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Isotopic Scintigraphy in Intrathecal Drug Delivery Failure: A Single-Institution Case Series

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ABSTRACT

Background: The aim of this study was to assess the feasibility and diagnostic accuracy of an optimized ^{111}Indium-diethylenetriamine-penta-acetic-acid single-photon-emission computed tomography (CT) (^{111}In-DTPA SPECT-CT) examination in patients with suspected intrathecal drug delivery (ITDD) failure.

Materials and Methods: Retrospective analysis of routinely collected observational data from a case series of patients in the setting of the academic Center for Pain Medicine, Departments of Radiology and Nuclear Medicine and Neurosurgery. Twenty-seven patients participated between January 2014 and January 2019. Thirty-six optimized examinations including standardized pump flow rate with additional SPECT-CT imaging and a stepwise standardized analysis were performed. A 10 mL mixture of medication and 20 MBq 111In-DTPA was injected into the pump reservoir. Planar and SPECT-CT images were acquired at 24, 48, and 72 hours (h) after injection and at 96 hours and/or seven days, if needed. All images were reassessed by the first two authors using an optimized procedure.

Results and Conclusions: Twenty-two abnormalities were identified in 21 examinations, with these abnormalities consisting of leakage (n = 7), spinal catheter obstruction (n = 7), and cerebrospinal fluid flow obstruction (n = 8). Interventions (n = 19) confirmed the cause of ITDD failure. A false-positive finding at follow-up (n = 1) and a false-negative finding (n = 1) were encountered. Sensitivity was 95% (20/21) and the specificity 93% (14/15). A significant difference ($p < 0.001$) was found between the accuracy of the conventical and the optimized analysis. The optimized ^{111}In-DTPA SPECT-CT examination is a powerful diagnostic tool for detecting the cause of ITDD failure.

Keywords: ^{111}In-DTPA SPECT-CT, computed tomography, diagnostic imaging, intrathecal drug delivery, scintigraphy, therapy failure

Conflict of Interest: Elmar M. Delhaas reports having received personal fees in the past from Medtronic, Inc., as a consultant outside of the submitted work; Aad van der Lugt reports having received grants from GE Healthcare, Siemens, Stryker, Medtronic, and Penumbra outside of the submitted work; and Frank J.P.M. Huygen reports having received grants and personal fees from Abbott and Grünenthal outside of the submitted work. In addition, Frank J.P.M. Huygen has a patent, 2022004, pending in the Netherlands. All other authors report no conflicts of interest concerning the materials or methods used in this study or finding presented in this paper.

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INTRODUCTION

Intrathecal drug delivery (ITDD) using an implanted pump system is a well-established treatment. Despite advancements in manufacturing technology and implantation techniques, a high incidence of adverse events and therapy failure is reported (1–4). Recently, new algorithms for diagnosing in ITDD failure have been reported (5–7). We follow *Saulino et al*. (5), who stated that catheter access port computed tomography (CAP-CT) myelography should be performed in advance of scintigraphy. However, it has recently been suggested that the application of CAP-CT myelography should be reserved for emergencies (6). Part of the advanced approach in ITDD troubleshooting is ^{111}Indium-diethylenetriamine-penta-acetic-acid (^{111}In-DTPA) scintigraphy (8–17). Given its long radioactive half-life time of 2.8 days, ^{111}In-DTPA offers unique possibilities in terms of dynamic imaging studies. After injection the tracer activity into the pump reservoir, images can be acquired for several days following the radiotracer distribution in the catheter system and the subarachnoid space without interrupting drug treatment (12–14,16). ^{99m}Technetium-DTPA also has been used for this purpose (8,12), but due to ^{99m}Technetium's limited half-life time of six hours, the pump used must be reprogrammed for a high delivery rate, which will hamper tracking of tracer spread with a regular flow rate. Furthermore, the pump reservoir, the inner pump tubing, and the spinal catheter must be emptied in advance to prevent a drug overdose due to the increased flow rate (8). Although ^{111}In-DTPA scintigraphy has been performed for several decades, published data are limited. Moreover, different scanning methods have been used, and there is no consensus on image interpretation, normal flow patterns, and diagnostic criteria for determining ITDD failure (14). In this retrospective study of routinely collected observational data, we assessed the feasibility and diagnostic accuracy of an optimized ^{111}In-DTPA protocol. This optimized ^{111}In-DTPA protocol includes standardization of the pump flow rate, the performance of additional single-photon-emission low-dose computed tomography (SPECT-CT) imaging, and the use of a standard evaluation format for image interpretation.

MATERIALS AND METHODS

We included all adult patients who underwent ^{111}In-DTPA scintigraphy for suspected ITTD failure evaluation between January 2014 and January 2019. In all patients, the Synchromed II pump (8637-20) with either the Ascenda or the 8731-catheter type was used. The different drug solutions were prepared by the hospital pharmacy. All patients with one exception were referred from other centers for ITTD troubleshooting. In all patients, conventional diagnostic modalities, including clinical history, a readout of the pump programming, assessment of accurate aspiration volume versus interrogated, plain radiography or CAP-CT myelography, failed to reveal the cause of ITDD failure. In 2014, the optimized ^{111}In-DTPA imaging and analysis protocol was implemented at the Center for Pain Medicine. Standardization of the pump flow rate allows the evaluation of tracer transit time, which is crucial for correct interpretation of the resulting images. From cerebral fluid flow studies (18,19), it is known that the upward flow from the caudal region to the cerebral cisterns takes 2–2.5 hours, with a steady state being reached after eight hours. With the infusion rate we use, in which the catheter tip is reached within 24 hours, the cerebral cisterns should unmistakably be visible at 48 hours after the filling of the pump due to both cerebrospinal (CSF) flow and passive tracer diffusion in CSF. The additional SPECT-CT is intended to provide more detailed information about the cause of flow disorder. This retrospective study was approved by the Medical Ethics Committee, along with a waiver of informed consent (MEC-2017-326).

^{111}IN-DTPA Scintigraphy

Approximately one week before the scheduled scintigraphy, a readout of the pump programming features was performed to obtain information on catheter properties and medication concentration. The expected transit time required to reach the catheter tip was calculated. When the catheter end was not achieved in 24 hours, the pump was programmed to administer a bridge bolus and monitored for adverse effects by our ambulatory clinic on location (20). This includes a bolus delivery of the old drug concentration at the rate necessary to empty the inner pump tubing and catheter when a new drug concentration has been added to the reservoir (21,22), which usually takes one to several days. Thus, it was not the dosage but the concentration of the drug solution that was changed. All the modified concentrations were prepared by the hospital pharmacy. The flow rate of the procedure was modified such that the tip of the intrathecal catheter was reached at 24 hours. This rate was calculated by adding the volume of the fixed inner pump tubing (0.25 mL) and that of the catheter. The volume was estimated by multiplying the catheter length by 0.0022 (mL/cm). In our patient population, the mean total volume was 0.210 mL (standard deviation 0.019), which resulted in a mean flow rate of 0.46 mL/24 h. At the Nuclear Medicine Department, 10 mL of each patient's medication mixed with approximately 20 MBq ^{111}In-DTPA (in 0.3–0.5 mL) was prepared under aseptic conditions. Next, a nurse practitioner emptied and refilled the pump reservoir with the prepared mixture using the standard refill technique. Subsequently, planar and SPECT-CT images were acquired at 24, 48, 72, and—if needed—96 hours and/or seven days after pump filling using a Siemens Symbia T16 SPECT-CT scanner (Siemens Healthcare, Erlangen, Germany). Planar images (256×256 matrix, medium-energy limited purposes collimator) were acquired from anterior and posterior of the pump/abdominal region, the thorax, and the head/neck region (10 min per view and 20 min at seven days postinjection). Next, SPECT-CT was acquired for verification, attenuation correction, and anatomical localization. SPECT parameters were 128×128 matrix, 60 views/detector, and 30-sec time per view. Low-dose CT parameters were 110 kV, 40 mAs, 0.6-sec tube rotation, 0.8 mm pitch, and 5-mm slice thickness.

^{111}IN-DTPA Scintigraphy Evaluation

The goal of the evaluation was to assess the cause of ITTD treatment failure. Potential causes could include pump motor stall, leakage at the pump-catheter connection, connection between the two catheter segments, or from the catheter itself, catheter occlusion, and/or CSF flow obstruction at the catheter tip or elsewhere in the spinal canal. The first two authors (EMD, DMEvA) evaluated the planar images using the conventional analysis, which was distilled from six case studies in the literature (12–16). In these studies, imaging was performed after 4–72 hours (13–17). In some publications, progression time of tracer through the catheter was calculated, and—if needed—the time for imaging was customized (16,17). All studies were performed without a standardized pump flow rate, without SPECT-CT (with the exception of one study) (17), and without a standardized stepwise

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imaging interpretation. In our study, when tracer activity progressed along the subcutaneous and intrathecal catheter part and the tracer was found to be evenly distributed (13) throughout the cerebral cisterns without any signs of leakage, the examination was regarded as normal (16). Next, the images were reassessed using the optimized ^{111}In-DTPA scanning and analysis protocol, taking the standardized pump flow rate into account and using a stepwise standardized interpretation of planar and SPECT-CT images. The stepwise and standardized interpretation of the images were based on the following:

- Step 1: Is the pump flow rate standardized?
- Step 2: Is access to the patient's file and previous imaging examinations available?
- Step 3: Is the pump visible, is any tracer activity around the pump visible, and does the activity in/around the pump exhibit a normal shape?
- Step 4: Are the abdominal horizontal catheter segments visible? Is normal tracer spread present in the subcutaneous part of the catheter from anterior to posterior?
- Step 5: Is tracer activity at the horizontal/vertical catheter transition normal or enhanced?
- Step 6: Is caudal (intrathecal, below the catheter insertion) spread of tracer activity visible? If yes, is tracer activity normal, enhanced, or broadened, and is tracer activity already present at the catheter-tip level?
- Step 7: Is tracer activity present in kidneys/bladder/elsewhere in the abdomen? When visible, is tracer activity already present at the catheter-tip level?
- Step 8: Is distribution of tracer activity in the lumbar and thoracic catheter segment in the spinal canal normal? Is the intensity of tracer activity increased, or does it have a broader aspect? Is increased tracer accumulation present at the catheter-tip level?
- Step 9: Is tracer activity visible in the spinal canal above the catheter-tip level and in the cerebral cisterns? Does it have a normal intensity? Are there relative differences in intensity?

Data Analysis

The sensitivity and specificity were calculated by comparing the results of the imaging assessment (conventional and optimized analysis), which served as the index test, with the final diagnosis after three months, which served as the reference test and was based on all relevant imaging and clinical and surgical information. A true positive (TP) result was thereby defined as when an abnormality could be demonstrated with the index test and the reference indeed revealed a cause of ITDD failure, a true negative (TN) when an abnormality was not found with the index test and the reference test, a false positive (FP) when an abnormality on imaging could not be confirmed by the reference test, and a false negative (FN) when the abnormality was overlooked on imaging. The accuracy of the conventional and optimized ^{111}In-DTPA analysis was compared using the McNemar Test with IBM SPSS Statistics Version 25.

RESULTS

Patients

Thirty-six ^{111}In-DTPA examinations were performed in 27 patients. In seven patients, the examination was performed twice, and, in one patient, it was performed three times. In all ^{111}In-DTPA examinations, including the drug delivery standardization procedures with bridge bolus, no adverse events were encountered. The results and the applied treatment are summarized in Table 1. Pump malfunctions and differences between the two catheter types were not observed. The results obtained with the optimized analysis (n = 1), including optimized planar (n = 16) and SPECT–CT (n = 1) or findings during intervention (n = 19), served as the reference standard (Table 1). With the conventional, 11 of 36 examinations revealed a suspected pump-catheter-related cause of ITDD failure, including leakage (n = 1), catheter obstruction (n = 4), CSF flow obstruction (n = 4), and only the pump being visible (n = 2), which revealed not be related to a pump malfunction. With the optimized ^{111}In-DTPA imaging and analysis protocol 22 abnormalities were found in 21 examinations: leakage (n = 7), catheter obstruction (n = 7), and CSF flow obstruction (n = 8). In one examination, two abnormalities were found, namely catheter obstruction and leakage at the pump-catheter connection (Figs. 1e and 2). Fifteen optimized examinations failed to reveal the cause of ITDD treatment failure. In 19 of the 21 positive examinations, interventions confirmed the cause of ITDD failure, but, for one positive examination, a surgical intervention was not performed. In one examination, the diagnosis of CSF flow obstruction based on limited rostral tracer distribution was found to be a FP finding at clinical follow-up. In the 15 normal examinations, one FN finding was encountered.

Leakage

Seven examinations revealed leakage. Only two were clearly identified on planar images, which showed only tracer activity in the pump or an abnormal pump shape (n = 1, Fig. 1i, dark gray arrow); additional SPECT-CT also confirmed presence of tracer activity around the pump in the pump pocket. The remaining five cases of leakage were found only with SPECT-CT: leakage in the pump pocket (n = 1) caused by a sheared catheter located in the pump pocket (Fig. 2g–j), retrograde backflow via a retained extrathecal-intrathecal catheter segment (n = 1, Fig. 1c), increased dorsal lumbar subcutaneous tracer accumulation due to dura leakage (n = 3). In one of these cases, the dorsal leakage also was associated with tracer activity in the pump pocket, probably caused by CSF passing backwards alongside the subcutaneous part of the catheter into the pump pocket. One false-negative finding was encountered when, due to persistent intrathecal baclofen (ITB) failure, a catheter replacement was performed based on the caudal tracer activity identified below the catheter insertion level, which was originally regarded as normal both on conventional and optimized. During surgical intervention, minor damage to the intrathecal catheter part was found.

Catheter Obstructions

Seven catheter obstructions were identified. Five were recognized at planar imaging with conventional due to augmented tracer activity at the catheter tip with a minimal rostral spread (n = 2, Fig. 1f), increased tracer activity at the abdominal horizontal-vertical lumbar catheter transition (n = 1, Fig. 1e), and tracer activity in the pump only (n = 1, Fig. 1g) with tracer activity in the kidneys and bladder (n = 1,Figs. 1h and 3a–c). In the latter patient, a granuloma at the catheter tip was detected during surgery. Two examinations were considered normal with conventional, but using optimized procedure, increased activity at the abdominal horizontal-vertical lumbar catheter transition was interpreted as consistent with obstruction (n = 2, Fig. 1e).

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Table 1. Patient Characteristics.

No.	Age/sex	Disorder	Symptomatology	Medication	Cath. tip	Planar results (CP)	TP/TN/FP/FN	Planar results	SPECT-CT results	TP/TN/FP/FN	Best standard reference	Final diagnosis	Treatment	Clinical result	Figure
						Conventional practice		Optimized practice							
1	54/f	FBS	Pain	M	T9	Only pump visible, renal activity	TP 1	Only pump visible, renal activity	Obstruction catheter	TP 1	Intervention	Granuloma catheter tip	Laminectomy replacement catheter	Limited improved	1F, 3
2	49/f	CP	Spasticity	B	T11	Only pump visible	TP 2	Only pump visible	Tracer in pocket	TP 2	Intervention	Pump-catheter disconnection with fluid in pocket	Replacement catheter	Spasticity under control	1G
3	54/f	MS	Spasticity	B	T9	Abnormal pump shape, leakage pocket	TP 3	Abnormal pump shape, leakage pocket	Tracer in pocket	TP 3	Intervention	Catheter leakage in pocket	Replacement catheter	Spasticity under control	1I
4	29/m	CP	Spasticity	B	T11	Normal	TN 1	Normal	Normal	TN 1	OP	Normal	Dose adjustments	Not improved	1A
5	44/f	CRPS	Dystonia	B	T3	Normal	TN 2	Normal	Normal	TN 2	OP	Normal	Dose adjustments	Unchanged	
6	66/f	Spinal spastic syndrome	Spasticity	B	T8	Normal	FN1	Normal	Leakage dorsal	TP 4	Intervention	Dural leakage	Epidural bloodpatch	Improved	
7	50/f	CRPS	Dystonia	B	T2	Normal	FN 2	Normal	Leakage dorsal	TP 5	Intervention	Dural leakage	Epidural bloodpatch	Dystonia under control	
8	53/f	CRPS	Dystonia	B	T10	Normal	FN3	Normal	Leakage dorsal, leakage pocket	TP 6	Intervention	Dural leakage, with fluid in pocket	Epidural bloodpatch + puncture pocket	Dystonia under control	
9	38/f	CRPS	Dystonia	B	T9	Normal	TN 3	Normal	Normal	TN 3	OP	Normal	Dose adjustments	Unchanged	
10	66/f	FBS	Pain	M	T10–11	Normal	TN 4	Normal	Normal	TN 4	OP	Normal	Dose adjustments	Unchanged	
11	70/f	SCL C6	Spasticity	B	T10-11	Normal	TN 5	Normal	Normal	TN 5	OP	Normal	Dose adjustments	Unchanged	
12	57/f	FBS	Pain	M/C	T7	Normal	TN 6	Normal	Normal	TN 6	OP	Normal	Dose adjustments	Unchanged	
13	57/m	SCL C5-6	Spasticity	B	T11	Normal	TN 7	Normal	Normal	TN 7	OP	Normal	Dose adjustments	Unchanged	
14	43/m	SCI C7	Spasticity	B	T8	Normal	TN 8	Normal	Normal	TN 8	OP	Normal	Dose adjustments	Unchanged	
15	36/f	CRPS	Dystonia	B	T8	Normal	TN 9	Normal	Normal	TN 9	OP	Normal	None	Unchanged	
16	49/f	MS	Spasticity	B	T9–10	Normal	TN 10	Normal	Normal	TN 10	OP	Normal	Dose adjustments	Improved	
17	60/f	MS	Spasticity	B	T9–10	Normal, caudal tracer distribution	TN 11	Normal, caudal tracer distribution	Normal, caudal tracer distribution	TN 11	OP	Normal	Dose adjustments	Unchanged	
18	60/f	MS	Spasticity	B	T9-10	Normal, caudal tracer distribution	FN 4	Normal, caudal tracer distribution	Normal, caudal tracer distribution	FN 1	Intervention	Catheter leakage (intrathecal)	Replacement catheter	Spasticity under control	
19	66/f	MS	Spasticity	B	T9	Normal, caudal tracer distribution	TN 12	Normal, caudal tracer distribution	Normal, caudal tracer distribution	TN 12	OP	Normal	Dose adjustments	Limited improved	
20	65/f	MS	Spasticity pain	B/M/C	T10–11	Normal, caudal tracer distribution	TN 13	Normal, caudal tracer distribution	Normal, caudal tracer distribution	TN 13	OP	Normal	Dose adjustments	Improved	1B
21	44/m	SCL C5	Spasticity	B	T7-8	Normal, caudal tracer distribution	TN 14	Normal, caudal tracer distribution	Normal, caudal tracer distribution	TN 14	OP	Normal	Dose adjustments	Unchanged	
22	66/m	Stroke	Spasticity	B	T11	Abnormal, caudal tracer distribution	TP4	Abnormal, caudal tracer distribution	Abnormal, caudal tracer distribution, leakage via retained catheter	TP 7	SPECT-CT	Leakage back via retained catheter	Dose adjustments	Minimal improved	1C
23	51/m	SCL C6	Spasticity pain	B/M	T5-6	Normal	TN 15	Limited obstruction rostral tracer distribution	Limited obstruction rostral tracer distribution	FP 1	OP	Normal	Dose adjustments	Limited improved	
24	46/m	SCI C5	Spasticity	B	T7-8	Normal	FN 5	Obstruction rostral tracer distribution	Obstruction rostral tracer distribution	TP 8	Intervention	CSF flow obstruction	Replacement catheter	Spasticity under control	5
25	57/m	FBS	Pain	M	T8	Obstruction rostral tracer distribution	TP 5	Obstruction rostral tracer distribution	Obstruction rostral tracer distribution	TP 9	Intervention	CSF flow obstruction	Replacement catheter	Pain under control	
26	64/m	SCL T12	Spasticity	B	T9–10	Obstruction rostral tracer distribution	TP 6	Obstruction rostral tracer distribution	Obstruction rostral tracer distribution	TP 10	Intervention	CSF flow obstruction	Restoration CSF-flow	Spasticity under control	
27	47/f	SCL T10	Spasticity pain	B/M	T11	Obstruction rostral tracer distribution	TP 7	Obstruction rostral tracer distribution	Obstruction rostral tracer distribution	TP 11	Intervention	CSF flow obstruction	Restoration CSF-flow	Spasticity under control, pain unchanged	
28	38/m	SCL T4	Spasticity	B	T7	Obstruction rostral tracer distribution	TP 8	Obstruction rostral tracer distribution	Obstruction rostral tracer distribution	TP 12	Intervention	CSF flow obstruction	Restoration CSF-flow	Spasticity under control	
29	46/f	SCL T10	Spasticity pain	B/M	T11	Obstruction rostral tracer distribution	TP 9	Obstruction rostral tracer distribution	Obstruction rostral tracer distribution	TP 13	Intervention	CSF flow obstruction	Restoration CSF-flow	Limited improved	1D, 4
30	37/m	SCL T4	Spasticity	B	T7	Obstruction rostral tracer distribution	TP 10	Obstruction rostral tracer distribution	Obstruction rostral tracer distribution	TP 14	Intervention	CSF flow obstruction	Restoration CSF-flow	Limited improved	
31	58/m	SCL C5-6	Spasticity	B	T11	Obstruction catheter	TP 11	Obstruction catheter	Obstruction catheter	TP 15	Intervention	Obstruction catheter	Replacement catheter	Spasticity under control	
32	59/m	SCL T5-6	Spasticity	B	T8	Normal	FN/FN 6 (7)	Obstruction catheter	Obstruction catheter + leakage pocket	TP/TP 16 (2x)	Intervention	Obstruction catheter (dorsal, lumbar transition) + leakage catheter (part in pocket)	Replacement catheter	Spasticity under control	1E, 2
33	46/f	SCL C6-7	Spasticity	B	T10	Obstruction catheter	TP 12	Obstruction catheter	Obstruction catheter	TP 17	OP	Obstruction catheter	Replacement catheter scheduled	Passed away conventional practice optimized practice	
34	43/m	SCI C7	Spasticity	B	T8	Obstruction catheter	TP 13	Obstruction catheter	Obstruction catheter	TP 18	Intervention	Obstruction catheter	Replacement catheter	Limited improved	
35	37/m	SCL T4	Spasticity	B	T7	Obstruction catheter	TP 14	Obstruction catheter	Obstruction catheter	TP 19	Intervention	Obstruction catheter	Replacement catheter	Only improved spasticity lower extremities	
36	66/f	FBS	Pain	M	T9	Obstruction catheter	TP 15	Obstruction catheter	No tracer distribution in spinal canal	TP 20	Intervention	Obstruction catheter	Removal system, termination treatment	Unchanged	1H

CP, cerebral palsy; CRPS, complex regional pain syndrome; FBS, failed back surgery; FN, false negative; FP, false positive; MS, multiple sclerosis; OP, optimized procedure; TN, true negative; TP, true positive.

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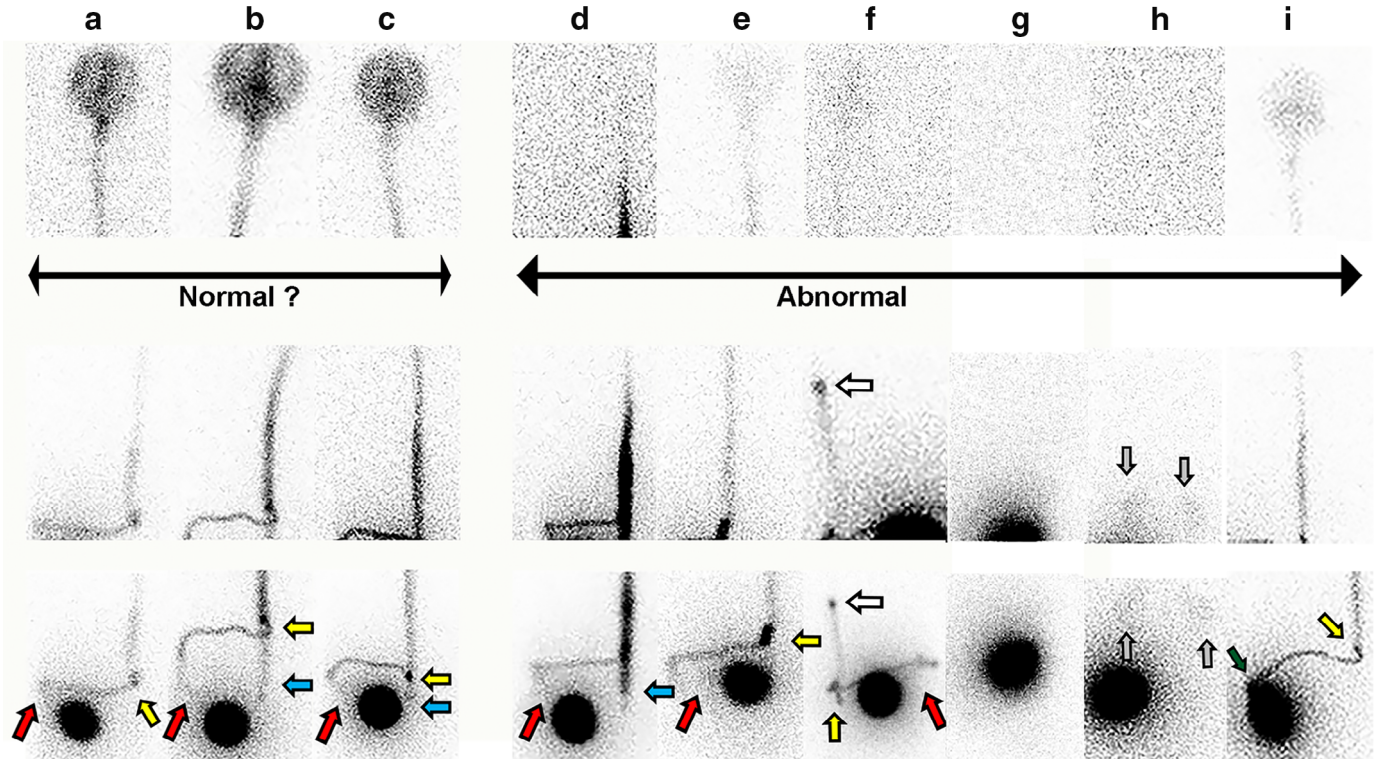

Figure 1. Examples of planar images from nine examinations with a standardized pump flow rate of the abdomen, thorax, and head regions (resp. lower, middle, and upper row). Upper row: normal (a, b, c) and reduced (d–i) tracer activity at the cerebral cisterns. Middle row: enhanced tracer activity at the catheter tip (f, white arrow), and renal tracer activity (h, gray arrows). Lower row: enhanced tracer activity at the lumbar horizontal-vertical transition (A–C,E,F,I, yellow arrows), invisible first catheter segment (a–f, red arrows), caudal tracer activity (b–d, blue arrows), only pump visible (g,h), renal tracer activity (h, gray arrows), abnormal pump shape (i, dark gray arrow), and enhanced tracer activity at catheter tip (f, white arrow).

CSF Flow Obstruction

Four obstructions were found at conventional. The optimized imaging and analysis protocol showed eight CSF flow obstructions, but one of these was a FP finding. The remaining seven showed an increase and broadening of caudal and lumbar tracer activity in combination with limited or invisibility activity in the cerebral cisterns (n = 5, Fig. 1d and 4), gradually increasing caudal activity over time in combination with reduced rostral flow (n = 1, Fig. 5), or only limited rostral flow (n = 1). In the FP case, improvement could be achieved with dose adaptations.

Accuracy of Conventional and Optimized Analyses

The conventional data showed TPs (n = 11), FPs (n = 0), TNs (n = 15), and FNs (n = 10). The calculated sensitivity was 52% (11/21) and the specificity 100% (15/15). The results of the optimized ^{111}In-DTPA SPECT-CT procedure revealed TPs (n = 20), FPs (n = 1), TNs (n = 14), and FNs (n = 1). The calculated sensitivity was 95% (20/21) and the specificity 93% (14/15). A significant difference ($p < 0.001$) was found between the accuracy of the conventional and the optimized procedure.

DISCUSSION

Based on the analysis of this retrospective study on observational routinely collected data, we confirmed the efficacy of our optimized ^{111}In-DTPA SPECT-CT examination. Moreover, it was found that optimized ^{111}In-DTPA SPECT-CT scintigraphy is a powerful diagnostic tool when conventional diagnostic modalities and the advanced tool of catheter access port CT myelography fail to reveal the cause of ITTD failure. Moreover, it was found that optimized ^{111}In-DTPA SPECT-CT scintigraphy is a powerful diagnostic tool when conventional diagnostic modalities and the advanced tool of CAP-CT myelography fail to reveal the cause of ITTD failure. Given the sensitivity and specificity of CAP-CT myelography, we prefer to perform it first in advanced diagnostic procedures. However, the dynamic character of scintigraphy provides the advantage of making it possible to follow the distribution of the drug through the drug delivery system and intrathecal space, which could prove helpful for diagnosis under certain circumstances. The radiation dose associated with CAP-CT myelography and scintigraphy is a concern; however, in a recent paper, the radiation doses associated with these techniques were found to be comparable (6). In most of the optimized examinations, we were able to correctly diagnose the cause of ITTD failure, which was an improvement compared to the conventional procedure. Our study indicates that planar imaging combined with SPECT-CT is an adequate technique for identifying and localizing functional alterations and to thus obtain a correct diagnosis. In chronic ITTD treatment, the penetration of the tracer activity into surrounding tissue can be hindered by a fibrotic layer around the pump, which could impede the diagnosis of leakage. The extremely intense tracer activity inside the pump also could be an obstacle for detection of aberrant fluid around it; however, image scaling of both planar and SPECT images could facilitate this by assessing

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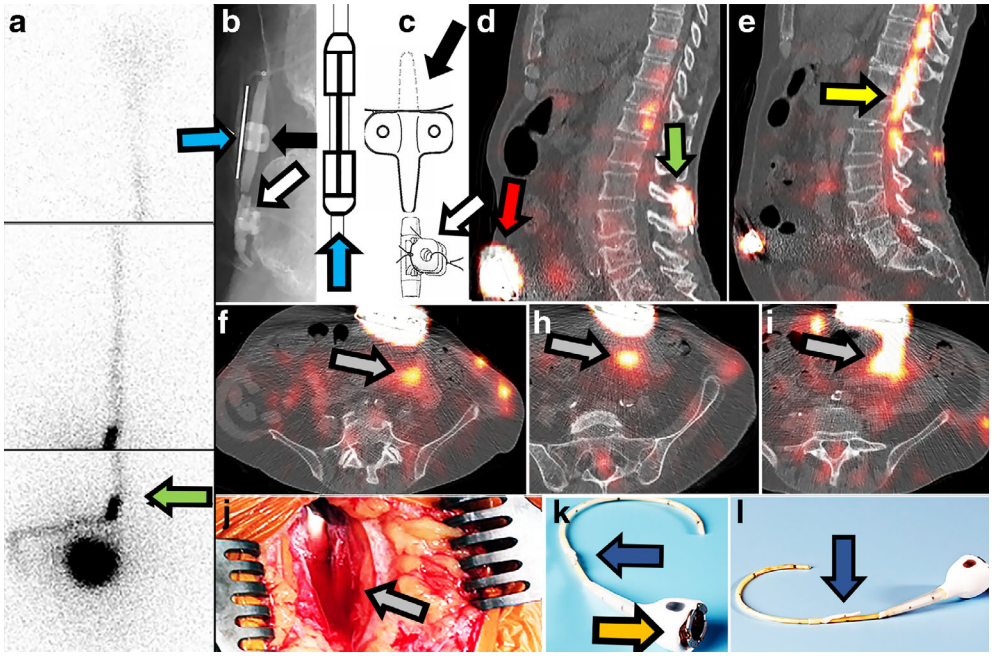

Figure 2. Sheared catheter and leakage in the pump pocket in a 59-year-old male with spasticity based on a spinal cord lesion at T5. Dorsal, at the abdominal/lumbar transition, tracer accumulation in the drug delivery system parts (a, green arrow), including needle-shaped catheter-catheter connector (b,c, blue arrows), anchor (b,c, black arrow), and retained old-type anchor (b,c, white arrow). The enhanced tracer activity at the dorsal abdominal/lumbar transition (a, lower row) combined with limited tracer activity in the cerebral cisterns (a, upper row) suggested a catheter obstruction. SPECT-CT fusion images show an abnormal pump shape (d, red arrow) and some fluid outside of the pump pocket (f–i, gray arrows). At surgery, the fluid in the pump pocket, which was caused by a sheared catheter, was confirmed (j, gray arrow). In addition, at surgery, a catheter obstruction at the abdominal/lumbar transition was found. Postexplantation imaging of the system showed a catheter-pump connector distortion (k, orange arrow) and a sheared catheter (k,l, purple arrow).

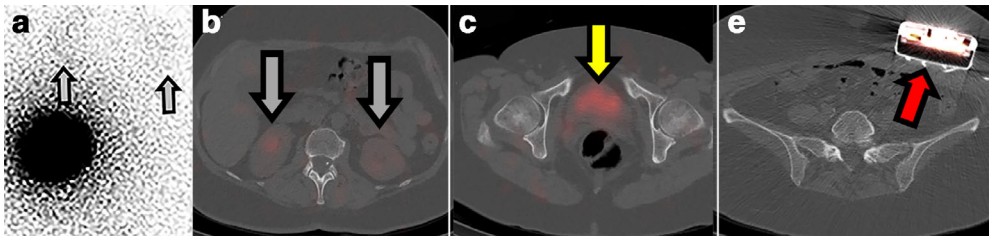

Figure 3. A 54-year-old woman with pain caused by failed back surgery, in which a readout of the pump revealed a normal pump delivery rate. Planar image (a) of the abdomen revealing a normally shaped pump but with subtle tracer activity in the kidneys (a, gray arrows) and without tracer activity in the catheter segments. SPECT-CT (b–d) confirmed tracer activity in the kidneys (b, gray arrows) and bladder (c, yellow arrow), and there were no signs of tracer activity around the pump in the pump pocket (d, red arrow). The subtle tracer activity in kidneys and bladder means that tracer must have passed the inner pump tubing and reached the pump access port, which excluded a pump device failure. The normal pump shape and lack of tracer activity around the pump in the pump pocket (a, d) make leakage at the pump catheter-connector also very unlikely. A subtotal catheter obstruction was therefore considered, although the lack of tracer activity in the catheter segments could not be fully explained. Magnetic resonance imaging revealed a granuloma at the tip of the catheter, which was confirmed at surgery.

the shape of activity in and/or around the pump. To ensure that imaging is performed after tracer activity has reached the catheter tip and to prevent potential misinterpretations, we implemented a standardized pump flow rate (where activity will reach the catheter tip within 24 hours) and changed the timing of scanning to 48 hours, 96 hours, and seven days after pump filling. On the one hand, without the standardization of the pump flow rate, the time required for tracer activity to reach the tip can be unclear, scanning could be performed at too early a point in time as result; on the other hand, the diagnosis of a partial obstruction characterized by a delayed and/or reduced rostral tracer activity visibility could be overlooked. The statement by previous authors that the presence of any amount of tracer activity in the intrathecal space (13) and the cerebral cisterns (16) indicates the absence of an abnormality is not justified.

Furthermore, imaging should not be limited to a single time point, as leakage and partial obstruction can become increasingly apparent over time. Increased tracer activity at the horizontal and vertical catheter transit position should be evaluated for possible over-projection of catheter parts, connector, and/or fixation anchor. Another concern is visible caudal tracer activity below the catheter insertion when the tracer has already reached the cisterns. We found that, in the majority of normal cases, intrathecal caudal tracer activity was not found below the level of the catheter insertion. This could be related to the extremely low-volume pump infusions in ^{111}In-DTPA imaging, which is in contrast to

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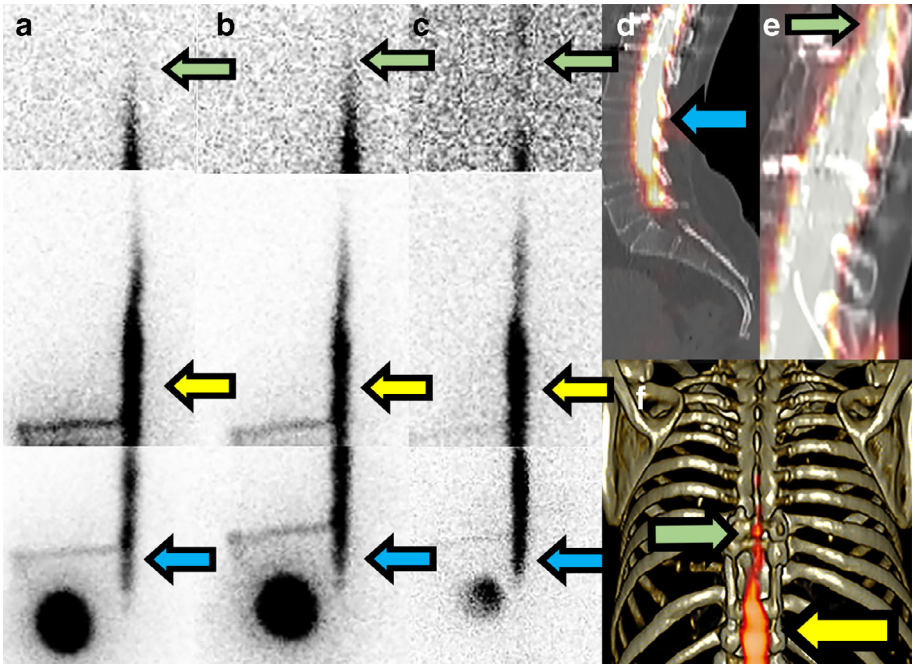

Figure 4. CSF flow obstruction in a 47-year-old female with spasticity with a spinal cord lesion at T10. Planar imaging at 48 hours (a), 72 hours (b), and seven days after injection (c) revealed increased caudal and lumbar tracer activity (blue and yellow arrows) and tapering of tracer activity with reduced rostral tracer spread (green arrows) and without tracer activity at the cerebral cisterns. SPECT-CT images (d, e) also showed increased tracer activity at the caudal-lumbar level (blue arrow) and tapering of tracer activity (green arrow). The 3D reconstruction image (f) clearly shows pronounced lumbar tracer activity (yellow arrow) and tapering of tracer activity (green arrow) more rostrally.

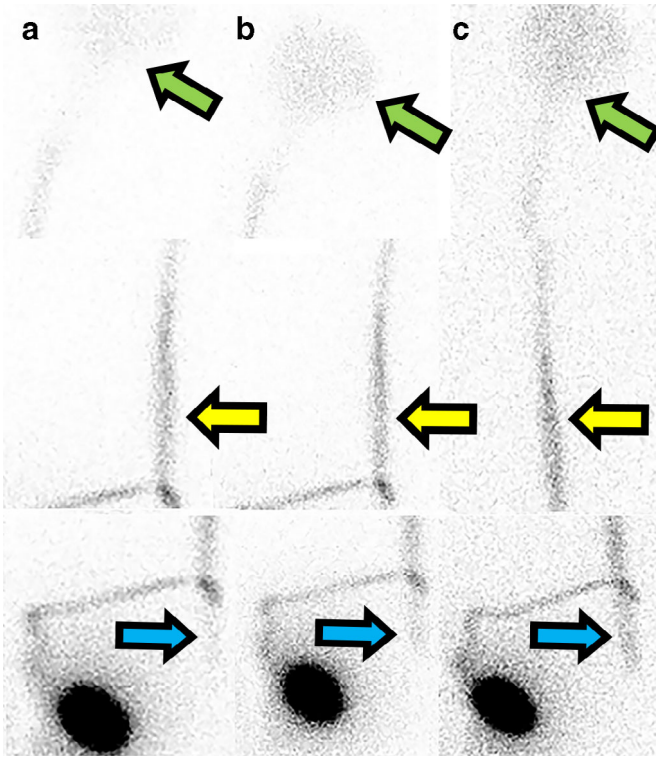

Figure 5. CSF flow obstruction in a 46-year-old male with spasticity caused by a spinal cord lesion at C5. Planar images at 48 hours (a), 72 hours (b), and seven days after tracer injection (c) show increasing caudal tracer activity (blue arrows) over time, pronounced tracer activity at lumbar level (yellow arrows), a thoracic gradient above the catheter tip level, and insufficient rostral tracer distribution with reduced tracer activity at the cerebral cisterns (green arrows). Images indicate the possibility of CSF flow obstruction.

radiographic examinations, where a large volume of contrast material is injected. When caudal tracer activity is present, the distinction between a normal variant and an abnormality cannot easily be made. From a clinical perspective, caudal tracer activity accumulation could be relevant in ITDD failure (23). In one of our cases, the catheter tip was positioned at level L5 for surgical reasons, and we found stagnation of tracer activity at that level without further transit upward, which was interpreted as an obstruction at tip level and the cause of ITDD failure.

To identify stagnation in drug delivery, it is crucial to assess the amount of tracer activity in the cerebral cisterns. A blockage of rostral tracer distribution with broad caudal, lumbar, and thoracic tracer activity is suspect when an obstruction occurs in rostral CSF flow. The analysis demonstrates that, with the optimized examination, we could not only estimate normal functioning or a malfunction of the delivery system but also, using the standardized pump flow rate, more easily diagnose an obstructed intrathecal rostral CSF flow. With SPECT-CT, we were able to confirm the suspected problems as revealed on the planar images, and we also could localize the problem.

Study Limitations

Routinely collected data are frequently used to improve patient care and health care efficiency. In our study, we evaluated the diagnostic role of ^{111}In-DTPA scintigraphy in suspected ITDD failure and attempted to improve the procedure and the evaluation of its results. However, the retrospective nature of the study hampered the application of reporting guidelines such as STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (24). To our knowledge, this analysis is the most extensive to date, although the sample size is rather small. In addition, a chronology bias (25) is present in this retrospective study, which may have influenced our conclusions. We reassessed all images to reduce the

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possibility of a misclassification bias. An observational bias might be present, as the initial conventional analysis and assessment with the optimized protocol were performed by different nuclear physicians as a routine clinical practice, whereas the reassessment was done by the authors. In cases where dose adjustment does not result in clinical improvement, a FN test could be the case; this is due to the fact that, as there are no other references, underestimation of the number of FN optimized practice procedures may result. However, the most critical limitations are the unstructured approach to data collection, the heterogeneous patient population, and the different causes of ITDD failure, all of which resulted in the absence of a harmonized reference standard to determine the exact cause of ITDD failure. Instead, we composed the reference based on all available data, including the index test, additional imaging modalities, surgery, clinical information such as the results of dose adaptations, and follow-up. Despite the bias in the design of this study, the data suggest that the optimized ^{111}In-DTPA SPECT-CT procedure is an indispensable step in determining the causes of ITDD treatment failure.

CONCLUSION

The results of this study indicate that an optimized ^{111}In-DTPA SPECT-CT imaging and analysis procedure is a powerful diagnostic tool when conventional examinations including clinical history, pump read out and aspiration, plain radiography, and CAP-CT myelography do not reveal the cause of ITTD failure. The method is crucial not only for determining suspected infusion system malfunction but also for examining possible obstruction to the rostral intrathecal distribution of medication. Sizable, prospective, multicenter cohort studies are needed to develop consensus criteria for determining the role of isotopic scintigraphy in ITDD troubleshooting.

Authorship Statement

Elmar M. Delhaas was the lead author, performed the literature review, developed the conception and the design, performed ITB treatment, assessed the scintigraphy procedures, discussed the clinical consequences of the imaging results, and performed the different drafts of the article and the final version; Daniëlle M.E. van Assema was involved in developing the conception and the design, assessed the scintigraphy procedures, discussed the clinical consequences of the imaging results, and was involved in the different drafts of the article; Alida C. Fröberg was involved in developing the conception and the design and assessed the scintigraphy procedures; Ben G.J.C. Zwezerijnen assessed the scintigraphy procedures, was involved in the different drafts of the article; Biswadjiet S. Harhangi was involved in developing the conception and the design, discussed the clinical consequences of the imaging results, and was involved in the different drafts of the article; Sander P.G. Frankema performed ITB treatment, discussed the clinical consequences of the imaging results and was involved in the different drafts of the article; Frank J.P.M. Huygen performed ITB treatment, discussed the clinical consequences of the imaging results and was involved in the different drafts of the article; Aad van der Lugt was involved in developing the conception and the design, assessed the scintigraphy procedures, discussed the clinical consequences of the imaging results, and was involved in the different drafts of the article; All authors critically revised the final draft article and approved the final version.

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COMMENT

Intrathecal drug delivery failure is a current clinical issues in patients with chronic pain and spasticity (1,2,3). Catheter and pump failures are known but how to assess is not well published. Conventional imaging with radiographs and catheter dye studies may not be sensitive to see drug delivery failures. This case series highlights the need to assess intrathecal drug delivery failures with further diagnostic interventions.

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