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Comparison of fluoroscopy-guided and blind techniques in intrathecal nusinersen administration

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Abstract

Background & Objectives: Intrathecal nusinersen administration is often performed using a blind technique without any imaging guidance. However, many patients with spinal muscular atrophy(SMA) have progressive and severe scoliosis, making intrathecal access challenging. In patients where intrathecal access is difficult, injections can be performed under imaging guidance, such as fluoroscopy. This study aimed to compare blind versus fluoroscopy-guided intrathecal nusinersen injections in patients with SMA, focusing on postprocedural pain and patient satisfaction. *Method:* SMA patients who underwent both blind intrathecal nusinersen injections and fluoroscopy-guided intrathecal nusinersen injections between January2022 and June2023 were retrospectively analyzed. Patient satisfaction (5-point Likert scale) and postprocedural pain levels (Numeric Rating Scale, 0–10) were assessed after both the blind and fluoroscopy-guided procedures, and the results were compared. *Results:* This study included 79 fluoroscopy-guided intrathecal nusinersen injections administered to 26 patients during the specified period. The satisfaction score for the fluoroscopy-guided technique (FT) was 5, while it was 2.32±1.31 for the blind technique (BT). Post-procedural pain in the FT was 0.73±0.72, compared to 4.77±1.58 in the BT. Satisfaction in the FT was significantly higher than in the BT, while postprocedural pain scores were significantly lower ($p<0.001$). Success rate was 71.5% with the BT, whereas it was 100% with the FT ($p<0.001$).
Conclusion: Administering intrathecal nusinersen with fluoroscopy guidance enhances patient satisfaction and minimizes postprocedural pain in SMA. Additionally, performing the injections under fluoroscopic guidance increases the success rate of the procedure and reduces the risk of potential complications. Therefore, in cases where intrathecal access may be challenging, such as in patients with scoliosis, nusinersen administration could be more appropriately performed by experienced practitioners using fluoroscopic guidance rather than a blind technique.

Keywords: Intrathecal nusinersen injection, image-guided injection, patient satisfaction score, spinal muscular atrophy

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive disorder resulting from mutations in the survival motor neuron 1 (SMN1) gene. This mutation leads to a shortage of SMN protein, causing the degeneration of alpha motor neurons, which in turn results in progressive muscle atrophy and weakness.[1] Prior to intrathecal nusinersen treatment, SMA was the leading genetic cause of mortality in childhood, with an incidence of roughly 1 in 10,000 live births.[2,3]

Nusinersen compensates for the genetic defect in the SMN1 gene by enhancing the production of functional SMN protein through the SMN2 gene.[4] Nusinersen improves motor and respiratory functions and prolongs survival in patients with SMA.[5,6] It has also been shown to delay the onset and progression of symptoms in presymptomatic

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patients.[7] However, since oligonucleotides cannot cross the blood-brain barrier, intrathecal administration is necessary.[8] Hence, intrathecal administration is required for all four loading doses and ongoing maintenance doses.[9]

Scoliosis and contracture, which occur secondary to muscle weakness in most SMA patients, make it difficult to perform lumbar puncture (LP), especially in those with a history of spinal surgery.[10,11] Imaging techniques (ultrasound [US], fluoroscopy, computed tomography [CT]), various devices (subcutaneous intrathecal catheter systems), and surgical procedures (lumbar laminotomy) have been used to facilitate intrathecal administration.[12-14] Each technique has advantages and disadvantages over the others. Many previous studies have shown the effectiveness of CT, fluoroscopy, and ultrasound in intrathecal injections.[8,15,16]

Patients and their families, grappling with the devastating effects of SMA, experience increased physical and mental trauma due to recurrent intrathecal nusinersen injections. We prefer to perform intrathecal interventions under imaging guidance because performing them using a blind technique traumatizes the patient, especially in those with complex spines, due to unsuccessful attempts, increasing the risk of infection, CSF (cerebrospinal fluid) leakage, agitation of the patient's family, and the extra financial burden brought by repeated hospitalizations. A case series by Zanfini *et al*. reported high patient satisfaction with ultrasound-assisted lumbar intrathecal nusinersen injections. However, in this study, all intrathecal injections were performed exclusively with ultrasound assistance, and patient satisfaction was not compared between ultrasound-assisted injections and other techniques, such as fluoroscopy-guided or blind methods.[17]

In the present study, we aimed to compare intrathecal injection under fluoroscopic guidance with the blind technique in terms of post-procedural pain, satisfaction, and complication rates. We also report our experience with intrathecal administration to encourage physicians to employ image guidance to facilitate the procedure.

METHODS

Study design and population

The study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. This study conforms to all STROBE guidelines and reports the required information accordingly (see Supplementary Checklist). After receiving institutional ethics committee approval (ethic no:09.2023.1415), we retrospectively evaluated patients who underwent fluoroscopy-guided intrathecal nusinersen between January 2022 and June 2023 at a tertiary hospital's pain management center. In our hospital, intrathecal nusinersen administration to SMA patients is first performed with a blind technique by other departments (neurology, pediatric neurology, or neurosurgery). If attempts at intrathecal administration with a blind technique fail or upon practitioner/patient request, the pain medicine department is consulted, and we perform the procedure under fluoroscopic imaging. Patients with SMA who underwent intrathecal nusinersen injection were scanned from the hospital database system. After applying the exclusion and inclusion criteria, this study was conducted with 26 patients who had intrathecal nusinersen injection for SMA. Inclusion criteria were patients diagnosed with SMA who underwent intrathecal nusinersen injection with both blind technique and fluoroscopic guidance. Patients with missing data in the system (one patient), those who could not be contacted (one patient), and those whose intrathecal injections were performed using only a blind technique (two patients) were excluded from the study. Patient satisfaction and post-procedural pain responses were collected after intrathecal nusinersen administrations performed using both the blinded technique (BT) and the fluoroscopy-guided technique (FT), and these data were analysed.

Procedures

The patients were positioned in the prone position and a pillow was placed under their lower abdomen. If the prone position was not possible, the patients were positioned in the left lateral decubitus position with maximum flexion of the hips and knees. The injection area was cleaned three times with povidone-iodine and then covered with a sterile drape, which had an opening placed over the injection site. In fluoroscopy, the interlaminar foramen was visualized by giving the required cranio-caudal angle in anteroposterior imaging. The largest interlaminar foramen was chosen for the procedure. The anesthesia team provided light sedation. Afterwards, local anesthetic (3 cc 2% prilocaine) was administered to the skin and subcutaneous tissue. A 22-gauge Quincke spinal needle was then carefully advanced

toward the interlaminar space under intermittent fluoroscopic guidance, using the loss of resistance (LOR) technique. After the LOR was felt in the epidural space, the needle was advanced a little further and after passing the dura, it was confirmed that the subarachnoid space was reached with CSF flow (Figure 1). If further confirmation was required, the depth of the needle was checked by taking a fluoroscopic lateral image. Subsequently, 5 mL of CSF was aspirated, and 5 mL (12 mg) of nusinersen was administered slowly over 2 min according to standard protocol. Patients were followed in the observation room for potential complications for an hour after the injection and were discharged with recommendations.

All procedures in both the BT and FT were performed under light sedation and local anesthesia. All patients (in both the BT and FT) were monitored in the observation room for potential complications for one hour after the injection. After that, patients were admitted to the service if necessary. Depending on the patient's condition, patients were discharged from the service within 1-4 hours. A pain medicine specialist with a minimum of 10 years of experience conducted all procedures. Intermittent fluoroscopic imaging was performed using the same Ziehm Vision R unit. Written and verbal consent was obtained from the patients before the procedure. To minimize radiation exposure, linear and circular collimation were employed in all procedures, adhering to the ALARA (As Low As Reasonably Achievable) principle.

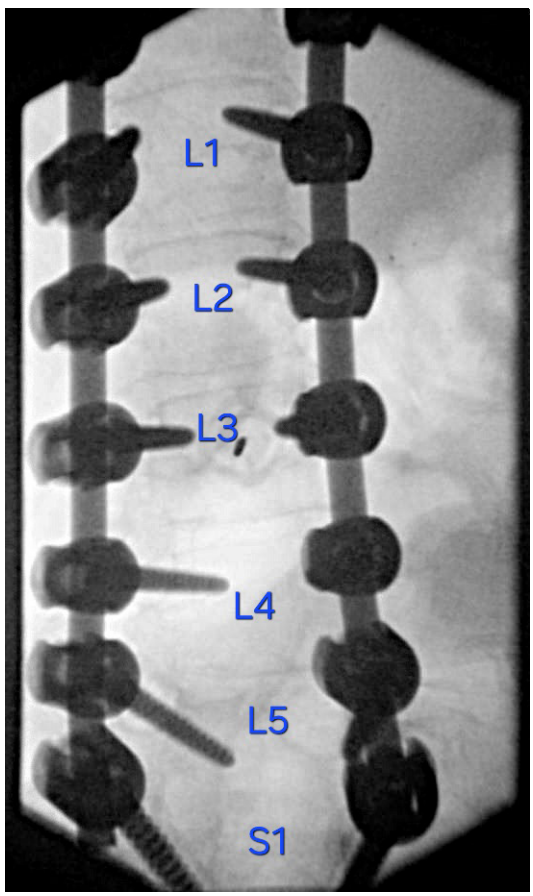

Figure 1. AP view during intrathecal nusinersen injection

Data collection

We collected all patient data from hospital medical documents, including demographic data, procedure type, radiation dose, radiation time, presence of scoliosis, postprocedural pain, Cobb angle of scoliosis, presence of instrumentation, and patient satisfaction score. A numerical rating scale (NRS 0-10) was used to assess postprocedural pain at 1 hour postop. Patient satisfaction scores were evaluated on a five-point Likert scale (from a value of 1-completely dissatisfied to a value of 5-completely satisfied) after the procedure.[17,18]

Statistical analysis

Statistical analysis was conducted using SPSS version 27.0.1 software (IBM Corp., Armonk, NY). Continuous variables were reported as mean (standard deviation) and median (interquartile range), while categorical variables were presented as counts and percentages. The chi-square test was applied to categorical variables. The Shapiro-Wilk test was used to assess the normality of quantitative data. The Mann-Whitney U test was used to compare non-normally distributed data, and the independent t-test was used for comparing normally distributed data. A p-value of less than 0.05 was regarded as statistically significant.

RESULTS

A total of 26 patients, 15 (57.7%) of whom were women, were included in the study. In these 26 patients, 239 intrathecal nusinersen injections were performed using the blind technique, and 79 intrathecal nusinersen injections were performed under fluoroscopy guidance. Type 2 was the most common form of SMA, observed in 14 patients (53.8%) (Table 1). All but 4 of the patients had scoliosis, and the severity of scoliosis was determined as mild, moderate, and severe in 5 (19.2%), 6 (23.1%), and 11 (42.3%) cases, respectively. Of all the patients, 10(38.5%) had a history of instrumentation surgery (Table 1).

Table 1: Demographic, clinical, and procedural characteristics

Variable		Results
Age (years)		18.23 (7-34)
BMI (kg/m2)		19.67 ± 4.24
Radiation duration (seconds)		40.04 (9-183)
Radiation dose (mGy)		4.98 (0.35-34)
Gender (n)	Male	11 (42.3 %)
	Female	15 (57.7 %)
SMA type (n)	Type 1	6 (23.1 %)
	Type 2	14 (53.8 %)
	Type 3	6 (23.1 %)
Instrumentation (n)	Yes	10 (38.5 %)
	No	16 (61.5 %)
Scoliosis (n)	No (Cobb angle <10°)	4 (15.4 %)
	Mild (10°-25°)	5 (19.2 %)
	Moderate (25°- 40°)	6 (23.1 %)
	Severe >40°	11 (42.3 %)

BT: Blind technique, **BMI:** Body mass index, **FT:** Fluoroscopy-guided technique

There was a significant difference between blind injection and fluoroscopy-guided injection in terms of both satisfaction score and postprocedural pain NRS scores (p<0.001). The success rate of the fluoroscopy-guided procedure was 100% and significantly higher than that of the blind technique (p < 0.001). (Table 2). The fluoroscopy-guided procedure was performed in the left lateral decubitus position in two patients where a prone position was not possible. In two procedures on one patient, a dry tap occurred during lumbar puncture, so a transforaminal approach was attempted; however, after it was unsuccessful, these procedures were performed through the cervical interlaminar space.

One patient who underwent a blind-method lumbar puncture developed CSF leakage and a fistula. Nine patients who underwent the BT experienced minor complications such as vomiting, dizziness, and headache. No major complications occurred in FT. Two minor complications, including dizziness and nausea, were observed in two patients in FT. The rate of minor complications was significantly lower in the FT (p = 0.017) (Table 2).

DISCUSSION

Intrathecal nusinersen administration is a treatment option for SMA that reduces the devastating effects of the disease and prolongs the life of patients.[5,6] The study showed that fluoroscopy-guided intrathecal nusinersen administration resulted in higher procedure success and patient satisfaction, as well as lower postprocedural pain and complication rates compared to the blind

Table 2: Comparison of blind technique versus fluoroscopic-guided injection

		BT (n=26 patients)	**FT (n=26 patients)**	**p**
Satisfaction score		2.32 ± 1.31	5	<0.001
Postprocedural pain (NRS)		4.77 ± 1.58	0.73 ± 0.72	<0.001
Major complication		1 (3.8%)	0 (0%)	0.313
Minor complication		9 (35%)	2 (7.7%)	0.017
		BT (n=26 patients, n=239 procedures)	**FT (n=26 patients, n=79 procedures)**	
Procedure Success	Yes	171 (71.5%)	79 (100%)	<0.001
	No	68 (28.5%)	0 (0%)	

BT: Blind technique, **FT:** Fluoroscopy-guided technique, **NRS:** Numeric rating scale

technique. These findings align with prior studies emphasizing the benefits of image guidance during intrathecal access.[12-14]

Nusinersen must be administered intrathecally as it does not cross the blood-brain barrier.[8] However, intrathecal injections in SMA patients are technically demanding due to frequent spinal deformities. The blind technique can be particularly challenging in this population. Therefore many techniques have been described for successful intrathecal puncture, including fluoroscopy, ultrasound, CT, and even surgery to facilitate intrathecal injections.[14,16,19] Although it may not be the perfect technique in every aspect for each patient, the procedure under imaging guidance has been shown to be particularly important in the presence of complex spine anatomy.[8,16] In a study involving 28 SMA patients by Garcia *et al*., 8 had complex spine anatomy. Of the 53 blind injections performed on these 8 patients, only 19 (36%) were successful, while all 34 CT-guided injections were successful.[8] Similarly, in our study, all 79 procedures performed under fluoroscopy guidance were successful (100%).

In intrathecal nusinersen administrations, various routes are used, including posterior midline, paramedian interlaminar, transforaminal, and caudal approaches.[11,19] If lumbar access fails, a cervical approach may be used.[14,20] If imaging-guided routes are unsuccessful, surgery may be needed for interlaminar space access.[16] Mendonca *et al*. evaluated nine SMA patients who had undergone spinal surgery, performing 57 lumbar punctures with CT prior to the procedure. In cases with no interlaminar space, a transforaminal approach using CT or fluoroscopy was applied, achieving 100% success. However, they reported a 5.2% adverse event rate, including headaches and radiculopathy.[21] Iwayama *et al*. reported high success and few side effects using fluoroscopy-guided paramedian approach. Headache was observed in three patients, back pain was observed in one patient, and nausea was observed in one patient.[15] In our study, fluoroscopy-guided intrathecal nusinersen was successfully administered to all patients except for one patient (two procedures) in the lumbar region. Since CSF could not be aspirated in the lumbar region, a transforaminal approach was attempted; however, after it was unsuccessful, an intrathecal nusinersen injection was successfully performed in the cervical region in that patient. No major complications were observed, and vasovagal reactions occurred in only 2 patients in FT. On the other hand, in the blind technique, one patient developed a CSF fistula as a major complication, while 9 other patients experienced minor complications, including vomiting, dizziness, and headache. Our findings, consistent with the literature, show that fluoroscopy-guided procedures have a lower complication rate and higher success than blind injections.

In the present study, both patients and their caretakers reported that the procedure required more attempts and took longer with the blind technique. Additionally, they indicated that injections performed with the blind technique were associated with more pain compared to those performed with fluoroscopic guidance. The increased pain experienced by patients undergoing the blind technique may be attributed to the prolonged procedure time, and a higher number of attempts. However, since quantitative records of the number of attempts and procedure time were not available for all patients in our study, the data could not be used for objective analysis. This assumption is therefore based on patients' subjective statements. A prospective randomized study is recommended to confirm these findings.

Alternative imaging techniques such as CT and ultrasound also have a role in facilitating intrathecal injections. However, while CT offers detailed imaging, it exposes patients to ionizing radiation, raising concerns about its repeated use, especially in younger populations.[22] Ultrasound, on the other hand, avoids radiation but has limitations in visualizing deep structures and may require multiple attempts, negatively impacting patient satisfaction.[11,17] Fluoroscopy, as used in this study, offers a balance between clear visualization and reduced radiation exposure compared to CT, while being more efficient than ultrasound in cases of challenging spinal anatomy.[11,17,22–24]

This study had some limitations. First, this study had a retrospective design and was conducted in a single centre. In addition, long-term changes in patient satisfaction were not examined. Although these are single-center results, we believe it is important to emphasize to physicians that patient satisfaction should be considered when selecting techniques for SMA patients struggling with the destructive process of the disease. Furthermore, records of the number of attempts and procedure time were not available for all patients, and data on the number of patients who required ventilator support were not available, as this was managed by the anesthesia team. Additionally, a cost analysis of the techniques was not performed, and therefore, a comparison could not be made.

Despite these limitations, a strength of this study is that it is the first study to compare patient satisfaction with blind versus fluoroscopy-guided intrathecal nusinersen administration.

In conclusion, performing intrathecal nusinersen under fluoroscopy guidance improves patient satisfaction and reduces postprocedural pain in SMA. In addition, performing the procedure with fluoroscopy guidance enhances the success rate while lowering the risk of potential complications. However, due to issues such as the unavailability of fluoroscopy in some centers, patient hospitalization requirements, and costs, blind injections or ultrasound-assisted intrathecal injections may be considered as initial approaches in patients without complex spine anatomy. Intrathecal nusinersen administration, particularly in cases where intrathecal access is challenging (e.g., in individuals with scoliosis), should be performed by experienced practitioners using fluoroscopic guidance rather than a blind technique.

DISCLOSURE

Data availability: The datasets supporting the findings of this study are available from the corresponding author upon reasonable request.

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