

research article

# Cone-beam computed tomography guided nusinersen administrations in adult spinal muscular atrophy patients with challenging access: a single- center experience

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**Background.** The challenging anatomic predispositions in adult patients with spinal muscular atrophy (SMA) preclude the conventional lumbar punctures. Consequently, an introduction of alternative method for intrathecal delivery of nusinersen is required. Cone-beam CT (CBCT) allows volumetric display of the area of interest, pre-procedural planning and real time needle guidance which results in accurate anatomic navigation. The aim of the study was to evaluate technical success, safety, and feasibility of CBCT lumbar intrathecal delivery of nusinersen in the adult SMA patients with challenging anatomical access.

**Patients and methods.** Thirty-eight adult SMA patients were treated in our institution. Patients with challenging access were selected by multidisciplinary board for image guided administration of nusinersen either due to implantation of the posterior fusion instrumentation, severe scoliosis defined as Cobb's angle > 40° or body mass index over 35. Technical success, radiation exposure and occurrence of adverse events were assessed.

**Results.** Twenty patients were selected, and 108 CBCT-guided procedures were performed. Each patient underwent at least 4 administrations. Transforaminal approach was performed in 82% of patients. The technical success was 100%, with primary success of 93.5%. The median radiation effective dose of the administrations was 5 mSv, the mean value equalled 10 mSv. Only mild adverse events were reported in the study.

**Conclusions.** CBCT-guided lumbar intrathecal administrations of nusinersen in an adult SMA population with challenging access was feasible and safe image guided method.

Key words: nusinersen; cone-beam CT; lumbar puncture

## Introduction

Antisense-oligonucleotide nusinersen (Spinraza, Biogen Netherlands, Netherlands) was the first approved intrathecal drug for treatment of 5q spinal muscular atrophy (SMA) experienced as safe and clinically beneficial for lifelong treatment of infants and children.<sup>1,2</sup> Growing evidence indicate safety

and efficacy even in some subgroups of adult patients.<sup>3-5</sup>

Intrathecal administrations of nusinersen require lumbar puncture. In the natural progression of SMA, particularly in type 2 and 3, patients may develop severe scoliosis.<sup>6</sup> In the most severe, type 1 SMA the patients rarely survive to adulthood, where as in type 4 being the mildest, involvement of the spine is

rare.<sup>6</sup> Debilitating scoliosis which requires surgery may not develop up to the onset of puberty and during childhood a conventional lumbar puncture is usually feasible.<sup>6</sup> In older patients factors such as altered spine anatomy, obliterated interlaminar space and obesity are commonly present and preclude the conventional lumbar puncture.<sup>6-8</sup> Consequentially, the need for reproducible and safe image-guided method for intrathecal administrations in adult patients has been accentuated.<sup>9</sup>

Several studies described successful techniques for administration of nusinersen in patients with challenging access. In these patients, successful interlaminar (IL) or transforaminal (TF) lumbar accesses have been performed under CT-, fluoroscopic- or ultrasound-guidance.<sup>7,10-14</sup> However, the possibility of spine deformity progression and the need for repetitive injections require a method with satisfactory deep soft tissue resolution and following the “as low as reasonable achievable” radiation principle.<sup>10,15,16</sup> The cone-beam CT (CBCT) allows volumetric display of the area of interest, pre-procedural planning and real time needle guidance which results in accurate anatomic navigation.<sup>17</sup> So far, only three studies described the use of CBCT for intrathecal delivery of nusinersen in children and adults.<sup>11,18,19</sup> However, up to our knowledge there are no larger studies on CBCT guided intrathecal nusinersen delivery that would present data only on adult SMA patients.

The purpose of this prospective study was to present a single-center experience on implementation of lumbar spine CBCT-guided intrathecal nusinersen delivery in consecutive adult SMA patients with challenging access to investigate the technical success, feasibility, and safety.

## Patients and methods

### Patients

The treatment with nusinersen has been available to the adult Slovenian patients with SMA in the University Medical Centre Ljubljana since the beginning of 2019. Thirty-eight adult SMA patients have undergone the repetitive treatment with intrathecal administrations in our institution from April 2019 to May 2021. Patients with challenging access were selected for CBCT-guided intrathecal nusinersen delivery.

The study was approved by the National Ethics Committee. An informed written consent from the patients was obtained before the beginning of the study.

### Inclusion criteria

The criteria for the group eligible for CBCT-guided lumbar punctures were determined by a multidisciplinary board team of neurologists and interventional radiologists. Patients with history of scoliosis corrective surgery with implantation of posterior fusion instrumentation, severe scoliosis defined as Cobb's angle > 40° or patients with body mass index (BMI) over 35 were included in CBCT-guided group.<sup>8,20,21</sup> The remaining patients underwent conventional lumbar puncture.

### Procedure

All procedures were performed on Siemens Artis Q (Siemens Healthineers, Erlangen, Germany) CBCT system with C-arm and navigational overlay in outpatient setting in the interventional radiology suite by interventional radiologists with more than 10-year experience in image-guided procedures.

Upon arrival to the interventional suite, the patients with implanted posterior instrumentation were placed in half lateral position to expose the curvature of the spine for TF approach. For IL approach either prone or half-lateral position was used. Following optimal patient positioning, a single rotation of a low dose CBCT was performed. Using the navigational computer program, the entry and target point were defined by the performing radiologist considering the safest and most feasible approach. For patients with history of spine surgery and posterior fusion instrumentation a TF approach was used as it was the only feasible option.<sup>20</sup> In this approach the trajectory line was positioned via the inferior portion of the intervertebral foramen to evade the exiting neurovascular bundle. IL approach was selected for patients without spinal instrumentation and visible interlaminar space.<sup>12</sup>

Lumbar punctures were performed under sterile conditions, local anesthesia was used. For the procedures 20 G spinal needles were used, the length of needle based on the distance from the skin to the target point.

Integrated laser of the C-arm marked the entry position of the needle on the skin. The target point position was visualized under intermittent fluoroscopic guidance using two orthogonal views (Figures 1, 2, 3). Once the needle tip reached the target point, an aspiration of cerebrospinal fluid (CSF) was performed to confirm the intrathecal position. Afterwards, 5 ml of CSF was aspirated, and 5 ml nusinersen solution was intrathecally delivered according to the manufacturer's instructions.

After the procedure the patients were surveilled for 4-6 hours before being discharged.

### Variables and data collection

Patient age, sex, BMI, type of SMA were recorded and spine anatomy was evaluated. For each procedure the type of the approach (TF or IL) with level of injection, total duration of the procedure from the arrival in the interventional suite to exiting, the technical success and peri-procedural adverse events (AE) were noted. Radiation exposure was calculated as effective dose (ED) as a product from dose-area product (DAP) and theoretical coefficient. The theoretical coefficient used in the equation was  $0.0012 \text{ mSv}/\mu\text{Gy}\cdot\text{m}^2$ . The data was obtained through patient databases and systematic questionnaire.

### Technical success

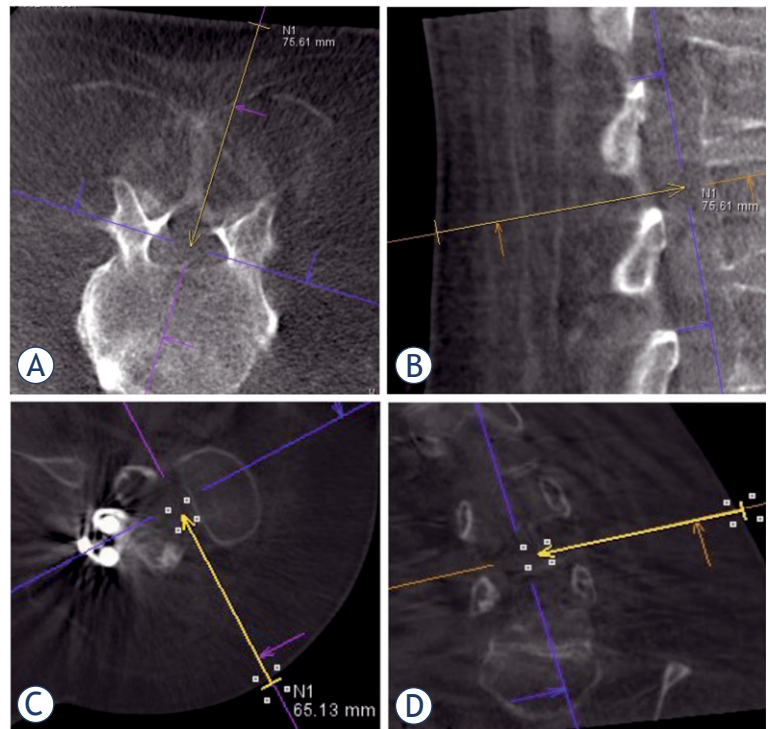
The technical success was defined by extraction of a macroscopically clear, no-blood-contaminated cerebrospinal fluid (CSF) with successful intrathecal application of 12 mg nusinersen.<sup>11</sup> Primary success was determined when a macroscopically clear CSF was extracted at first attempt without further repositioning of the needle. Secondary success was defined for procedures that required additional attempts for secure access at the same or another level during the same procedure.

### Adverse events

Peri-procedural AEs that occurred during the first 24 hours were recorded in accordance with the Society of Interventional Radiology guidelines.<sup>22</sup> AEs were noted during the peri-procedural surveillance period and reported by the patients upon their next regular clinical visit at the outpatient department. The patients assessed the overall discomfort and pain level during the CBCT-guided nusinersen intrathecal delivery using the Visual Analogue Scale (VAS).

### Statistical analysis

Calculations were performed with statistical spreadsheet computer program SPSS Inc. (SPSS for Windows, Version 22.0. Chicago, SPSS Inc). The normality of variable distribution was obtained using the Shapiro-Wilk test. Statistical analyses were performed using t-test for independent variables and Mann-Whitney test.



**FIGURE 1.** Cone-beam CT orthogonal reconstructions demonstrating the planned needle trajectory. (A), (B). Planning the interlaminar approach (yellow arrows); (C), (D). Planning the transforaminal approach (yellow arrows).

## Results

### Patients

20 patients (53%) were found eligible for CBCT-guided intrathecal nusinersen delivery. Seventeen patients had severe scoliosis, ten patients had posterior fusion instrumentation and two patients were obese. In 18 patients (47%) intrathecal administrations were possible by conventional lumbar puncture and were not included in our study. Patient characteristics are presented in Table 1. None of the patients withdrew from the CBCT-guided intrathecal nusinersen delivery.

### Procedure

During the study 108 CBCT-guided procedures were performed. Each patient underwent at least 4 administrations. The patient with most administrations had 8 administrations. The predominant approach to the spine was TF with L2-L3 or L3-L4 being the most frequent levels of lumbar puncture. For IL approach L3-L4 level was most frequently chosen (Table 2). Total procedure time was approximately 1 hour (Table 2).

**TABLE 1.** Patient characteristics for cone-beam CT (CBCT)-guided intrathecal nusinersen delivery patients and classical lumbar puncture patients

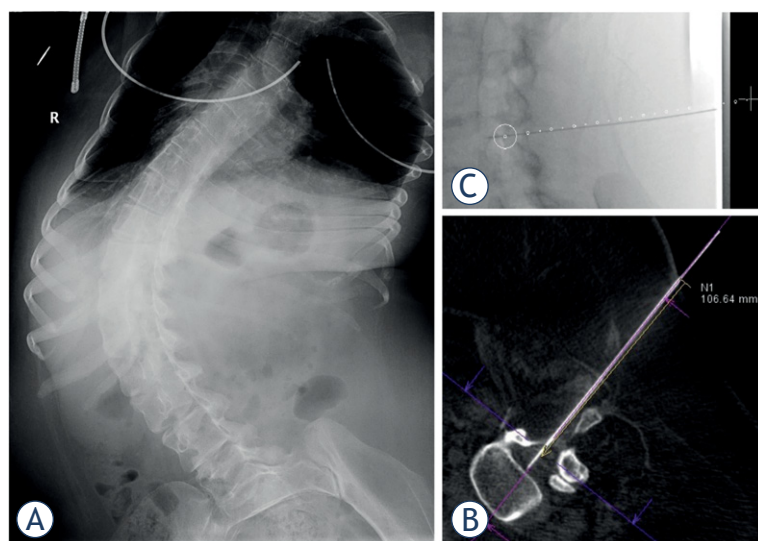
	CBCT-guided	Classical lumbar	P-value
Male sex (%)	10 (50)	12 (67)	
Age at first administration, median (range) year	33.5 (20–62)	44.5 (19–69)	0.62
BMI, median (range) kg/m <sup>2</sup>	23.4 (14.2–41.8)	24.7 (14.3–33.6)	0.08
SMA type 2 (%)	13 (65)	0	
SMA type 3 (%)	7 (35)	15 (83)	
SMA type 4 (%)	0	3 (17)	
Posterior fusion instrumentation due to scoliosis (%)	10 (50)	0	
Severe scoliosis (%)	17 (85)	N/A	

BMI = body mass index; N/A = not available; SD = standard deviation; SMA = spinal muscle atrophy

**TABLE 2.** Procedure summary

	Interlaminar	Transforaminal	Total
L1-L2 (%)	0 (0)	4 (4)	4 (4)
L2-L3 (%)	7 (6)	48 (44)	55 (50)
L3-L4 (%)	10 (9)	35 (32)	45 (41)
L4-L5 (%)	2 (2)	3 (3)	4 (5)
Number of procedures (%)	19 (18)	89 (82)	108 (100)
Duration per procedure, mean $\pm$ SD min	63 $\pm$ 21	60 $\pm$ 26	62 $\pm$ 25

SD = standard deviation



**FIGURE 2.** (A). A 22-year-old female with severe scoliotic deformity of the spine; (B). The nusinersen administration was performed with interlaminar approach under cone-beam CT -guidance; (C). Introduction of the needle following the planned trajectory (white dotted line) to the target point (white circle).

## Technical success

All CBCT-guided procedures were technically successful. Primary success was achieved in 101 (94%) procedures. In others secondary success was achieved; 2 IL and 5 TF approach.

## Effective dose

The median ED for all administrations was 5.5 mSv (interquartile range 2.7–13 mSv) and mean 10 mSv (standard deviation 11 mSv). There was no difference in median ED between patients with posterior fusion instrumentation in comparison to the patients without (5 mSv *vs.* 5.8 mSv). There was a statistically important difference in median ED for obese patients in comparison to other patients (12 mSv *vs.* 5 mSv,  $p = 0.004$ ). ED for every application is presented in Figure 4.

## Adverse events

Median value of patients' subjective assessment of pain level on the VAS scale for CBCT-guided procedures was 4. After the CBCT-guided procedures, twelve patients (60 %) at least once experienced headaches or low back pain (Table 3). Two patients (10 %) additionally experienced pain in the upper extremity due to positioning during the procedure. One patient (5%) reported radiating pain in the leg. AEs were labeled as mild, since no or nominal therapy was required.<sup>22</sup> There were no AEs in the remaining 5 patients (25%).

## Discussion

We report our experience on implementation of lumbar spine CBCT-guided intrathecal nusinersen delivery in consecutive adult SMA patients with challenging access. Evidence gained support good technical success, safety, and feasibility of CBCT-guided intrathecal nusinersen delivery.

The patient selection in our study was multidisciplinary, prospective, and based on inclusion criteria which considered the anatomy of the adult SMA patients. Additionally, to criteria regarding scoliosis and history of corrective surgery, we also acknowledged the patients' general constitution. This problem was so far addressed in only one study in a patient with BMI of 28, in which the intrathecal administration was performed under CT-guidance.<sup>10</sup>

Only few studies have reported their experience in CBCT-guided intrathecal administrations

of nusinersen.<sup>11,18,19</sup> An early study utilized CBCT for needle positioning in three TF procedures in children.<sup>18</sup> The authors reported later switch to fluoroscopy guidance as the performing physicians gained confidence with the intrathecal deliveries.<sup>18</sup> A later study analyzed lumbar punctures with TF approach in seven adult patients.<sup>19</sup> The latest study by Weaver *et al.* presented the largest group of 28 patients for CBCT-guided intrathecal nusinersen delivery.<sup>11</sup> In these studies the CBCT-guided lumbar intrathecal delivery was performed in both children and adult patients, whereas our study focused only on adult patients.<sup>11,18,19</sup> In our study CBCT-guided procedures were predominantly performed by the TF approach, a similar experience previously described by Weaver *et al.*<sup>11</sup> IL approach was not possible either due to severe scoliosis or no visible interlaminar space on CT after the posterior fusion instrumentation. Therefore, our data is in line with previous study, which acknowledges that a growing population of SMA patients requires alternative to the IL approach.<sup>18</sup>

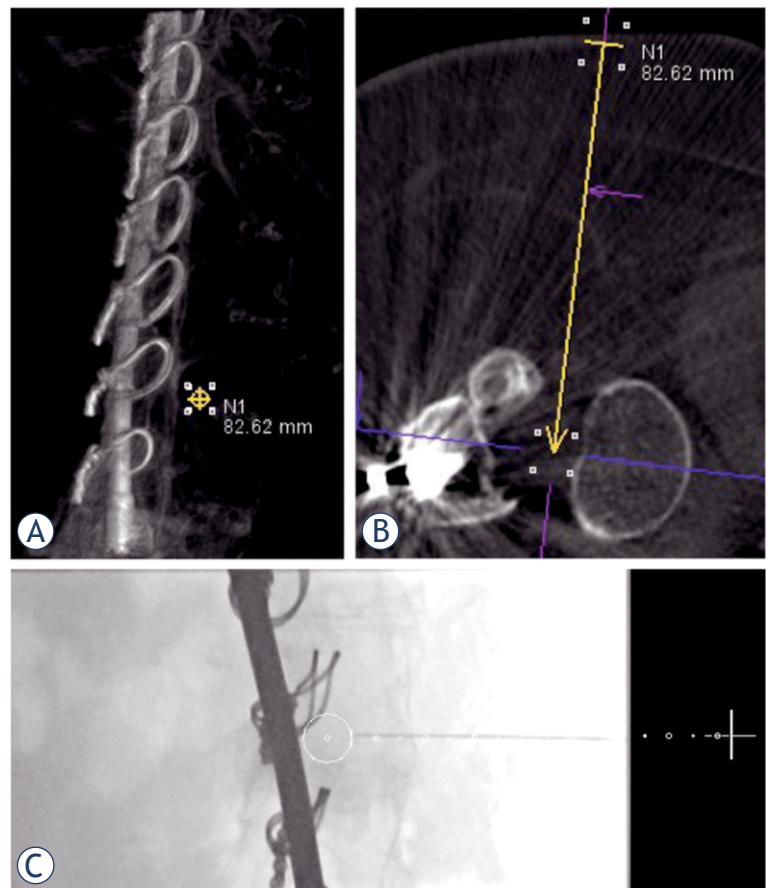
Technical success of the CBCT-guided administrations was achieved in all patients. Only in few procedures secondary success was noted. This is in accordance with the study by Weaver *et al.* which reported high primary success rate for TF approach performed by both CBCT and fluoroscopy.<sup>11</sup> Similarly, high technical success is reported in studies utilizing CT as image-guidance.<sup>7,12,20,23</sup> However, while we specifically determined the technical success according to successful approach to the intrathecal space, other studies defined technical successes ambiguously; namely a primary success in most of the studies was not defined.<sup>7,12,20,23</sup> Two CT-guided studies reported a high (95% and 96.2%) single puncture attempt, which was comparable to our primary technical success.<sup>12,23</sup>

In contrast to other CBCT studies, only mild peri-procedural AEs were reported in ours. Weaver *et al.* reported 4% occurrence of mild AEs such as radicular pain and headaches as well as 0.5% of severe AE such as meningitis.<sup>11</sup> Shokuhfar *et al.* recorded one case (10%) of bilateral radiculopathy.<sup>19</sup> Although no severe AEs were noted in our study, the aforementioned studies raise attention to the potential risks one must take into consideration before the procedure. In the study we also report AEs from the patients that underwent conventional lumbar punctures. In comparison to patients after the conventional lumbar puncture, patients after the CBCT-guided punctures reported lower intensity and duration of low back pain. This finding is contrary to the findings by Carrera-Garcia *et al.*<sup>8</sup> A

**TABLE 3.** Adverse events for cone-beam CT (CBCT)-guided intrathecal nusinersen delivery patients and classical lumbar puncture patients

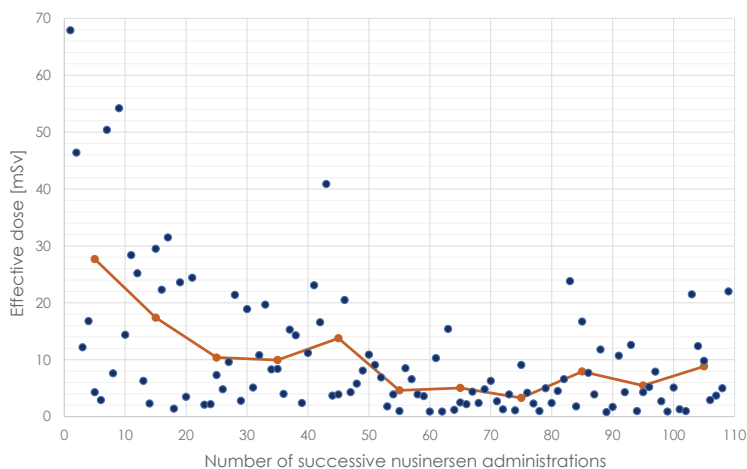
	CBCT-guided (n = 108)	Conventional lumbar (n = 112)	P-value
Headache occurrence (%)	18 (17)	42 (37)	
Headaches VAS, median (range)	2 (0-10)	4.5 (0-10)	0.12
Headaches duration day, median (range)	0.05 (0-5)	2 (0-6)	0.05
Low back pain occurrence (%)	11 (10)	40 (36)	
Low back pain VAS, median (range)	0 (0-2)	2.75 (6)	< 0.01
Low back pain duration day, median (range)	0 (0-4)	2.45 (0-14)	< 0.01

VAS = visual analogue scale



**FIGURE 3.** (A). A 42-year old female after corrective surgery for scoliosis; (B). Transforaminal approach planning before needle introduction (yellow arrow); (C). Introduction of the needle following the planned trajectory (white dotted line) to the target position (white circle).

possible explanation might be the high proportion of primary technical success which minimized the trauma to the spinal meninges and the peridural



**FIGURE 4.** Scatter plot presenting effective dose for each cone-beam CT-guided procedure (blue dots) and calculated average trend line with orange dots for every ten procedures.

mSv = milli severt

membrane which are abundant in nociceptors and other sensory receptors.<sup>24</sup>

Direct comparison with other CBCT-guided studies regarding radiation was not possible due to differences in reported units.<sup>11,19</sup> In comparison to our study, three CT-guided studies performed predominantly on adult patients reported lower ED of around 2.5 mSv, whereas Spiliopolus *et al.* reported higher average ED of 12.7 mSv.<sup>3,7,23,25</sup> Plausible rationale for these findings may be differences in population characteristics. Patients with posterior spinal instrumentation are expected to receive higher radiation exposure than the patients without fusion instrumentation.<sup>25,26</sup> Contrary to this observation our data did not reveal any ED differences regarding spine instrumentation. However, the EDs for the two obese patients proved to be higher in comparison to the other patients.

There was a decline in the average ED over the course of the study time, a finding that is in line with other studies.<sup>12,26</sup> The following factors need to be accounted for the initial high ED. The highest contributing factor to the initial high ED was patients' repositioning with CBCT reacquisition. The patients were repositioned as they either found the initial position uncomfortable or the target region was insufficiently depicted on acquired CBCT or the most comfortable patients' position did not allow optimal CBCT acquisition. Physicians' experience to adjust for specific anatomical considerations was also important in ED reduction. Thus, good cooperation between radiographers and performing physicians plays a key role in radiation exposure reduction. It is important to understand

that each adult SMA patient is specific with differences in anatomical considerations, thus patient-tailored approach needs to be implemented.

There are few limitations that need to be noted. One might argue that this is only a single-center study. A multi-center comparison is not realizable since we are the only institution performing these procedures in our country. Furthermore, it would be difficult to standardize protocol in between organizations due to specifics of such a group. Here we report consecutive patients with standard protocol, which provides important insight in clinical work. Additionally, only partial comparison between other studies with CBCT-guidance was possible since there were differences in patient characteristics and methodology.<sup>11,18,19</sup>

## Conclusions

This single-center prospective study supported the use of CBCT-guided lumbar intrathecal administrations of nusinersen in an adult SMA population with challenging access as feasible, technically successful, and safe image guided method.

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