisition

Since April 2019, the Korean National Health Insurance Service (HIRA) has provided reimbursement for nusinersen therapy in patients with SMA who have a genetically confirmed diagnosis with disease onset before 3 years of age and do not require permanent respiratory support. From April 2019 to July 2023, a total of 44 patients with SMA received nusinersen therapy at our hospital. For cases where a blind lumbar puncture approach was challenging, CT-guided injections were performed. This study included all 34 patients who, regardless of age or SMA type, underwent at least one CT-guided injection. One procedure was excluded because of missing



Fig. 1. Imaging metrics in CT-guided nusinersen injection. These images depict the 2nd (**A**) and 13th (**B**) CT-guided transforaminal injections in a 28-year-old woman. In A, angle (**a**) represents the needle angle with a vertical line and angle (**b**) represents the needle angle with the skin. In B, length (**c**) signifies needle length and length (**d**) denotes intrathecal needle advancement. The needle foramen is divided into anterior (A), middle (M), and posterior (P).

imaging data. Patient information was extracted from electronic medical records and PACS. This included birth date; injection date; onset date; diagnosis date; first injection date; spondylodesis; sex; treatment duration; number of lumbar punctures; number of CT-guided injections; total number of injections; injection level at the lumbar spine; laterality; performer experience; adverse events such as postprocedural puncture site pain, headache, radicular pain, fever, and nausea; radiation dose; procedure time; and CT scan number during the procedure.

Motor function assessment

Motor function scores were collected at baseline, at month 2, and subsequently at 4-month intervals. Based on the HIRA program guidelines, reimbursement is discontinued when there is a consecutive decline in motor function scores on two occasions, each measured at 4-month intervals. To assess motor function in SMA patients under 24 months of age, the HINE-2 is mandated by HIRA. For patients with Type 2 or 3 SMA who are over 24 months of age, the HFMSE is utilized. Consequently, for patients who initiated treatment before reaching 24 months of age, both HINE-2 and HFMSE assessments are required. In addition to the mandatory assessment tools required by HIRA, the CHOP-INTEND score was additionally administered to all patients included in this study, regardless of the age at treatment initiation. This was performed to allow consistent comparison of motor function across all patients and capture subtle changes in motor function in more severely affected SMA patients.

CT-guided transforaminal injection protocol

According to our hospital protocol, if blind lumbar puncture fails or following spinal fusion surgery, intrathecal nusinersen delivery is performed through CT-guided transforaminal injection. On the day of the procedure, the participating physical therapist assessed the HFMSE, HINE, and CHOP-INTEND scores before each intervention. Then, if a patient complained of pain from a previous procedure, prophylactic pain control was administered via intravenous infusion of tramadol (50 mg) mixed with normal saline (100 mL). The procedure was performed by a randomly assigned team comprising one MSK radiologist with 4 years of experience in performing the procedure and six fellowship trainees with < 1 year of experience. Before the procedure, an entry point was designated through a pre-scan, followed by needle advancement. Subsequently, a CT scan, including only the specified region, was performed to modify the needle course. If the needle entered the thecal sac, a final scan was performed. A 22G spinal needle was used in all procedures, and local anesthesia was administered using lidocaine. All procedures were performed using the same CT equipment (SOMATOM Force; Siemens Healthcare, Erlangen, Germany). Patients were surveyed for the presence and severity of postprocedural pain at the puncture site using a numeral rating scale, and any other adverse events were documented upon admission to the ward after the intervention. Patients were asked to rate their pain on a scale from 0 to 10, categorized as follows: 1–3, mild pain; 4–6, moderate pain; 7–10, severe pain.

Metrics in CT-guided transforaminal injection

Measurements of needle length, intrathecal needle advancement, needle location in the foramen, needle angle with V line, needle angle with V and H lines, and needle angle with skin were obtained from the last images of the CT-guided injection (Fig. 1). Needle length was defined as the distance from the skin entry point to the needle tip, whereas intrathecal needle advancement was defined as the distance from the thecal sac entry point to the needle tip. The needle location in the foramen was defined by dividing the foramen into anterior, middle,

and posterior thirds. Three needle angles were measured—needle angle with the V line, the angle between a line perpendicular to the ground (or CT table) and the needle; needle angle with the V-H line, the smaller angle between a line perpendicular to the ground and the needle or between the ground and the needle; and needle angle with the skin line, the angle between a line perpendicular to the patient's skin and the needle. Therefore, smaller values of the needle angle with the V line and needle angle with the skin indicate a more vertical entry of the needle to the ground and skin, respectively, whereas a smaller needle angle with the V and H lines suggests a more vertical or horizontal needle entry to the ground.

Statistical analysis

To investigate the impact of each independent variable on the outcomes, linear mixed models were employed considering repeated measurements in each patient. The independent variables used were: Sex (reference: women), BMI (kg/m²), injection age (years), spondylodesis (reference: none), CT-guided injection number, spinal level (reference: L2/3 & L3/4), laterality (reference: right), performer experience (reference: <1 year), needle length (mm), needle angle with vertical line (°), needle angle with vertical and horizontal line (°), needle angle with skin (°), intrathecal needle advance (mm), needle location in foramen (reference: anterior), prophylactic pain control (reference: none), CT scan number, procedure time (s), pre-procedure HFMSE, pre-procedure HINE, and pre-procedure CHOP INTEND. The dependent variables were defined as pain (presence or absence), pain severity, radiation dose, and procedure time. Univariate models were initially used, and variables showing significance were selected for multivariate analysis. A *p*-value of <0.05 was considered statistically significant. Multicollinearity was assessed for the variables selected from the univariate models. In cases where multicollinearity was suspected, separate multivariate analyses were performed for each variable. Subsequently, a subgroup analysis was performed for cases in which pain was equal to or greater than 1. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Data availability

The datasets generated during and/or analyzed during the study are available from the corresponding author on reasonable request.

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References

- 1. Pearn, J. Incidence, prevalence, and gene frequency studies of chronic childhood spinal muscular atrophy. J. Med. Genet. 15, 409-413 (1978).
- Ogino, S., Leonard, D. G., Rennert, H., Ewens, W. J. & Wilson, R. B. Genetic risk assessment in carrier testing for spinal muscular atrophy. Am. J. Med. Genet. 110, 301–307 (2002).
- 3. Sugarman, E. A. et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: Clinical laboratory analysis of >72,400 specimens. *Eur. J. Hum. Genet.* 20, 27–32 (2012).
- 4. Crawford, T. O. & Pardo, C. A. The neurobiology of childhood spinal muscular atrophy. Neurobiol Dis 3, 97-110 (1996).
- 5. Lefebvre, S. et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 80, 155–165 (1995).
- 6. Mercuri, E., Sumner, C. J., Muntoni, F., Darras, B. T. & Finkel, R. S. Spinal muscular atrophy. Nat. Rev. Dis. Prim. 8, 52 (2022).
- 7. Singh, N. K., Singh, N. N., Androphy, E. J. & Singh, R. N. Splicing of a critical exon of human Survival Motor Neuron is regulated by a unique silencer element located in the last intron. *Mol. Cell Biol.* **26**, 1333–1346 (2006).
- 8. Passini, M. A. et al. Antisense oligonucleotides delivered to the mouse CNS ameliorate symptoms of severe spinal muscular atrophy. Sci. Transl. Med. 3, 72ra18 (2011).
- 9. Finkel, R. S. et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N. Engl. J. Med. 377, 1723–1732 (2017).
- 10. Łusakowska, A. et al. Long-term nusinersen treatment across a wide spectrum of spinal muscular atrophy severity: A real-world experience. Orphanet. J. Rare Dis. 18, 230 (2023).
- 11. Rao, V. K., Kapp, D. & Schroth, M. Gene therapy for spinal muscular atrophy: An emerging treatment option for a devastating disease. J. Manag. Care Spec. Pharm. 24, S3-s16 (2018).
- 12. Khorkova, O. & Wahlestedt, C. Oligonucleotide therapies for disorders of the nervous system. Nat. biotechnol. 35, 249-263 (2017).
- 13. Arnold, W. D., Kassar, D. & Kissel, J. T. Spinal muscular atrophy: Diagnosis and management in a new therapeutic era. *Muscle Nerve.* **51**, 157–167 (2015).
- 14. Wurster, C. D. et al. Intrathecal administration of nusinersen in adolescent and adult SMA type 2 and 3 patients. J. Neurol. 266, 183-194 (2019).
- 15. Neil, E. E. & Bisaccia, E. K. Nusinersen: A novel antisense oligonucleotide for the treatment of spinal muscular atrophy. J. Pediatr. Pharmacol. Ther. 24, 194–203 (2019).
- 16. de Groot, I. J. et al. 184th enmc international workshop: Pain and fatigue in neuromuscular disorders: 20–22 May 2011, naarden, the netherlands. *Neuromuscul. Disord.* 23, 1028–1032 (2013).
- 17. Sagerer, E., Wirner, C., Schoser, B. & Wenninger, S. Nociceptive pain in adult patients with 5q-spinal muscular atrophy type 3: A cross-sectional clinical study. *J. Neurol.* 270, 250–261 (2023).
- Middlebrook, M. Disease severity, self-stigma of disability, and positive coping skills in adults with spinal muscular atrophy (SMA) (College of Saint Elizabeth, 2023).
- Panda, P. K., Ramachandran, A., Verma, P. K. & Sharawat, I. K. Behavioral problems in infants and young children with spinal muscular atrophy and their siblings: A cross-sectional study. *Eur. J. Paediatr. Neurol.* 42, 47–52 (2023).
- 20. Monserrate, A. E. et al. Factors associated with the onset and persistence of post-lumbar puncture headache. *JAMA Neurol.* **72**, 325–332 (2015).

Author contributions

All authors (Hong Seon Lee, Hyunjoo Lee, Young-Mock Lee and Sungjun Kim) contributed to the conception and design of the study. Material preparation, data collection, and analyses were performed as described equally by Hong Seon Lee and Hyunjoo Lee. The first draft of the manuscript was written by Hong Seon Lee and Hyunjoo Lee, and all authors commented on previous versions of the manuscript. All the authors have read and approved the final version of the manuscript.

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Declarations

Competing interests

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Consent to publish

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Additional information

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