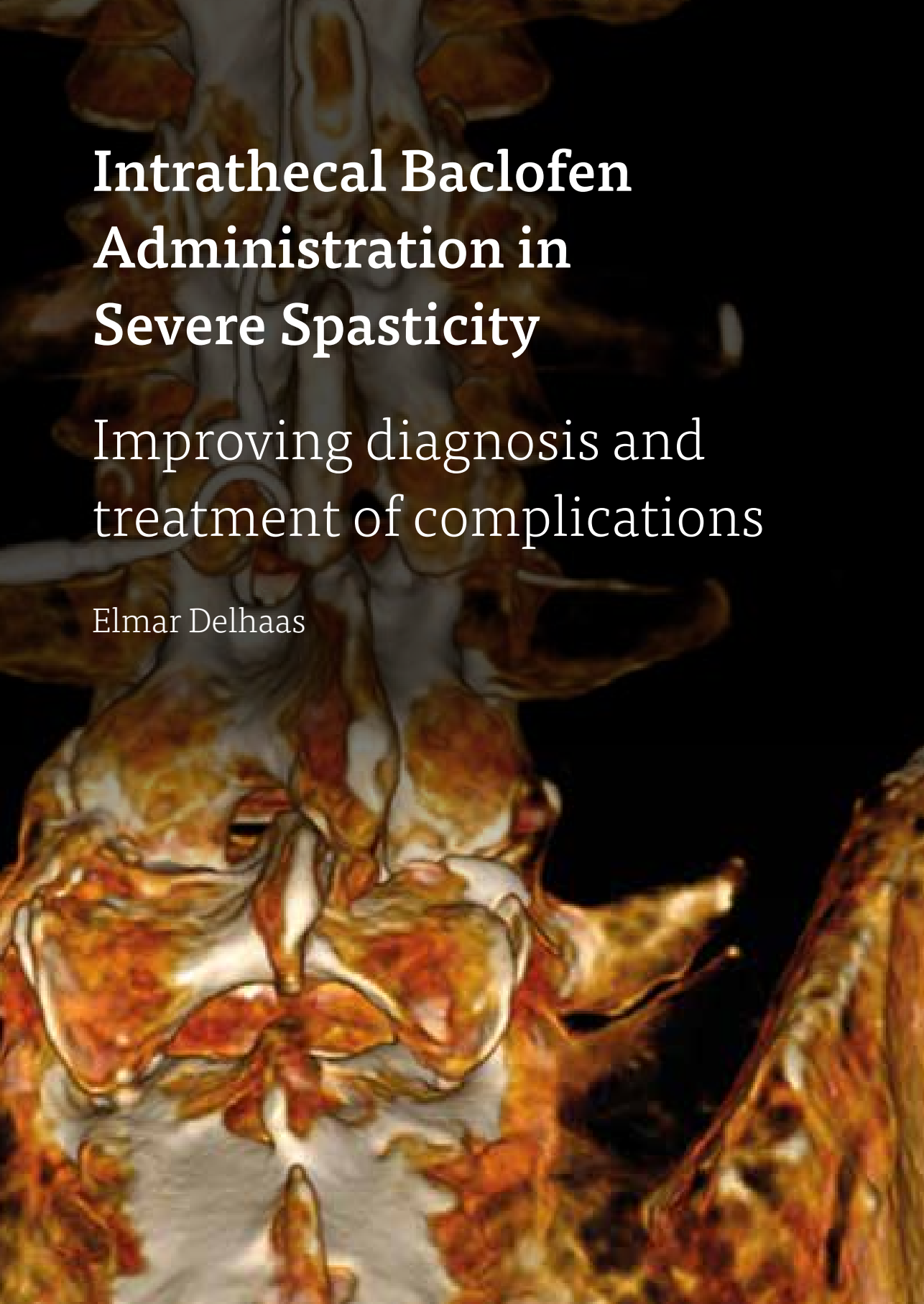

Intrathecal Baclofen Administration in Severe Spasticity

Improving diagnosis and treatment of complications

Elmar Delhaas

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Intrathecale toediening van baclofen bij ernstige spasticiteit
Verbetering van de diagnose en behandeling bij complicaties

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Voor Elly

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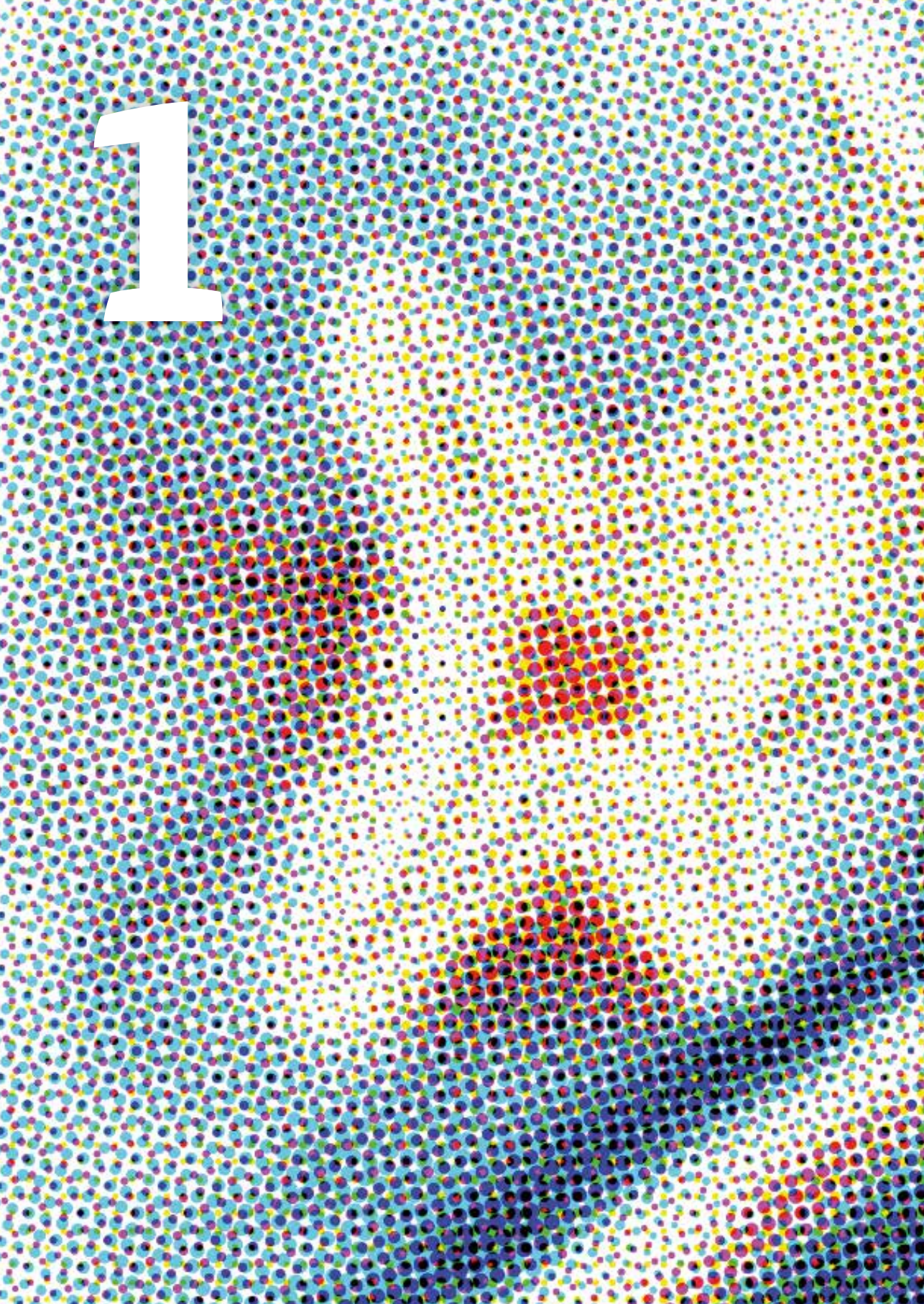
1

Introduction, aim of the study

Spasticity

Spasticity is a major symptom of the upper motor neuron (UMN) syndrome. This syndrome results from damage of the descending cortical-reticulospinal motor pathways at the cortical, brainstem, or spinal cord level. Causes include a lack of oxygen flow to the brain before, during, or after birth (cerebral palsy), an acquired brain lesion or spinal cord lesion, ischemic or hemorrhagic stroke, and multiple sclerosis.

Although the incidence of spasticity is not known with certainty, it likely affects over 12 million people worldwide.[1] Of people with multiple sclerosis, more than 85% have at least mild spasticity, and 35% have moderate to severe spasticity that frequently modifies their activities.[2] In the post-stroke population, 38% to 60% of individuals encounter spasticity one year after a stroke.[3-6] Furthermore, approximately 75% of patients who survive a traumatic brain lesion,[7] up to 78% of patients with a traumatic spinal cord lesion,[8,9] and 77 to 89% of individuals with cerebral palsy[10-12] eventually experience spasticity.

After the onset of UMN syndrome, spasticity does not develop immediately but evolves over the course of days, weeks, or even months.[13] The syndrome is then characterized by paresis, increased muscle tone, spasticity (Fig.1,2) and in patients with a spinal cord lesion on T6 or higher levels (Fig. 1)[14-18] or an acquired brain lesion[19-21] by episodic attacks of sympathetic hyperactivity ("sympathetic storm").

Clinical spasticity symptoms include clonus, the clasp-knife phenomenon, hyperreflexia, muscle spasms, and the Babinski sign. The symptoms may vary considerably from slight to severe hypertonia, which may lead to contractures. Spasticity may be localized to certain regions of the body, or it may even be generalized. When it is generalized, daily care

Figure 1. Severe hypertonia of upper extremities complicated by excessive perspiration as result of paroxysmal sympathetic hyperactivity after traumatic brain injury. Splints and dressing material in the hands are applied to inhibit pressure on the palm.

Figure 2. Severe hypertonia of upper and lower extremities and opisthotonos after near-drowning. Splints are applied to prevent contractures of the equinovarus position of the foot.

can be challenging, and discomfort becomes an essential part of daily life.[22,23]

Spasticity may be painful, especially if it pulls joints into abnormal positions and prevents their normal movement. Moreover, spasticity may not be present all the time; it may be related to, or worsened by, physiological and psychological triggers.[24] Pregnancy, posture, cold weather, circadian rhythm, and skin conditions have been identified as potential triggers. Patients' self-reports have suggested that bowel- and bladder-related issues, the menstrual cycle, mental stress, and tight clothing trigger also an increase in spasticity. Nonetheless, even without any trigger, the degree of spasticity can vary from day to day, and even throughout the day and night. Although spasticity can make daily care more difficult, some degree of spasticity of the lower extremities can be positive,[7] since it can help with standing upright, performing pivot transfers, or even walking, using the limb as a cane.[8,25,26]

A variety of strategies is available for the management of spasticity. In cases of mild of spasticity a watch-and-wait strategy without treatment may be more appropiate.[7] When spasticity causes pain, interferes with daily living activities or nightly sleep, leads to increasing levels of functional disability, or poses problems for care, treatment is indicated.[7] Because spasticity is a multidimensional problem, its treatment is best provided by an experienced multidisciplinary team. All treatments start with daily range-of-motion exercises.[27] The next step, in cases of insufficient response, is oral spasmolytic medication.[7,22,28,29] Although oral medication may be effective, it can, at higher dosages, cause unwanted adverse effects, such as sedation or changes in mood or cognition. For localized spasticity, botulinum toxin chemo-denervation is becoming increasingly the treatment of choice because of its effectiveness, ease of use, and low rate of adverse effects.[30,31] Generalized severe spasticity of both the upper and lower extremities can be effectively treated using intrathecal baclofen administration.

Intrathecal baclofen drug delivery

Richard Penn was the first to describe intrathecal baclofen administration (ITB) in 1984 using an implantable drug delivery system for intractable spasticity in 1984.[32] In the same year, the therapy was introduced and applied in the Netherlands. The first patient was a young woman with cervical spinal cord injury and severe spasticity caused by complications in pain treatment. Her spasticity could be controlled with a lumbar intrathecal test bolus injection of 50 µg of baclofen. For continuous ITB, we implanted a pump connected to an intrathecal catheter. Up to now, the patient has been successfully treated with ITB.

Principles of ITB

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. The chemical structure of baclofen matches the structure of this neurotransmitter and is a vigorous and selective GABA-B receptor agonist.[33,34] ITB causes receptor stimulation, leading to the presynaptic suppression of hyperreflexia, which is why it is used in spasticity treatment. Due to the blood–brain barrier,[35] oral administration leads to relatively low cerebrospinal fluid (CSF) concentrations, which makes the treatment insufficient for moderate to severe spasticity.[36] Unlike oral administration, ITB achieves high CSF levels,[35,37-39] resulting in a high concentration of baclofen in the spinal cord. The high concentration results in improved reduction of spasticity with fewer side effects than can be achieved with oral administration. The side effects of ITB administration are similar to those of oral administration, but they occur much less frequently. ITB is therefore associated with a significantly lower dose (100 times or more), a

predominantly spinal cord effect, and minimal systemic absorption.[35]

Clinical application

ITB is indicated for therapy-resistant, disabling, generalized spasticity of spinal or cerebral origin. We perform screening for eligibility at a rehabilitation center which include the evaluation of reduction of spasticity after test bolus injection (Fig. 3). First the patients receive an intrathecal test bolus injection of 50 µg by lumbar puncture. The dosage can be increased by 25 µg each day, up to a maximum of 100 µg in case of insufficient result of lower doses. Patients with a residual standing or walking function are hospitalized for one day for external intrathecal catheter insertion. Thereafter, the next step of testing performed at the rehabilitation center with an external infusion pump for continuous baclofen infusion via the indwelling intrathecal catheter. With daily dose titration, functional improvement can be determined. A patient is a candidate for ITB when the screening reveals a two-point reduction in the total scores on spasticity scales. Hospitalization (or rehospitalization) is then scheduled for the implantation of the drug delivery system, which consists of the inserted intrathecal catheter that is subcutaneously tunneled and connected to the implanted pump in a prepared abdominal pocket.

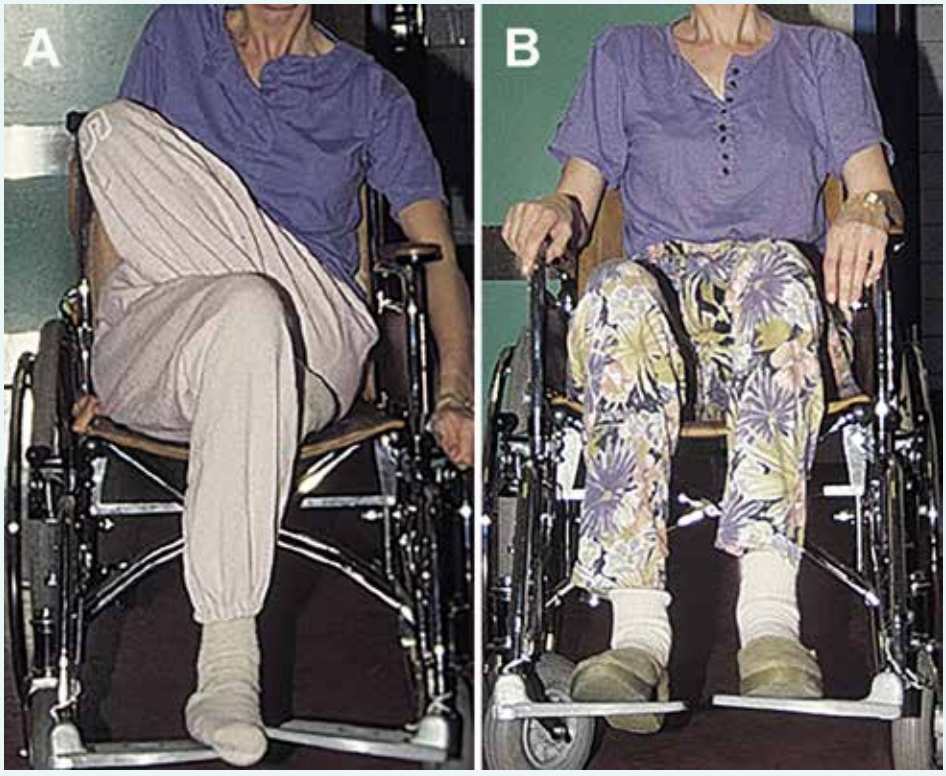

Figure 3. Severe adductor/flexor hypertonia of the lower left extremity in multiple sclerosis. Status before (A) and after (B) lumbar puncture with injection of 50 µg baclofen.

Implantable drug delivery system

In the early 1980s, a critical discussion began about the type of the implanted pump for ITB should be a constant flow pump[40-42] or a programmable pump.[37,43] Continuous drug administration with an implanted fixed-rate delivery device which does not need a battery is less expensive than a programmable system. Over time, it became apparent that optimal ITB treatment was hindered by a constant flow pump, which lacked the flexibility to alter the amount of baclofen. Programmable devices enable drug dosages to be modified without interventions such as aspiration of the pump reservoir content and refilling with a different drug concentration; such interventions are necessary with fixed-rate delivery systems. In contrast a programmable device can be controlled or deactivated when necessary, such as in case of drug delivery failure. Today, the programmable SynchroMed II peristaltic roller pump (Medtronic Inc., Minneapolis, MN, USA) is commonly used for ITB.

Currently, about 30,000 devices are yearly implanted for the relief of pain and spasticity. The battery life of the pump was initially four years, which has been increased to seven years. We use the 20 ml variant of the pump for ITB. We have implemented a limited refill period of up to three months based on the unknown stability of the pump's medication solution at body temperature. Except for a corrosion problem that could lead to a pump stall, the delivery system has proven reliable and suitable for clinical practice. The device is 3 Tesla MRI compatible without the need for emptying the reservoir. However, interrogation of the pump must be performed to ensure the pump has correctly reactivated after an MRI procedure. Occasionally, a restart is delayed for a couple of hours after exiting the MRI magnetic field. Compatibility with MRI does not mean that every ITB patient is suitable for a MRI examination. When the pump is implanted in the area under examination, substantial image distortion and artefacts make assessment of abnormalities difficult or even impossible.

Several intrathecal catheter types for the pump have been developed. Currently, two types, the 8731SC catheter and Ascenda catheter, are normally used. Since catheters remain in situ for many years, some older catheter types are currently still implanted. Problems in intrathecal drug delivery are mainly related to the catheter and include obstruction, kinking, fracture, defective pump connectors, disconnection of both catheter parts, and dislocation.[44,45] Adaptation of the surgical technique[46,47] and improved catheter materials have led to a decrease in the incidence of problems. Although the Ascenda catheter seems to have less catheter problems, its poor opacity is problematic, as this can hinder the identification of the potential cause of catheter failure.

Collaboration between a university medical center and a home-based Ambulant Care Clinic in ITB troubleshooting

ITB-treatment has a niche character and a fragmentation of the availability. We discussed with health insurance companies the possibility of concentrating care in a specific number of centers of expertise. Because we could offer a regional solution to the fragmented nature of the care currently provided for ITB the companies agreed to cooperate in the establishment of an ITB hub at Erasmus University Medical Center in close cooperation with the Rijndam Volwassenen Revalidatie rehabilitation center and the home-based Ambulant Care Clinic Care4homecare. This approach represents a solution to the logistical requirements in patient selection, the implantation of a drug delivery system, and ITB aftercare.

For adequate troubleshooting, around-the-clock availability of expertise for patient relief, pump analysis and programming expertise, the

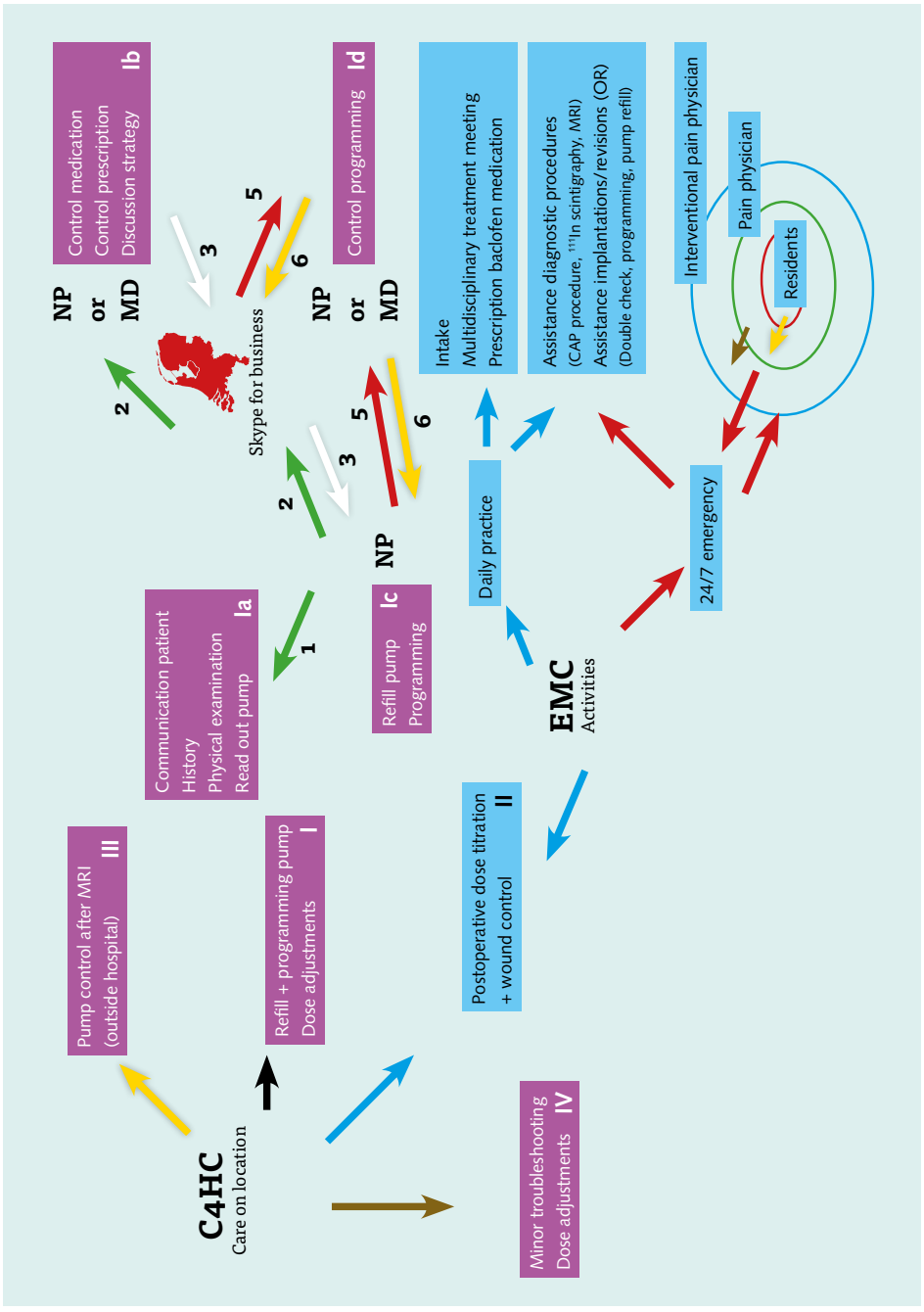

Figure 4. Activities of the nurse practitioners.

ability to "double-check" highly concentrated medication and pump programming, advanced radiological diagnostics, and an operating room and intensive care are required. However, in particular, achieving 24-hour availability for such a "double-check" service would not be straightforward. Therefore, in order to offer around-the-clock care, we decided to collaborate with the home-based Ambulant Care Clinic (Fig. 4). This decision was based on the extensive experience of the Clinic's nurse practitioners of the handling of drug delivery devices. Due to the aftercare activities that they provide for the more than 400 patients who have implanted pumps, the staff of the Ambulant Care Clinic has unique experience in ITB pump handling. For this reason, we decided to arrange partial employment at the Erasmus University Medical Center for the Clinic's nurse practitioners. These nurse practitioners can thus support the daily practice of patient treatment. In addition, they can contribute to satisfying the logistical need for the around-the-clock availability of experienced troubleshooting physicians by providing the constant on-call support of skilled ITB nurse practitioners required for double-checking medication and pumps. The double-check is crucial not only for guaranteeing the standard "five rights"[48] (the right person, right drug, right dose, right route of administration, and right time) but also for managing the complex pump programming.

Previous studies

In 1984 a longitudinal clinical ITB program was started to implement ITB as an optimal treatment that would be immediately accessible to all patients who needed it. The primary goal was to improve the quality of life of patients with spasticity. Before the start of this ITB program, we were already focused on the intrathecal administration of opioids[49-54] for chronic and tumor-related pain. Experience with different pump devices for pain treatment gave us the opportunity to develop clinical experience with ITB quickly.

The initiated ITB studies focused on clinical efficacy,[44,55] measurement of the severity of spasticity using surface electromyography,[56] urological aspects,[57] dystonia,[58] a Seldinger technique for subarachnoid catheterization,[59] ^{111}Indium-DTPA scintigraphy,[60] side effects, and complications.[44,55] Furthermore, we explored ways to receive reimbursement, reduce barriers to patients obtaining the treatment, and motivate stakeholders to support the therapy.

Since the first publication of Penn, many studies on ITB have reported striking results.[22,44,55,61-70] Despite these reports, a high complication rate including drug delivery failure and an insufficient workup and infrastructure for problem solving remained.[44,45,71-75] In addition, we still encounter a substantial undertreatment and a delayed initiation of ITB.[2,36] Multiple factors play a role. Physicians are not aware about the beneficial effects of ITB treatment. ITB treatment has a limited availability due to the complexity of workup and treatment with complicated pump-related features (communication with the pump; controlling, refilling, and programming the dose; the infusion rate; and bridge bolus adjustments). ITB is a time-consuming treatment requiring long-term aftercare, which also includes burdensome wheelchair taxi or ambulance transportation to the hospital for pump refills and dose-adaptations. ITB treatment results in additional costs for patients and accompanying (in)formal caregivers. The treatment is also accompanied by device related problems, in particular the spinal catheter, and 24-hour troubleshooting capacity is needed.

The above mentioned issues are the main reason for the studies in this thesis, aiming to improve ITB aftercare, the diagnosis of ITB related complications and treatment of ITB treatment failure.

Current studies

Improvement of ITB aftercare

It is not easy to achieve the goal of providing ITB treatment to all patients with spasticity who could benefit from this invasive treatment. One of the barriers is the long-term follow-up of ITB which has only been provided by hospitals or neuromodulation centers. However, aftercare including transport to the hospital or neuromodulation center is often a burden for severely handicapped patients which has been a reason for not seeking therapy. This problem could be substantially mitigated by performing aftercare with a dedicated team in the patients' own setting by using telemedicine for real-time communication with the expert center for consultation and remote control on delivery of medication. Therefore, we initiated a program for the development and evaluation of a home-based Ambulant Care Clinic (Care-4homecare). The aim was to provide high-level standard care in close cooperation with neuromodulation centers, whereby the treatment is performed by ITB-trained nurse practitioners, supervised by medical specialists who were on call around the clock. With this approach, ITB becomes more available and affordable for patients with severe spasticity. The first step in the development of the Ambulant Care Clinic was to acquire official recognition In the Netherlands for the clinic by the Ministry of Health, Wellbeing, and Sport. After the obtained approval, the next step was to obtain financial support for the demonstration of quality and safety of the approach.

Diagnosis and treatment of ITB failure

For adequate ITB troubleshooting, the following requirements are needed: around-the-clock availability of professionals with expertise in pump analysis, and pump programming, advanced radiological diagnostics, an operating room and intensive care. The implementation of optimal troubleshooting is a complex issue.[76] I witnessed that for ITB troubleshooting the diagnostic procedures were too limited or performed too late, and that surgical interventions were frequently conducted without, or with limited, diagnostic procedures.[62,70,71] I was also concerned that the consequences of the sudden termination of ITB treatment, which can be life-threatening, sometimes seemed to be unrecognized or underestimated.[72,73] For this reasons we organized a 24-hours optimized structure for ITB troubleshooting in the Erasmus MC, University Medical Center Rotterdam. In this thesis, I report on the studies on improvement of the diagnostic procedures and initiation of some specific treatments.

More precisely, the specific objectives of the thesis are:

- to evaluate the safety and efficiency of a home-based ambulant clinic for aftercare (Chapter 2),
- to describe the various causes of ITB failure (Chapter 3,6,7),
- to assess the role of radiological and nuclear imaging techniques in identifying the cause of ITB failure (Chapter 3,5,6),
- to investigate the optimization of radiological and nuclear imaging techniques (Chapter 3-5),
- to investigate the role of low-dose single-energy computed tomography (CT) as a replacement for plain radiography (Chapter 4,5,7),
- to evaluate the appropriateness of cerebrospinal fluid (CSF) flow restoration in case of spinal canal obstruction (Chapter 8),
- to report about emergency ITB treatment in severe, intractable autonomic dysreflexia as a result of an ITB withdrawal syndrome (Chapter 9).

Outline of this thesis

This thesis is divided into 11 chapters. After the introduction and the aim of the study in Chap-

ter 1, Chapter 2 describes the development and evaluation of a home-based Ambulant Care Clinic for ITB aftercare on location. Chapter 3 is dealing with the analysis of plain radiography in intrathecal drug delivery failures. Chapter 4 reports the result of a pilot study for a routine replacement of plain radiography by low-dose single-energy CT. Chapter 5 describes the results of catheter access port (CT) myelography in intrathecal drug delivery failures in a large patient group. Chapter 6 describes the results of ^{111}Indium diethylene-triamine-penta-acid-(DTPA) scintigraphy in a large patient group. Chapter 7 gives an overview of complications associated with intrathecal drug delivery systems. Chapter 8 reports a preliminary case series on the restoration of rostral cerebrospinal fluid flow to solve treatment failure caused by an obstruction in long-term ITB. Chapter 9 outlines a case report of ITB as emergency treatment in severe, intractable autonomic dysreflexia in cervical spinal cord injury. In Chapter 10 the results of the previous studies are discussed.

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2.

Efficiency and safety of aftercare with intrathecal baclofen on location

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ABSTRACT

Objectives

Patients with intractable spasticity treated with intrathecal baclofen (ITB) need regular evaluation and aftercare in an outpatient clinic or pain clinic setting. Logistically, this can be challenging. A solution could be to perform treatment at the patient's home setting. In the Netherlands, a project of the Dutch Healthcare Authority was initiated to deliver ambulatory ITB-related services via a home-based Ambulant Care Clinic. This aftercare is performed by nurse practitioners (NP) with support from a medical specialist. The scope of the study was to investigate the efficiency and safety of ITB-care for patients with severe disabling spasticity in their home setting.

Materials and Methods

A retrospective analysis of prospectively collected data; Patients with congenital or acquired spasticity were treated with ITB (1st April 2011 to January 1st, 2016) using an implanted programmable pump system were referred to the home-based Ambulant Care Clinic by various neuromodulation centers in the Netherlands. All study parameters were part of the standard intake and follow-up documentation.

Results

Of the 900 patients treated with ITB in the Netherlands, 239 were referred to the home-based Ambulant Care Clinic and included in this study. Mean age was 45.5 (range 7-82) years; 52% lived at home; the average satisfaction score was 9 (scale 0-10); and 0.29% had (serious) adverse events (60% of clinical manifestations were prevented by remote double-check control). Certifications for patient safety and quality standards were obtained.

Conclusion

The concept of ITB aftercare on location demonstrated efficacy and safety in the described setting. For trouble-shooting, close collaboration with a neuromodulation center is necessary and can be arranged in chain-based care.

Introduction

It has been shown that the administration of intrathecal baclofen (ITB) via an implantable drug delivery system provides a reduction of intractable severe spasticity. Regarding long-term use only data from observational studies are available; these studies showed secondary benefits including fewer side-effects, improvement in activities of daily living, less sleep disturbance, and fewer care needs.[1-9]

Until now, long-term follow-up of ITB has only been performed in a hospital setting. However, this is often inconvenient for severely immobilized patients and sometimes makes it impossible to provide therapy. Despite the advantages of ITB therapy, this inconvenience may be one of the reasons for the substantial under-treatment and/or an often 'too late' initiation of ITB.[5] These problems might be reduced by performing ITB aftercare in the patient's own surroundings (e.g. at home, in a nursing home or in disabled community). Therefore, we developed a home-based Ambulant Care Clinic to provide high-level standard care in a close cooperation with some of the neuromodulation centers.

We obtained recognition as a home-based Ambulant Care Clinic of the Ministry of Health, Wellbeing and Sport. For the provision of home based specialized medical care, no regular fi-

nancial reimbursement was available. However, since the Ministry offers financial support for new projects to stimulate innovations in healthcare, our 'home-based Ambulatory Care Clinic Neuromodulation' activity was accepted as an innovation project. One of the requirements for approval of this project was the demonstration of quality and safety.

Materials and Methods

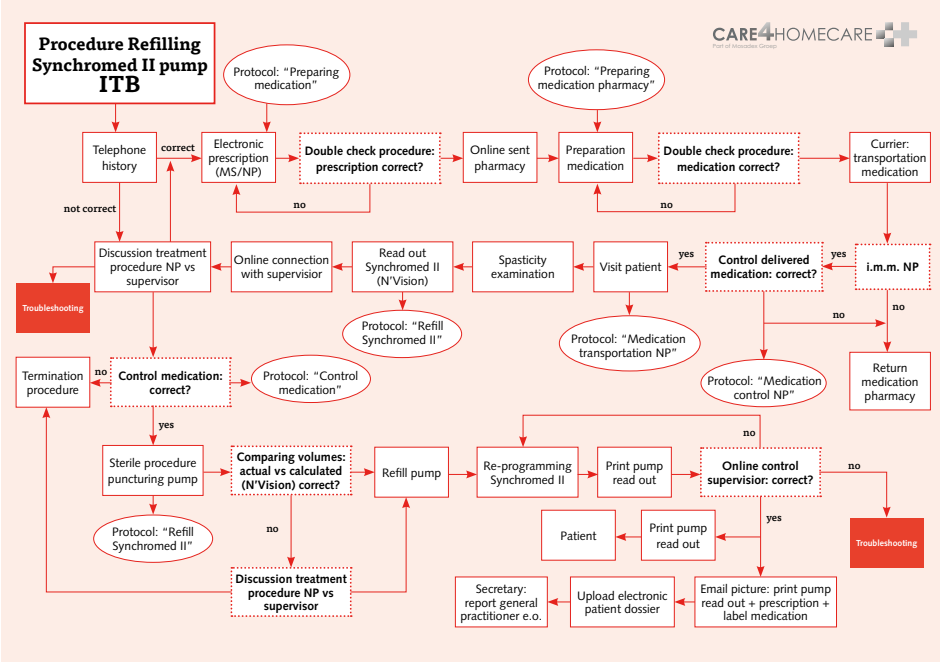
We performed a retrospective analysis of prospectively collected data, investigating the efficacy and safety of delivery of home based ITB aftercare in the period of 1st April 2011 to January1st, 2016.

The study was approved by the local Medical Ethical committee (2018-1221). After referral to the home-based Ambulant Care Clinic patients gave consent for the treatment at the initial visit. Due to the retrospective character of the study the local Medical Ethical Committee waived away the requirement to obtain informed consent.

Only patients with severe disabling spasticity were eligible, and these were treated with ITB using an implanted programmable pump system (SynchroMed II, Medtronic Inc., Minneapolis, USA) and referred to the home-based Ambulant Care Clinic by neuromodulation centers. Patients had to have achieved a stabilized dose for at least three months before their referral.

After referral for aftercare, there followed an initial visit from a specialized physician and nurse practitioner (NP). During the visit the ITB aftercare on location concept was explained, and informed consent and medical history were obtained, followed by a physical examination and a read-out of the pump settings.

In addition to this, in the first three years for the initial visit we used a standard questionnaire where patients were asked about the burden of traveling to the center for their ITB aftercare. At the following visits we gathered information and entered it in the electronic patient file including the reason for the visit, performed



activity, printouts of the programming pump, any (serious) adverse events, complaints, annual patient satisfaction scores, and travel time/distance to the center. We recorded the number of pump refill visits during the study period, as well as the additional visits for dose adjustments.

Via an annually applied anonymous questionnaire, patients provided their feedback on the ITB management service and their satisfaction level with the service. In case of official complaints, we started a complaints procedure.

In our setting we have chosen to work with NP's (NP: Master's Degree in Advanced Nursing Practice). In our country, NP's are allowed to perform medical tasks independently. They are obliged to follow training every year. A re-registration will follow after 5 years only if all of the training requirements have been met. In the first 3 months working with ITB, the NP's are trained on the job by a medical specialist and an experienced nurse practitioner and work on an observer basis. During the next year they receive intensive supervision. In addition, weekly multidisciplinary patient meetings and 3 monthly intervision sessions are held. During their work, the NP's are supervised by a medical specialist or a (colleague) NP. The team is available on call 24/7. For percutaneous pump refills, patients were visited at least every 90 days as well as, if necessary, for dose adjustments and/or troubleshooting. We performed visits at the patient's home, a nursing home, a community for disabled persons, or (in case of a temporary stay) in the rehabilitation center or hospital.

One week before the appointment, a NP prepared the visit. The NP prescribed a baclofen solution and (after being checked by a second nurse practitioner or medical supervisor) and digitally sent the prescription to the pharmacy. After receiving the medication, the NP checked the prescription and medication label and stored the medication at room temperature. Two to three days before the visit, the NP telephoned the patient or caregiver to enquire about the clinical status of the patient; if this was not stable, the condition was discussed with the medical supervisor. On location, the NP made a brief note of medical history (focusing on spasticity treatment), performed a physical examination, and used telemedicine (encrypted bi-directional video connection via the 3G or 4G-broadband, Cisco Jabber Video Telepresence software version 4.7, Visions Connected, Amsterdam, The Netherlands). The screen-to-screen connection gives the supervisor and another NP or medical specialist access to communicate with the patient and the NP on location, as well as remote visual control of the prescription and the syringe label. After this, the connection was terminated, and the NP performed the refill and/or dose adjustments and programming procedures. After refilling the pump under aseptic conditions, the NP made another telemedicine application for remote visual control of the pump programming printout. If the supervisor observed an error in programming an immediate correction was made. Occasionally we video-recorded the procedure either at the request of a physician or for training purposes. The NP documented the results in the electronic patient file. The patient received a printout of the pump programming session. Finally, the NP sent a consultation letter to the patient's physician(s). If requested, a brief consultation letter was left behind after the visit.

The equipment included a synthetic, washable three-compartment trolley, separating sterile and non-sterile material, a box for medication storage during transport, a pump programmer (N'Vision, Medtronic, Minneapolis, USA), a mobile printer, a laptop and a mobile telephone. The small laptop computer had an integrated camera and a built-in dongle device allowing wireless broadband access. Also, the supervisor (based at the headquarters of the ambulant clinic) was provided with a computer with identical features.

Data records

For safety management, we followed the Dutch Technical Agreement 8009 'Safety management system for hospitals and organizations which administer hospital care. This embeds patient safety in healthcare practices. It enables risk identification, the implementation of improvements and evaluations, and modification of policies. It also includes the '5 rights', i.e. the "right patient, right action, right time, right cues, right reason".[10] The team adhered to these rights: i.e. used the appropriate concentration of medication and the appropriate pump programming. Throughout the study all (serious) adverse events (S)AE) were recorded at each visit and discussed at our 6-weekly multidisciplinary team progress meetings. A subheading was made of the (S) AE that occurred due to surgery, as well as hospital-related and long-term related complications.

All visits, telephone calls and patient consultations were reported in an electronic patient dossier, including the referral letter, physical examination, treatment, medication and printouts of the pump programming.

For prospective and retrospective risk management of near-incidents we applied the 'Healthcare Failure Mode and Effect Analysis' (HFMEA) of the 'National Center for Patient Safety' (NCPS).[12] In case of a high risk of frequency and severity of consequences we made an extensive PRISMA Medical analysis (Prevention Recovery Information System for Monitoring and Analysis)[11] to manage structural human errors in practice.

External audits

A quality and safety certification procedure were performed annually by an independent professional inspection institute (KIWA, Rijswijk, the Netherlands). The certificate demonstrates that the home-based Ambulant Care Clinic met the necessary requirements for efficient and safe management and verifies that the related processes were correctly performed, and, in a way, which enables the clinic to be sustainable. For the audit, the home-based Ambulant Care Clinic had to describe all protocols and procedure descriptions together with descriptive flow charts. The hygiene audit process included a 'spot check' whereby the NP (upon patient's consent) was accompanied and observed by a hygiene auditor. As part of the annual audit, the supervising pharmacist carried out an assessment of medication delivery and transportation.

From 1st April 2011 to 1st January 2016, 239 patients of the current total population of 900 patients were referred to the home-based Ambulant Care Clinic. Table I presents the demographic and baseline characteristics. Multiple sclerosis (MS), cerebral palsy (CP) and spinal cord injury (SCI) were the most frequently reported etiologies of spasticity.

At the start of the homed-based Ambulatory Care Clinic, nine hospitals in the Netherlands were treating patients with ITB. In addition to the hospitals, there were also satellite centers, e.g. rehabilitation centers refilling and/or making dose adjustments. The majority of patients live at home: 28% live in a nursing home and 20.1% live in a community for disabled persons.

Communications

At the start of the study, 3G broadband was used for online videoconferencing. From 2014 onwards, 4G broadband was available and used. In the 3G broadband era, on 5 occasions the connection was insufficient to establish a video feed. Three patients allowed the use of their own WiFi; for two patients the only solution for control was a real-time telephone call. At the end of 2014, the telecommunication provider (KPN) delivered coverage to 98.4% of the inhabitants and 96% surface coverage

Results

Disease	MS	SCI	Stroke	CP	CRPS	Other spinal	Other cerebral	Total
Male	26	31	7	44	0	8	18	134
Female	49	7	8	26	7	1	7	105
	75	38	15	70	7	9	25	239
Age (years)								
Mean	54.1	55.7	55,.	29.6	55.3	61.5	34.4	45.58
Range	(29-82)	(22-81)	(36-75)	(8-70)	(35-66)	(42-82)	(7-74)	(7-82)

Table I. Demographic and baseline characteristics of the aftercare population (n=239).

throughout the Netherlands. Since then, very few connection problems have been encountered.

Feasibility

During the first three years, 143 patients referred to the home-based Ambulant Care Clinic were asked about the burden of travelling (Fig. I). Of these, 104 were able to answer the questionnaire themselves; their mean score was 5.7 (out of 10, where a score of 10 indicates the highest burden); and 47 patients scored 7 or higher. Of the 39 patients who were unable to answer the questions themselves, their caregivers answered the question on burden of traveling with a mean score of 6.4 (Fig. II). Data was missing for 8 patients.

Patients were also asked: 'If traveling is a burden, what kind of negative effect does it have: lack of energy, fatigue, increase of spasticity, increase of pain, or something else, please describe' (Fig. III).

Although 11 patients scored 1 for burden of traveling, all patients experienced one or more negative consequences. Most patients experienced a lack of energy: 67% of the patients who answered themselves, and 64% of those whose caregivers gave the answers on their behalf (Fig. IV).

Satisfaction

Patients and caregivers were positive about/satisfied with the ITB on location. All patients reported increased convenience from home-based Ambulant Care Clinic when compared to standard aftercare by visiting a medical center.

Safety evaluation

From a total of 6,807 procedures, 11 AE's and 9 SAE's were registered. In one patient, a low reservoir alarm created discomfort, but no harm. The wound management was adjusted because of postoperative deviant wound edges. After replacement of the pump, hematoma was reported post-operatively. One patient called in during duty hours with increased spasticity; earlier that day the patient had undergone an access-port procedure in the hospital. Investigation showed that, prior to discharge, the priming bolus had been omitted. We discussed the AE with the staff of the hospital and an adaptation was made in the work process to prevent this in future.

On two occasions, patients developed signs of underdosage (a mild increase of spasticity and

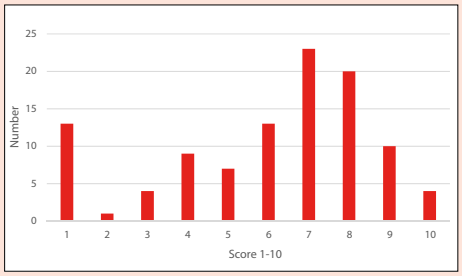


Figure I. Burden of traveling, patient. N=104.

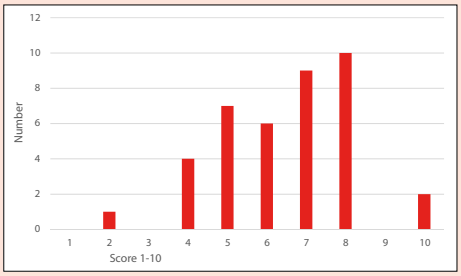


Figure II. Answer on burden of traveling for patients. N=39.

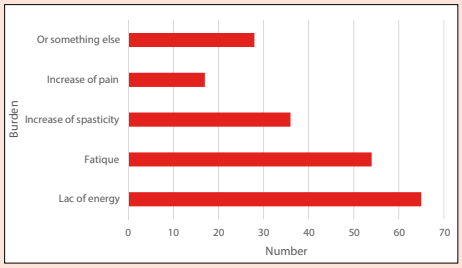


Figure III. Consequences of traveling, patients. N=104.

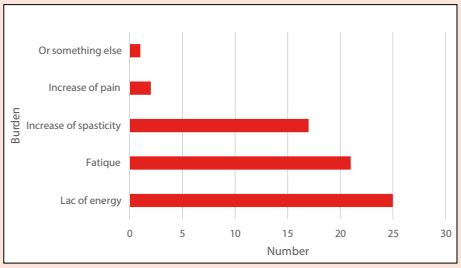


Figure IV. Caregivers' answer consequences on burden of traveling for patients. N=39.

some sweating) between the refill intervals. Our protocol for this situation involves aspiration of the reservoir content. In both instances an empty reservoir was found, probably due to an inadvertent pocket injection. The pump was refilled, and a reduced dose adjustment was made. Another patient was again initiated with oral baclofen, this happened after patient was relocated to another nursing home. The local geriatrician telephoned our team reporting that the patient was somnolent. Careful case history revealed double treatment and the oral baclofen was immediately discontinued.

Serious adverse events

In three other refills in obese patients the pump was emptied normally and indicated a correct needle position; however, later on it appeared that the volume was injected outside the pump. Over time dyspnea occurred (in 2 patients); in one case this was diagnosed as pneumonia and was not recognized by the patient's own geriatrician as a moderate withdrawal syndrome. Both patients were hospitalized, and both recovered fully after refilling the pump and dose adjustment. In one patient there was an increased discrepancy between the calculated and the actual volume of the pump reservoir; this patient was referred to hospital and the pump was replaced. The older pump was returned to Medtronic for further investigation.

The remaining SAE's occurred during the postoperative stage of treatment, or after analysis of the patient's ITB system. Due to established collaboration with the neuromodulation centers, when the SAE occurred the first contact with the patients was via the ambulatory care clinic. The SAE's included: meningitis, withdrawal after incorrect pump programming, withdrawal after incorrect pump refilling with medication outside the pump, wound care, and liquor leakage. In one SAE, a patient received

the incorrect dosage of oral medication from a caregiver in the nursing home which led to hospitalization and temporary cessation of ITB. In total, 81 mistakes were reported. In the first year, two incidents were related to availability during duty hours; for this, an immediate adaptation was made to the method of working. Seven incidents of pump programming errors were reported; in all cases the double-check procedures prevented clinical manifestations. In two cases no order was made to prepare the syringe before the pump was refilled, which necessitated a rush order. The highest number of incidents (21) was related to appointments, in particular when dose adaptations had to be made between the normal scheduled procedures. On six occasions, erroneous archiving of patients' information in the electronic patient dossier had to be corrected. On nine occasions, incidences were reported due to delivery of the medication via the cooperative pharmacist, and five incorrect preparations were found.

HFMEA and PRISMA Medical analyses

The retrospective HFMEA analyses included improvements in; appointments, reporting delay, mistakes with patient data, and the labeling of medication syringes. As prospective subjects we performed: triage telephone call by the secretaries, transport, storage medication, on-line connections, pump refill procedure, and evaluation of the collaboration between Erasmus University Medical Center and Rehabilitation Center Rijndam adult rehabilitation population. For the PRISMA Medical analyses we included; medication preparation and transport, motor stall pump device, and refilling outside the pump.

External audits

The annual quality and safety certification procedure performed by KIWA showed no non conformances. The degree of involvement of the entire team was acknowledged. All 240 protocols and procedure descriptions (with related descriptive flow charts) were described. The audit of the hygienist and the supervising pharmacist also showed no deviations. The healthcare insurance company 'Achmea' granted a quality and safety award (Page 240).

Discussion

This study has shown the feasibility and safety of a home-based Ambulatory Care Clinic for ITB management in a domestic setting using telemedicine for real-time remote communication. Applying the concept prevents burdensome traveling to a medical center for severely handicapped patients. The importance of this was shown by the satisfaction scores. An important finding was that 51.9% of the patients were living at home, which has a considerable beneficial impact on the family's daily life. The majority of these patients received professional help for basic care. Routine aftercare in a home setting is very important, particularly since this avoids travel to an ITB center.

Telemedicine includes a growing variety of applications and services to provide equal access to medical support, irrespective of geographic circumstances.[12] This term covers our activities, and implies a more specific application using interactive video communication[13]. The present study was performed in a small country with relatively short travel distances. In less densely populated countries with greater travel distances the related problems might be more extensive.

In our study a lower incidence of complications was observed than in the subject literature. Whether there is a specific relationship between the treatment in the hospital or at home was not part of the scope of our study, so that we can not comment on the matter.

Our concept could help to optimize the quality of life of patients who suffer severely. This was demonstrated by the extended growth of the test population; we performed aftercare in ≥ 25% of the entire ITB population in the Neth-

erlands. The prevention of substantial adverse events demonstrated the value of the double-check procedures. We agree with Bradford et al.[14] that providing care at home should not involve a reduction of standards, implying that the double check should be included. The feasibility of the use of a laptop computer or tablet[14] to conduct double-checks using an e-health technique has been demonstrated without contravention of the existing standards. We found that obesity played an important role in the three adverse events during pump refill.[15] Finding the small refill membrane and the risk of needle dislocation during syringe changes are important parts of the process. Particularly in a 40-ml pump, a change of syringe could result in an (unrecognized) injection outside the pump. Good collaboration in case of troubleshooting with a medical center is indispensable. Direct referral of patients in case of problems is also very important. On the other hand, it is important that the patient stays as briefly as possible in a medical center; aftercare in their own surroundings is guaranteed by a home-based Ambulatory Care Clinic. Although time consuming, during a process of continuous improvement of treatment, the Ambulatory Care Clinic recognized that the HFMEA and the extended PRISMA Medical analyses should be conducted in routine practice.

A limitation of our study is that due to its retrospective character, we were not able to make a comparison of the adverse event data of the home-based ambulatory clinic with hospital-based data. This might have created a stronger argument that the home-based ambulatory group can be treated as safely as the hospital-based group. The problem is that the hospital-based patients are treated in different hospitals, and unfortunately, we do not possess the relevant data. Further research into this is therefore recommended.

Conclusions

The concept of home-based Ambulatory Care Clinic has clearly shown its feasibility and safety and can prevent a patient's burdensome traveling to a medical center for pump refills and dose adjustments. The encrypted bi-directional videoconferencing with 4G connection has proven its reliability and enabled communication with patients, and the performance of double checks on medication and procedures. Close cooperation with a neuromodulation center in case of problems is indispensable and can be arranged in chain-based care. In this way clinical standards can be preserved for complex treatment. The method can be valuable for application elsewhere, particularly in countries with long traveling distances between care centers. The Dutch Healthcare Authorities are convinced about the research results and have included ITB-aftercare, performed by a home-based Ambulatory Care Clinic, as a fixed component in healthcare with associated reimbursement structure.

Comments

The authors describe an interesting model for ITB follow-up care in a home-based setting, decreasing the burden for disabled patients who would otherwise have to travel long distances to a center. The program, implemented by medically-supervised nurse practitioners, demonstrated good outcomes and high patient satisfaction. It is a model that could be replicated in many settings.

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*****

This is a very exciting study proving the safety and efficiency of utilizing NPs in the role of routine pump management in the outpatient/ home setting.

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Boston, MA, USA

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The manuscript in the discussion and conclusion should reinforce that ITB is a safe therapy - the incidence of issues for all of the patient contacts are quite low – this would be helpful in debunking the "danger" of ITB and further addressing barriers to care and implementation (at home, can't travel, too many complications of ITB, if can't travel to office then more likely to have complications regarding management) – so many issues can be added in discussion to highlight safety, ability to refill or manage not in office but remotely.... access and awareness of efficacy and safety is key - this will help with that treatment barrier.

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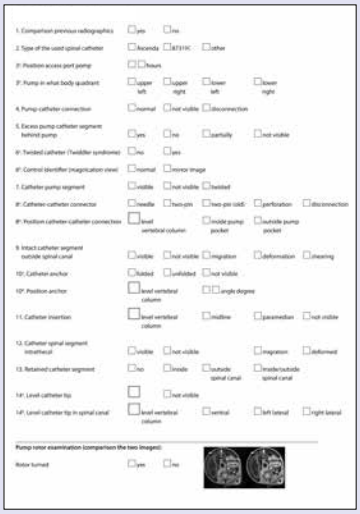
3

Plain radiography in patients treated with intrathecal drug delivery using an implantable pump device



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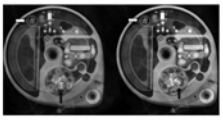
1. Comparison previous radiographics	☐ yes	☐ no			
2. Type of the used spinal catheter	☐ Ascenda	☐ 8731SC	☐ other		
3[a]. Position access port pomp	☐☐ hours				
3[b]. Pump in what body quadrant	☐ upper left	☐ upper right	☐ lower left	☐ lower right	
4. Pump-catheter connection	☐ normal	☐ not visible	☐ disconnection		
5. Excess pump catheter segment behind pump	☐ yes	☐ no	☐ partially	☐ not visible	
6[a]. Twisted catheter (Twiddler syndrome)	☐ no	☐ yes			
6[b]. Control identifier (magnication view)	☐ normal	☐ mirror image			
7. Catheter pump segment	☐ visible	☐ not visible	☐ twisted		
8[a]. Catheter-catheter connector	☐ needle	☐ two-pin	☐ two-pin (old)	☐ perforation	☐ disconnection
8[b]. Position catheter-catheter connection	☐ level vertebral column		☐ inside pump pocket	☐ outside pump pocket	
9. Intact catheter segment outside spinal canal	☐ visible	☐ not visible	☐ migration	☐ deformation	☐ shearing
10[a]. Catheter anchor	☐ folded	☐ unfolded	☐ not visible		
10[b]. Position anchor	☐ level vertebral column		☐☐ angle degree		
11. Catheter insertion	☐ level vertebral column		☐ midline	☐ paramedian	☐ not visible
12. Catheter spinal segment intrathecal	☐ visible	☐ not visible		☐ migration	☐ deformed
13. Retained catheter segment	☐ no	☐ inside	☐ outside spinal canal	☐ inside/outside spinal canal	
14[a]. Level catheter tip	☐	☐ not visible			
14[b]. Level catheter tip in spinal canal	☐ level vertebral column		☐ ventral	☐ left lateral	☐ right lateral

Pump rotor examination (comparison the two images):

Rotor turned ☐ yes ☐ no



Plain radiography image report.

ABSTRACT

Objectives

Intrathecal drug administration using an implanted pump system is well established in intractable spasticity and pain. However, despite continuous advancements in manufacturing technology, adverse events related to the pump and catheter still occur. Most of them, such as migration, damage, disconnection and occlusion, are related to the spinal catheter. The aim of this overview is to update radiologists on how plain radiography of the implanted delivery system for intrathecal drug administration should be interpreted and to increase awareness for the need of urgent and timely multidisciplinary troubleshooting.

Methods

Plain radiographic images of patients treated with intrathecal drug administration using an implantable drug delivery system were analyzed in a multidisciplinary setting at our (university) referral center for complications in intrathecal drug administration.

Results

Examples of catheter-related adverse events are described and a proposal is made for stepwise interpretation of standard plain radiographic images.

Conclusion

Plain radiological images are the mainstay for the diagnosis of catheter-related adverse events in intrathecal drug delivery. Radiologists play an important role in an early diagnosis. An awareness of abnormal radiological findings seems important to avoid a life-threatening withdrawal syndrome.

Keywords

Radiography, diagnostic imaging, spinal infusions, implantable infusion pumps, adverse events.

Teaching points

- Untimely cessation of intrathecal drug delivery can lead to a life-threating withdrawal syndrome.
- Initially mild symptoms can lead to an exacerbation of a withdrawal syndrome.
- Most intrathecal catheter-related problems are visible on plain radiography.
- Common causes of catheter problems are migration, lacerations, occlusion and disconnection.
- Knowledge on implanted intrathecal catheters is crucial for interpretation of plain radiography.

Introduction

For over 30 years intrathecal drug delivery systems have been successfully applied in thousands of patients for the management of spasticity[1,2] and dystonia (both intrathecal baclofen)[3], and for chronic pain (intrathecal analgesic drugs)[4,5]. Compared with oral administration, infusion directly into the cerebrospinal fluid (CSF) has an extended treatment effect and with fewer unwanted side-effects[1,6]. There is general consensus that intrathecal therapy should be reserved for patients who have an insufficient response to more conservative therapies and/or for patients who experience serious side-effects[7].

Despite generally favorable and safe outcomes[8,9] and continuous advancements in manufacturing technology, pump and catheter-related adverse events still occur[10]. Although the benefits usually outweigh the risks[11], even limited exposure to adverse events remains a problem. Early recognition of com-

plications and their prompt management is needed.

Most of the drug delivery device-related adverse events are caused by intrathecal catheter failure[12-14]. Approximately 15-40% of patients experienced catheter complications[2,15-18]. With the new developed Ascenda catheter instead of the older silicone catheters, a tremendous reduction from 18% to 1.1% was reported by Motta[19]. The main reasons for this are migration, lacerations, occlusion, and disconnection of the catheter, which cause a sudden cessation of intrathecal drug administration. Abrupt interruption of intrathecal baclofen delivery can present within several to 48 h with a spectrum of signs and symptoms. Then, the initially mild symptoms of exacerbation of spasticity, fever, excessive sweating, and pruritus can escalate to a life-threatening multi-organ failure. During time hyperthermia develops with values up to 42˚ Celsius[20], accompanied by nausea, respiratory distress, hypotension, tachycardia, hallucinations, delirium, disorientation, psychosis, sometimes with seizures, rhabdomyolysis with increased creatinine kinase levels resulting in disseminated intravascular coagulation and a multi organ failure[21-30]. In rare cases, intrathecal baclofen withdrawal can even be fatal[31,32]. The symptoms are probably related to the release of excitatory neurotransmitters that occurs when baclofen-mediated inhibition GABA-B effect is abruptly interrupted[33-36]. The heterogeneous symptoms occurring during withdrawal of intrathecal baclofen and of intrathecal opioid treatment, may result in misdiagnosis, wrong referrals and (eventually) in a disastrous treat-

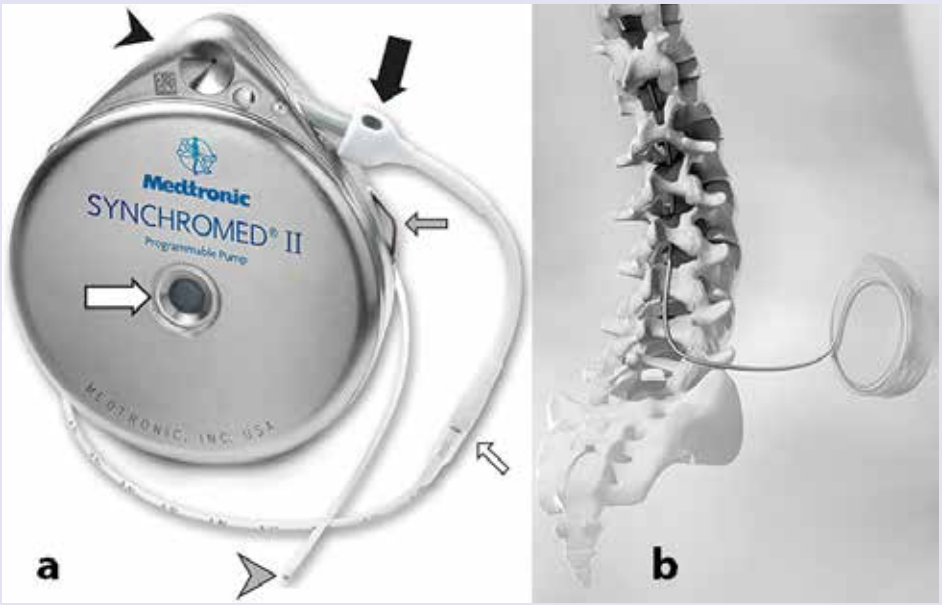


Figure 1. Implanted, programmable pump system. External view and drawing of implanted pump and intrathecal catheter 8731 ceter access port. Pump with the catheter access port (black arrow head), pump catheter connection (thick black arrow), refill membrane (thick white arrow) and suture loops for fixation (thin gray arrow), catheter-catheter segment connection (thin white arrow), titanium catheter end (gray arrow head).

	Unsutured pump-catheter connection (Ascenda, 8731SC)
	Sutured pump-catheter connection (old catheter)
	Catheter-catheter connection (Ascenda)
	Catheter-catheter connection (8731SC)
	Unfolded catheter fixation anchor (Ascenda)
	Folded catheter fixation anchor (8731SC)
	Unfolded catheter fixation anchor (8731SC)
	Titanium tip catheter

Table 1. Explanation of the symbols.

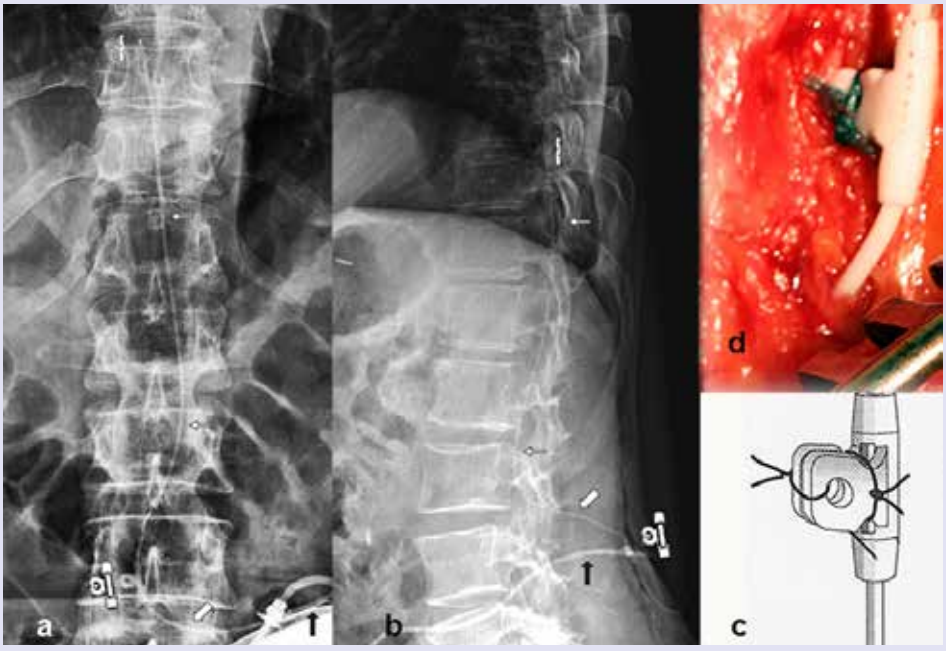


*Figure 2. Anterior-posterior (a) and lateral (b) plain radiography of the lumbar spine, in vivo image (d) and artist rendering (c) of the typical **folded** fixation anchor (with anchor symbol), large diameter catheter pump segment (black arrow), small diameter outside spinal canal (thick white arrow), and intrathecal (small white arrow, catheter end symbol) segment of the 8731SC catheter.*

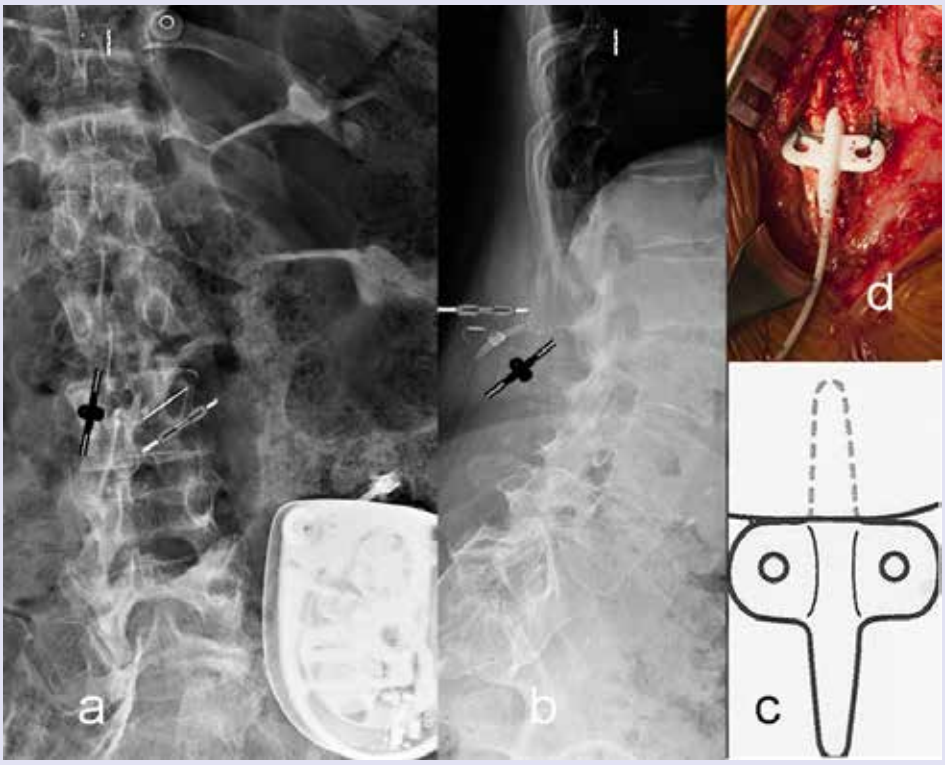


Figure 3. Anterior-posterior (a) and lateral (b) plain radiography of the lumbar spine, in vivo image (d) and artist rendering (c) of the typical unfolded fixation anchor of the Ascenda catheter. The small diameter catheter pump is hardly visible. The only reference points (3a, b) are the needle connector (needle symbol), the unfolded anchor (anchor symbol), and the titanium catheter tip (catheter end symbol).

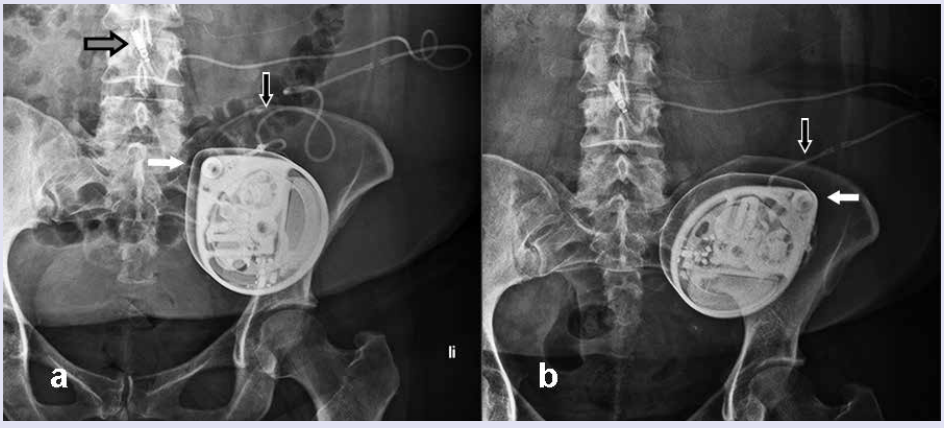


Figure 4. Reel syndrome with signs of withdrawal syndrome in a 52-year-old woman with dystonia in CRPS. The apex of the pump is turned from the 11:00 to the 02:00 o'clock position (white arrow). Because of the visible traction on the catheter (black arrow), the pump must be rotated several times about the horizontal axis.

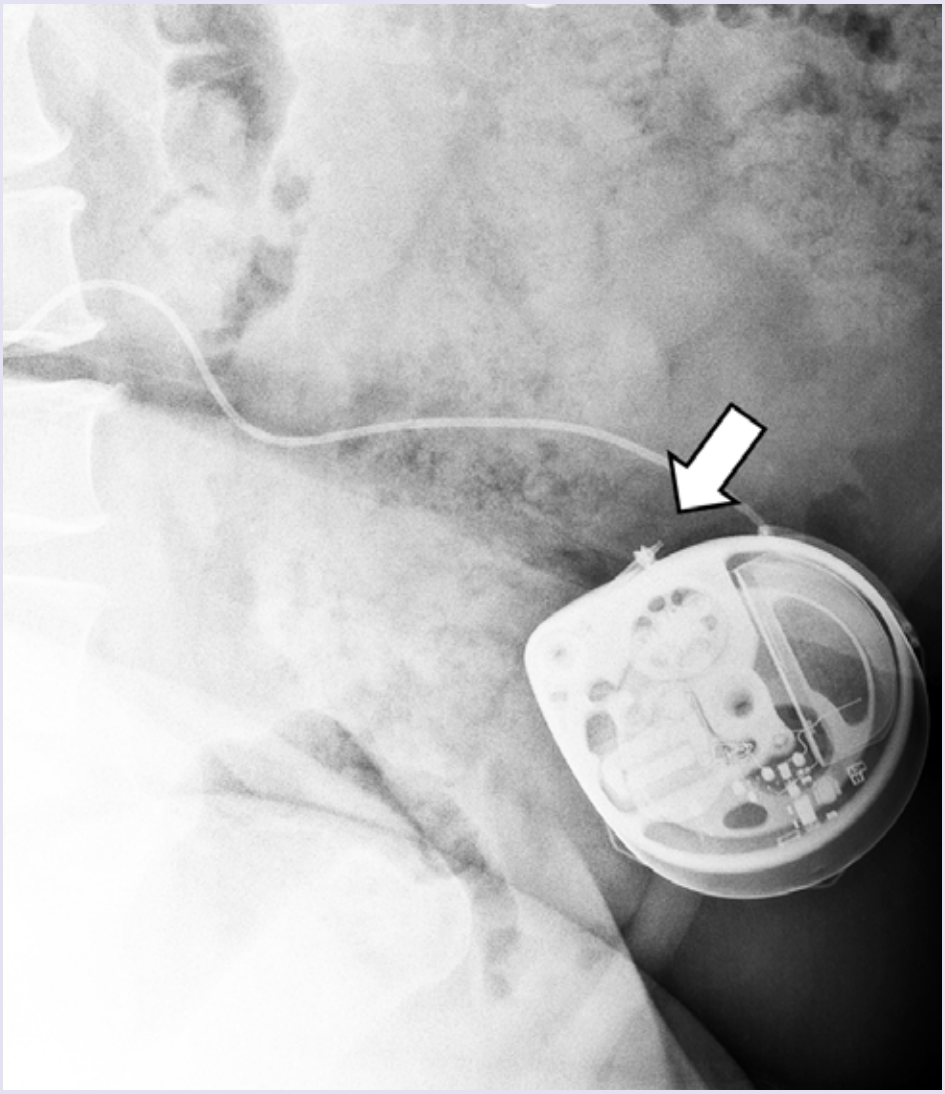


Figure 5. Disconnection at the pump-catheter site (white arrow) with signs of withdrawal syndrome in a 52-year-old woman with dystonia in complex regional pain syndrome.

ment delay. An additional problem is the referral of the patient in good time to a specialized center, which is a requisite for successful treatment[37]. Different imaging techniques, including plain radiography, fluoroscopy with contrast material injection via the access port of the pump, CT myelography, MRI and ^{111}In-dium-DTPA scintigraphy, are used to diagnose malfunction of the drug delivery system[14, 38-43]. Of all these imaging modalities, plain radiography is the most important, especially in an acute situation. Furthermore, a rigorous and adequate interpretation of the images by the radiologist is crucial to make a correct diagnosis

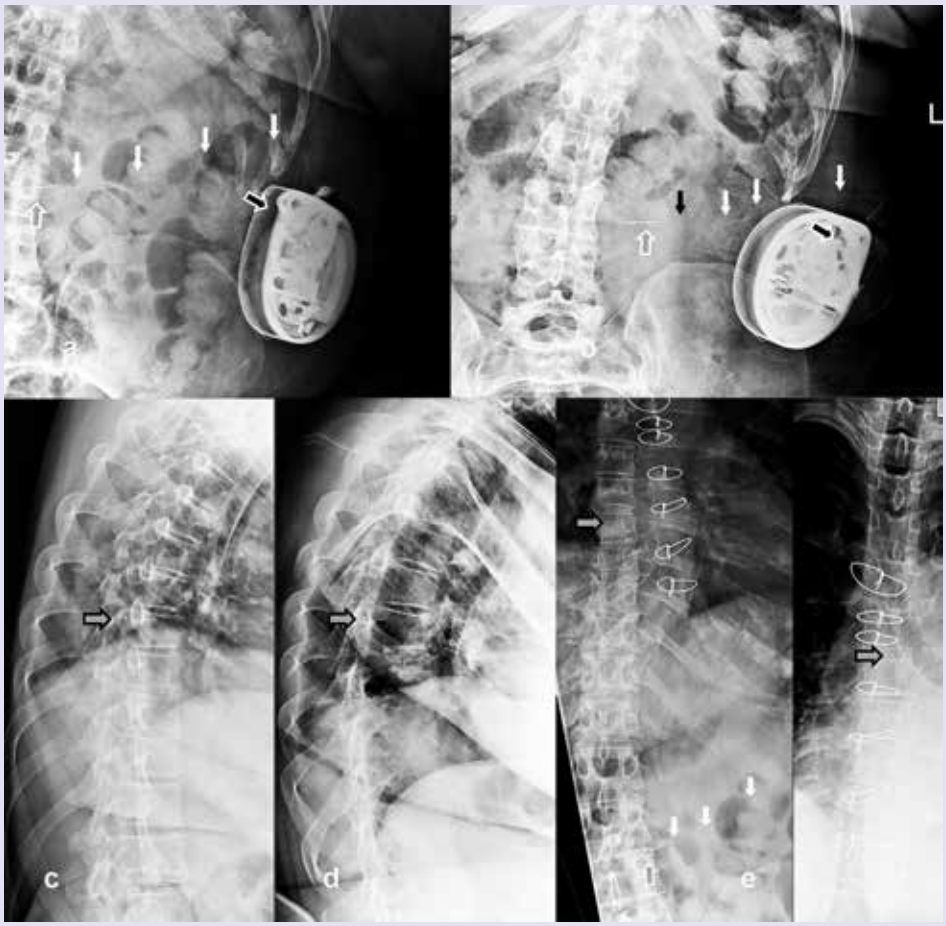


Figure 6. Reel syndrome with signs of withdrawal syndrome in a 45-year-old extremely obese woman with spasticity in multiple sclerosis. Baseline plain radiography (a, c, e) with follow-up images after 4 weeks (b, d, f). The apex of the pump is turned from the 11:00 (a) to the 02:00 (b) o'clock position (black-white arrow). The Ascenda needle connector is moved from the original position (a) to a more lateral position (b) (gray-white arrow) with disconnection of catheter pump segment (black arrow). The Ascenda catheter is hardly visible (white arrows). The tip of the catheter is unchanged (c-f) at level T8 (gray-black arrow).

and, if necessary, implement (urgent) interventions.

This overview aims to offer the radiologist a systematic approach for the evaluation of all parts of the intrathecal delivery system on plain radiography. This may help radiologists to identify causes of drug delivery failures in emergency and in chronic situations.

Materials and methods

Below we describe the most commonly used: i) intrathecal drug delivery system, ii) intrathecal catheter, and iii) surgical implantation technique.

Intrathecal drug delivery system

Although several pump systems are available, the implantable Synchromed II pump

(Medtronic, Minneapolis, USA) is by far the most rigorously tested and most applied implanted programmable device, worldwide. Here, we focus on this pump only.

The implantable Synchromed II pump and the related intrathecal catheters have received

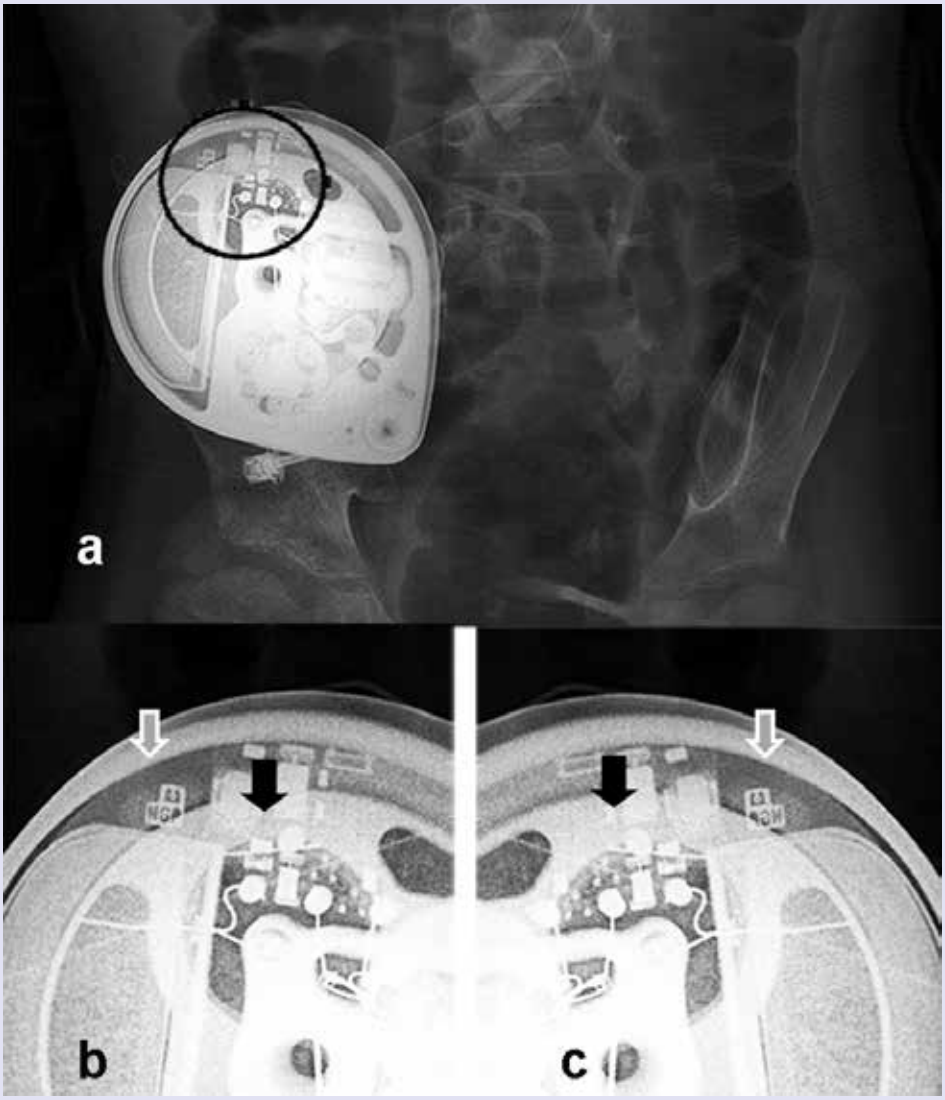


Figure 7. A magnification view of the black circle (a) shows the radiopaque pump identifier consisting of the logo of the manufacturer and three alphabetic letters (white arrow) with visible electronics (b) into the left-hand side (black arrow). For (some) odd rotations of the pump to the vertical axis (Twiddler's syndrome), the pump is located on the head, which can be recognized by the logo in mirror image, and the electronics to the right-hand side (c).

the 'Conformité Européenne' (CE) mark and are approved by the U.S. Food and Drug Administration (FDA) for treatment of pain and spasticity. During continuous intrathecal drug delivery, the prescribed medication is administered through an intrathecal catheter, connected with an implantable programmable pump system. The pump provides precise intrathecal drug delivery to patients with spasticity or chronic intractable pain. Via the refill septum, which is in the center of the device (Fig. 1a), the reservoir is filled percutaneously. The gas below the reservoir exerts pressure which advances the drug into the inner tubing of the pump. The accompanying programmer device enables the delivery rate and mode to be programmed. A rotor system pushes the programmed dose with precision through the catheter access port via the catheter into the intrathecal space.

Intrathecal catheter

Over time, several catheter types for the implantable Synchromed II pump have been developed and are commercially available. Although two types of intrathecal catheters (the 8731SC, and the Ascenda) are currently available, older types are still in use. Determining the type of implanted catheter via plain radiography is important for correct interpretation.

The 8731SC catheter is **normally visible** on plain radiography (Fig. 2). The pump-catheter connection is sutureless and the two segments of the catheter have a different diameter, i.e. the pump segment of the catheter has a larger outer diameter than the spinal segment. Furthermore, the 8731SC catheter is provided with a two-pin catheter-catheter connector, a **folded V-wing anchor** which is fixed on the fascia, and has a catheter-end with six side holes and a round titanium tip. The folded V-wing in the 8731SC catheter locks the catheter in place (Fig. 2cd) and is, therefore, important for the diagnosis of catheter disorders. A partially or completely unfolded anchor (see Fig. 9) creates a major risk for dislodgement, potentially leading to a complete migration.

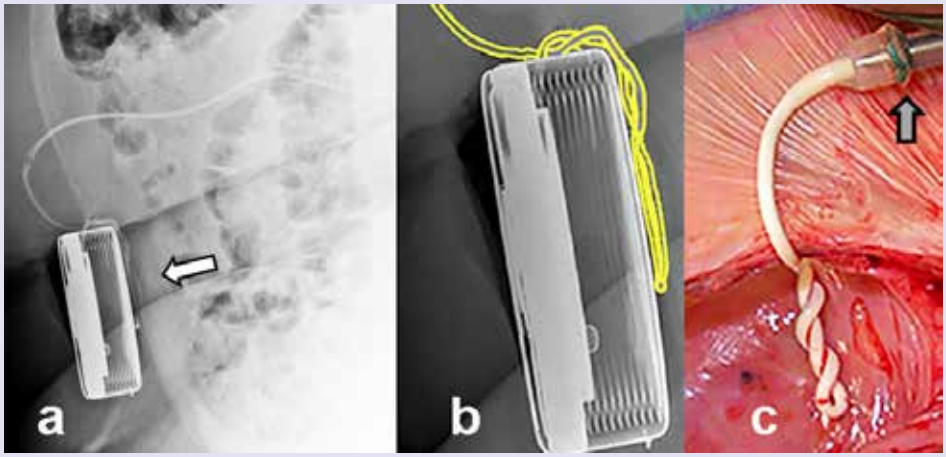


Figure 8. Twiddler's syndrome with signs of withdrawal syndrome in a 51-year-old woman with dystonia in complex regional pain syndrome. A repeatedly twisted old type catheter is visible on lateral plain radiography behind the implanted pump (white arrow) (a), magnification of the pump with artist rendering (b) and an in-vivo image (c). The catheter is fixed to the pump with an old sutured connector (gray arrow).

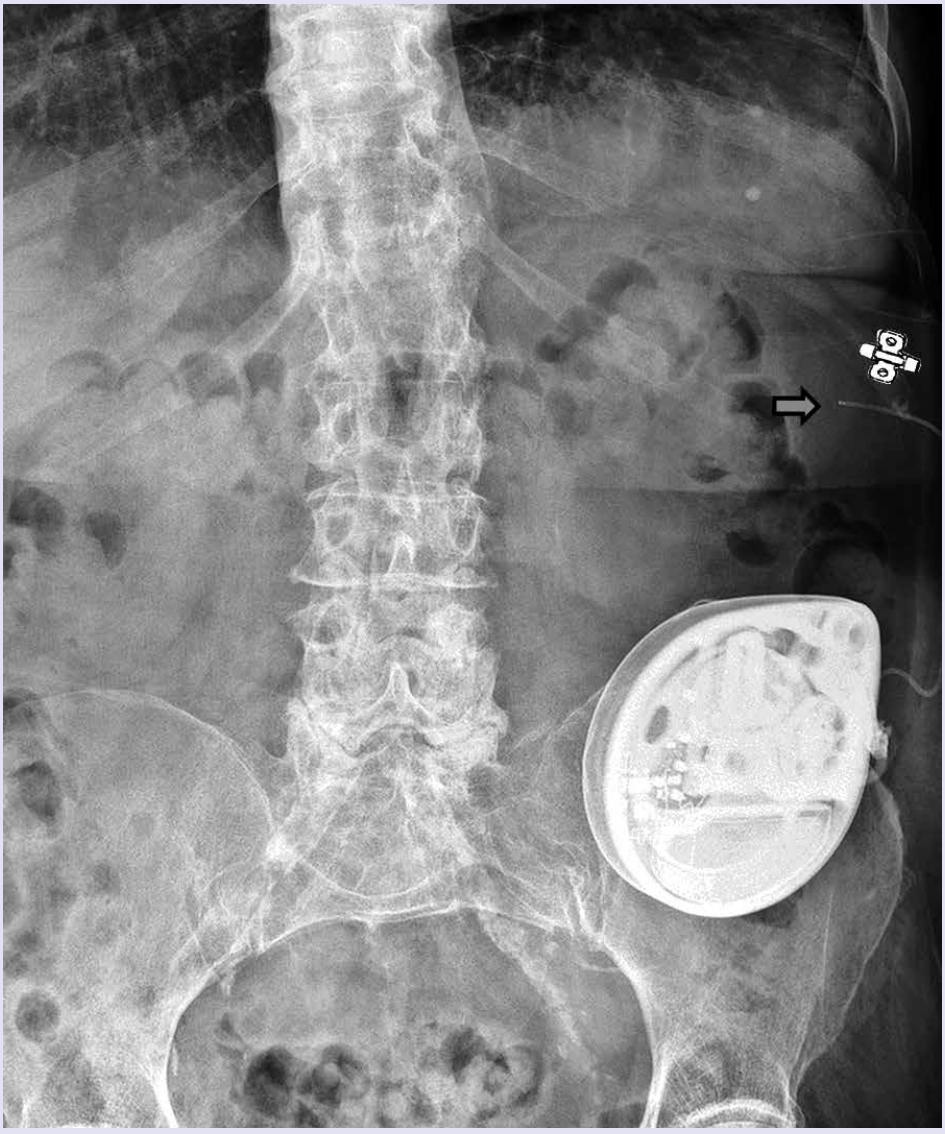


Figure 9. 8731SC catheter migration (gray arrow) caused by an open V-wing anchor (anchor symbol) in an 80-year-old woman with intractable pain and spasticity caused by failed back surgery syndrome, with a spinal cord lesion (SCL) T12 treated with intrathecal baclofen.

The Ascenda catheter (Fig. 3) has a **poor opacity** and the pump-catheter connection is also sutureless. Both catheter segments have the same diameter and are connected to each other with a needle connector. The fixation on the fascia is conducted by an **unfolded V-wing anchor** (Fig. 3cd). This catheter also has a catheter-end with six side holes and a round titani-

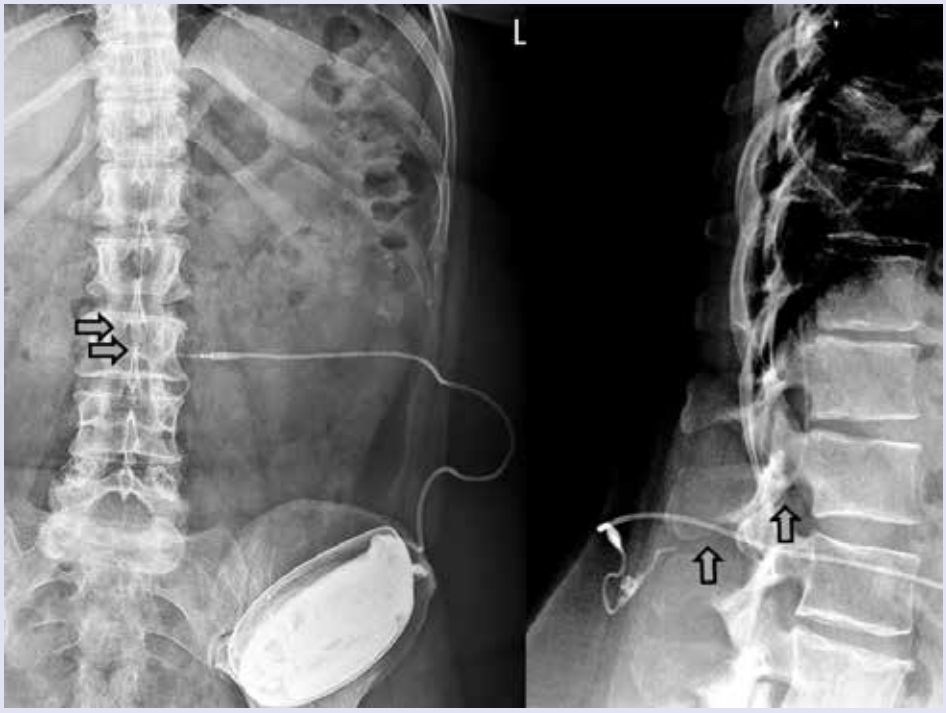


Figure 10. Sheared catheter 8731SC (gray arrow) with retracted segment partially outside the spinal canal, with no cerebrospinal leakage and no clinical signs of postural spinal headache or an intracranial hypotension syndrome, in a 48-year-old woman with cerebral palsy treated with intrathecal baclofen.

um tip. In contrast to the 8731SC catheter, the unfolded V-wing in the Ascenda catheter locks the catheter in place.

Older catheters have a sutured pump-cateter connection and distinct differences in anchoring (this could even be absent), different catheter-catheter connection, different catheter ends, and the presence or absence of a mushroom-shaped titanium tip. Either a so-called 'one' piece catheter type with only a connection at the pump, or a two-segment catheter are used.

Surgical implantation technique drug delivery system

Implantation is performed under local anesthesia with intravenous sedation or general anesthesia, With the patient in lateral decubitus position, a 3-4 cm dorsal midline incision is made at the planned implantation level up to the muscular fascia. On level L2-L3 or L1-L2 a silicone catheter is obliquely inserted into the intrathecal space, using a 15 (8731SC catheter) or 16 Gauge (Ascenda catheter) introduction (Tuohy) needle. The introduction needle is inserted 1-2 cm using a paramedian approach[44] to prevent catheter shearing and crushing by the frequent movements of the vertebral spinal process when a midline approach is applied. Under fluoroscopy the catheter is advanced to the mid-thoracic level[45-47]. Some physicians claim that positioning of the tip at the high thoracic, or even cervical position, gives a better result on the upper extremities, however, this

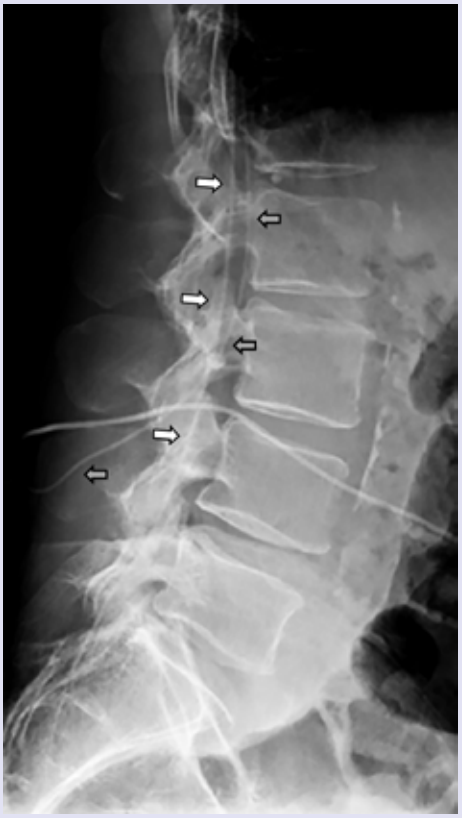


Figure 11. A 62-year-old man with treatment-resistant spasticity was successfully treated for many years with intrathecal baclofen. During exacerbation of the clinical symptomatology, the catheter 8731SC was found to be torn off and left behind in the spinal canal (white arrow). For further treatment, a new catheter, of the same type was inserted (gray arrow).

has not yet been proven[48,49]. At the abdominal site a subcutaneous pocket is made in which the pump is placed and sutured using the outside suture loops of the pump. The pump catheter segment is sutureless connected to the pump and tunneled from the pump pocket to the dorsal incision where it is connected to the spinal catheter part. The excess catheter length should be placed dorsal to the pump in the pocket.

Radiologic examination after implantation of an intrathecal drug delivery system

Since the quality of the perioperative fluoroscopic images is insufficient for detailed information, routine postoperative plain radiography is performed after all of the surgical procedures and manipulations. For adequate interpretation, plain radiography of the pump and the entire implanted catheter in two directions is required[38].

Development of a stepwise interpretation schedule

A stepwise interpretation of the standard plain radiographic images has been developed (Appendix) to offer the radiologist a systematic approach for the evaluation of all parts of the intrathecal delivery system on plain radiography. This stepwise interpretation is based on expert opinion.

Results

The normal and abnormal plain radiographic findings are described in a 14-step approach, a pump roller examination is also described.

Fourteen-step interpretation of standard plain radiographic images (Page 42)

Step 1 Previous radiographs available?

Comparison with previous radiological examinations is required to detect subtle or overt changes in the location and position of the pump and catheter.

Step 2 Type of catheter used

Primarily the use of a 8731SC catheter (Fig. 1a, 2, 5, 9, 10, 11), an Ascenda catheter (Fig. 3,6) or an older one (Fig. 4, 8) should be determined.

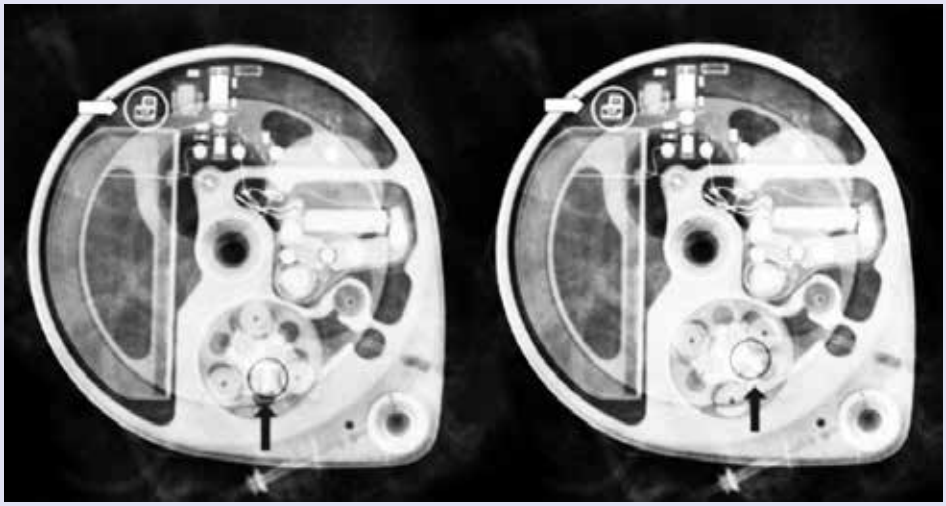


Figure 12. In this pump rotor examination, a normal rotation was found (change position 3 points wing, black arrow). The white arrow shows the pump position identifier (Fig. 7).

Step 3 Pump position

The position of the pump is described by reporting the pump apex (Fig. 1a, 3-7, 9, 10, 12) the location in clock position, and the abdominal quadrant in which the pump is placed. To exclude pump rotations, it is important to compare the current pump position with previous radiological images. Rotations about the horizontal axis are known as the Reel syndrome[50, 51] (Fig. 4, 6), resulting in traction on the catheter and risk of disconnection at the level of the pump-catheter (Fig. 5) or catheter-catheter connection (Fig. 6b).

Step 4 Pump-catheter connection

On plain radiography, the pump-catheter connection is clearly visible (Fig. 2-5, 9).

Step 5 Excess pump catheter segment behind the pump

In common practice, the excess catheter length is positioned behind the pump. In case the catheter surplus is located above the pump reservoir, refilling with medication or injecting contrast material in the catheter access port might result in catheter puncturing. Catheter perforation can result in dose adjustment problems, or even in a severe withdrawal syndrome[40].

Step 6 Control identifier

With the magnification view the radiopaque identifier with the company logo and three alphabetic letters can be recognized opposite the pump apex (Fig. 7). When the pump is rotated around its longitudinal axis an odd number of times, the identifier is visible as a mirror image. This rotation was originally described in cardiac pacemakers[52] and is known as the Twiddler's syndrome. The rotation can occur either spontaneously or as result of repeated twiddling with the device by the patient. The syndrome has also been described in an implanted pump for intrathecal drug administration[53]. After several rotations (Fig. 8), the catheter will occlude, rupture or dislodge resulting in termination of the drug delivery.

Step 7 Catheter pump segment

The 8731SC thick-walled pump catheter seg-

ment is clearly visible (Fig. 1a, 2, 5, 10) and in most cases the spinal segment is also visible (Fig.2, 9, 10, 11). The lack of opacity of the Ascenda catheter creates problems with visualization of the pump segment (Fig. 5, 6). Normally, this segment is clearly visible in older catheters.

Step 8 Catheter-catheter connector

The standard position of the clearly visible catheter-catheter connector is near the spine (Fig. 3, 4, 6a, 10). However, if the connection is placed in the pump pocket, recognition can be difficult. In the 8731SC catheter the connector is visible as a two-pin connector (Fig. 10), in the Ascenda catheter as a needle (Fig. 3, 6abe), and in older catheters often as a sharp small two-pin connector.

Step 9 Spinal segment of the catheter outside the spinal canal

The spinal segment of the 8731SC catheter has a smaller diameter than the pump segment and seems to be vulnerable to twisting, migration (Fig. 9) and shearing (Fig. 10). The pump segment and the spinal segment of the Ascenda catheter have the same small diameter. The improved mechanical properties make it less vulnerable. Kinking cannot be demonstrated on plain radiography in all implanted catheters. For a definite conclusion, additional investigations, such as injection of contrast material or scintigraphy, are needed.

Step 10 Different anchors

A folded anchor in the 8731SC catheter (Fig. 2) and an unfolded anchor in the Ascenda catheter (Fig. 3) are present. In older catheters both folded and unfolded anchors can be found. At the anterior-posterior view anchors are often poorly visible (Fig. 3a), while on the lateral image they are adequately visible (Fig. 3b).

Step 11 Catheter insertion, midline or paramedian?

Inserting an intrathecal catheter using the midline approach raises the risk of catheter crushing due to spinal column movements (Fig. 10). Therefore, a paramedian approach is the standard implantation technique.

Step 12/13 Spinal intrathecal catheter segment

Due to the poor visibility of the Ascenda catheter, the thoracic or the cervical vertebral column catheter segment is inadequately imaged. This leads to lack of information on the position of the catheter.

Due to the titanium end, the radiopaque tip can be recognized (Fig. 3 ,6). Attention must be paid to retained catheter fragments (Fig. 11). This can occur at the time of catheter insertion, removal, or as a late complication[54,55]. There is no consensus about the treatment of retained fragments. Both conservative[54,55] (Fig. 11) and surgical treatment[54,56] are performed. Nevertheless, serious complications like subarachnoid hemorrhage[41,57,58] and migration into the ventricle[58] are reported. Special attention must be paid if an intrathecal fragment also remains partially outside the spinal canal. Leakage of CSF with the development of postural headache, a pseudomeningocele[58] or even an intracranial hypotension syndrome could occur. However, sometimes no CSF leakage is present (Fig. 10). In a conservative approach the position of the retained catheter fragment should be followed-up over time.

Step 14 Radio-opaque catheter tip

In the latest catheters, a titanium tip has been built into the end of the catheter, in these intrathecal catheters, on plain radiography this tip is recognized as a ball at the end of the catheter (Fig. 2, 3, 6).

Special pump roller examination

If the rotor of the pump stalls, a two-tone emergency alarm will sound. After interrogation with the device programmer the device display indicates a 'Motor Stall'. When no motor stall is indicated and this is not derived from the pump logs, a roller study should be performed in case failure is suspected (Fig. 12). In this procedure, the pump is programmed in the continuous infusion mode, using a preset, without activation and with a priming bolus of 10 microliters with a duration of 1 min. With fluoroscopy, the rotor is visualized, thereby reducing the aperture. A plain radiographic image is made and the preset bolus delivery is activated. After 2 min, a new plain radiographic image is made and the two images are compared. In a normal pump function, the rollers have moved approximately 60° from their original position. The extra radiopaque dot on one of the roller arms helps to visualize the roller movement (Fig. 12).

Discussion

Although intrathecal drug administration using an implanted pump system has been employed for many years in therapy-resistant spasticity and intractable pain, knowledge on diagnostic imaging during adverse events remains limited. The main reasons for this limited knowledge include i) the diminished frequency of catheter-related treatment failures due to advancements in manufacturing and ii) the limited application of the treatment in different clinics. While plain radiography is the mainstay for the diagnosis of drug delivery device-related adverse events, radiologists play an important role in early diagnosis. An awareness of typical radiographic images in relation to intrathecal catheter failure is important to avoid a (sometimes life-threating) withdrawal syndrome. The most frequent causes of drug delivery failure are migration, damage, disconnection, and occlusion of the spinal catheter. In our opinion, applying the presented 14-step analysis and increasing the awareness of abnormal radiological findings will help physicians to avoid a life-threatening withdrawal syndrome.

A limitation of this proposal is that our approach has not yet been validated but is based on our expert opinion. Due to the present lack of high-quality evidence, we strongly believe that, as a first step in quality improvement, the current variation in radiological practice should be avoided. The stepwise approach, as proposed by our group, might be an effective first step towards raising the quality of care related to troubleshooting for intrathecal drug delivery with implanted systems.

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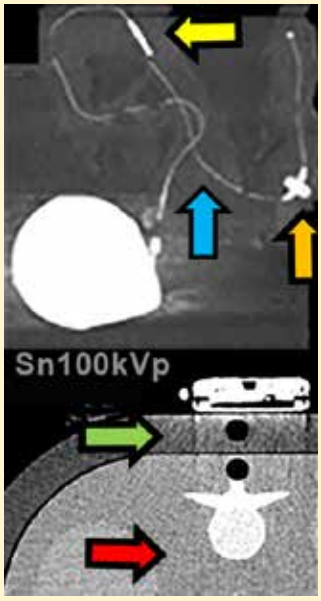
4

Low-dose computed tomography with two- and three-dimensional postprocessing as an alternative to plain radiography for intrathecal catheter visualization: A phantom pilot study



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ABSTRACT

Objectives

In intrathecal drug delivery, visualization of the device has been performed with plain radiography. However, the visibility of the related structures can be problematic. In troubleshooting, after the contrast material injection via the catheter access port, a CT scan has been used. In troubleshooting, we also used a non-contrast CT scan with 2D and 3D reconstructions. With the current phantom study, we aimed to obtain high-resolution imaging of a poor opaque catheter with the use of a low-dose single-energy 2D and 3D CT scan with limited radiation exposure as a substitute for plain radiography.

Materials and Methods

The catheter was placed into a fatty substance and mounted on an anthropomorphic abdomen phantom followed by CT with varying kVp settings and with added tin beam filtering. Dose levels corrected based on the spinal catheter tip on T8 would result in a calculated effective dose in the range of the mSv's calculated for the plain X-ray examination.

Results

Ultimately, Sn100 kVp has the best trade-off between visibility, artifacts, and noise for a fixed dose. Although 3D VRT imaging was challenging at this low dose level, we could make a full evaluation possible with complementary 2D projections.

Conclusion

We could correctly identify the catheter and related structures, which supports the investigation of this in vivo and side-by-side evaluation with plain radiography. If found superior, then this technique may be able to replace plain radiography while providing better visualization and acceptable radiation exposure.

Keywords

Catheter opacity, CT 2D/3D reconstructions, intrathecal drug delivery, phantom study

Running Title

Intrathecal catheter opacity 2D/3D low-dose CT

Introduction

Intrathecal drug administration using the implantable SynchroMed II delivery device (Medtronic Inc., Minneapolis, United States) is well established in treating intractable pain, spasticity, and dystonia. Despite generally favorable and safe outcomes and continuous advancements in manufacturing technology, adverse events related to the pump and catheter still occur.

Visualization of the pump and catheter is performed after device implantation and in troubleshooting to confirm the correct pump and catheter positioning. Historically, the cornerstone for the diagnosis of a catheter-related problem was plain radiography, which was in most cases, but not in all, acceptable in the older catheter types.[1] However, the opacity of the latest developed clinically used Ascenda catheter is more problematic (Fig. 1A, 5C).[1]

In troubleshooting, we, therefore, extended the plain radiography with catheter access port (CAP) CT myelography with high-resolution two- (2D) (Fig. 1B) and three-dimensional

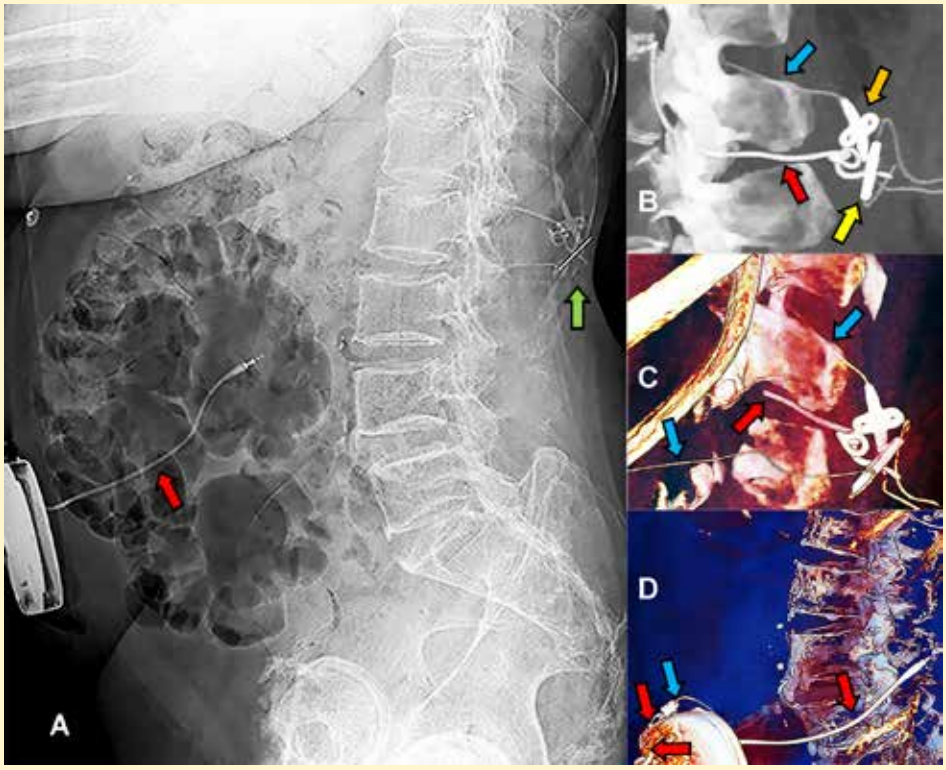

Figure 1. Visibility of spinal catheter with CT in troubleshooting Plain radiography: invisible Ascenda catheter and visible type 8731SC catheter segment (A, red arrow), and dorsal to the spine, several hardly recognized structures of both catheters on (A, green arrow). Zoomed two-dimensional maximum intensity projection (B) and three-dimensional volume rendered images (C, D) revealed visible Ascenda structures: catheter (blue arrow), catheter–catheter connector (yellow arrow), and fixation anchor (orange arrow), as well as retained 8731SC catheter parts (red arrow).

(3D) (Fig. 1C, 1D),[2-8] reconstructions based on maximum intensity projection (MIP),[9] multiplanar reformation (MPR),[9] and volume rendering techniques (VRTs).[9] With this approach, we could provide optimal visualization of the entire catheter pathway (Fig. 1B–1D)[7] and reduce beam-hardening artifacts around the implanted titanium pump. Normally, compared to plain radiography, CT has the disadvantage of an increased radiation dose. With the current phantom study, we aimed to obtain high-resolution imaging of the Ascenda catheter with the use of a low-dose single-energy 2D and 3D CT scan with limited radiation exposure as a substitute for plain radiography. Based on this experience we now intend to replace plain radiography by CT in all cases where imaging of the pump and catheter is needed.

Materials and Methods

We tested the visualization of the Ascenda catheter placed into a fatty substance and mounted on an Anthropomorphic Abdomen Phantom (QRM GmbH, Moehrendorf, Ger-

many) with a 2.5 cm fat equivalent extension ring (Fig. 3). We performed a low-dose single-energy spiral CT scan (SECT) using a multi-slice CT scanner (SOMATOM Drive VA62A, Siemens Healthcare GmbH, Erlangen, Germany). Scans were performed with varying kVp settings (80, 100, 140) and with added tin (Sn) beam filtering (Sn100, Sn140) to evaluate a trade-off between the catheter visibility, the pump beam-hardening artifacts, and the X-ray energy level. Because an Sn filter at 80 kVp and 120 kVp is not available, this setting was not used. By adapting the tube load (in mAs), three scans per kVp setting were performed with three fixed values of the dose length product (DLP) for a 20 cm scan range on the phantom: 15, 30, and 60 mGy*cm. These dose levels, corrected for an average 50 cm scan range based on the spinal catheter tip on T8, would result in a calculated effective dose of, respectively, 0.6, 1.1, and 2.3 mSv. These values are approximately less than, virtually equal to, and more than the dose level of 0.7 mSv previously used in plain X-ray examination of the old catheters in a standard patient.

Results

Single energy Sn100kVp
mA modulation: active
kV modulation: off
Target CTDIvol standard patient: 1,5 mGy
Collimation: narrow n*0,6 millimeter
Rotation time: 0,5s (faster in case of motion)
Pitch: 0.9
Contrast: no
Breath hold command
Smooth & medium algorithm
Strong iterative reconstruction (4-5)
Coronal/sagittal MPR & MIP
Oblique VRT
Additional iMAR images if needed

Figure 2. Single energy protocol low-dose CT.

The protocol with a DLP of 30 mGy*cm has an optimum radiation dose level for all kVp settings because the lowest dose resulted in poor visualization and the highest dose resulted in better visualization than needed. A low energy level of 80 kVp had the highest contrast between the catheter and the surrounding tissue, benefiting catheter visualization, but also had the highest level of beam-hardening artifacts around the pump. The highest energy level of 140 kVp with added Sn filtering had minimal artifacts, but the reduced contrast caused the catheter visibility to become insufficient. Sn filtering resulted in increased dose efficiency with an improved signal-to-noise ratio for the same dose in this phantom study (Fig. 3, 100 kVp versus Sn100 kVp). Ultimately, Sn100 kVp has the best trade-off between visibility, artifacts, and noise for a fixed dose (Fig. 3). The clinical CT settings are summarized in Figure 2. Although 3D VRT imaging was challenging at this low dose level, we could make a full evaluation possible with complementary 2D MIP and MPR projections (Fig. 4,5). However, with Sn filter, not all metal-related artifacts that obscure adjacent tissues could be suppressed. Additional improvement in visualization of the pump, proximal catheter and surrounding soft-tissue structures[10] could be achieved with the use of metal artifact reduction (MAR) algorithm (iMAR [Siemens], Smart-MAR [GE Healthcare], O-MAR [Philips], SEMAR [Canon])[11] which suppresses the scattering in the images caused by the metal pump (Fig. 5).

Discussion

A low-dose CT scan for visualization of the pump and catheter with an equivalent radiation dose to conventional plain radiography is feasible. To extend CT with 2D and 3D reconstructions will be of value for the postoperative evaluation of a normal drug delivery system and for the proper diagnosis in troubleshooting. The optimal DLP was 30 mGy*cm with

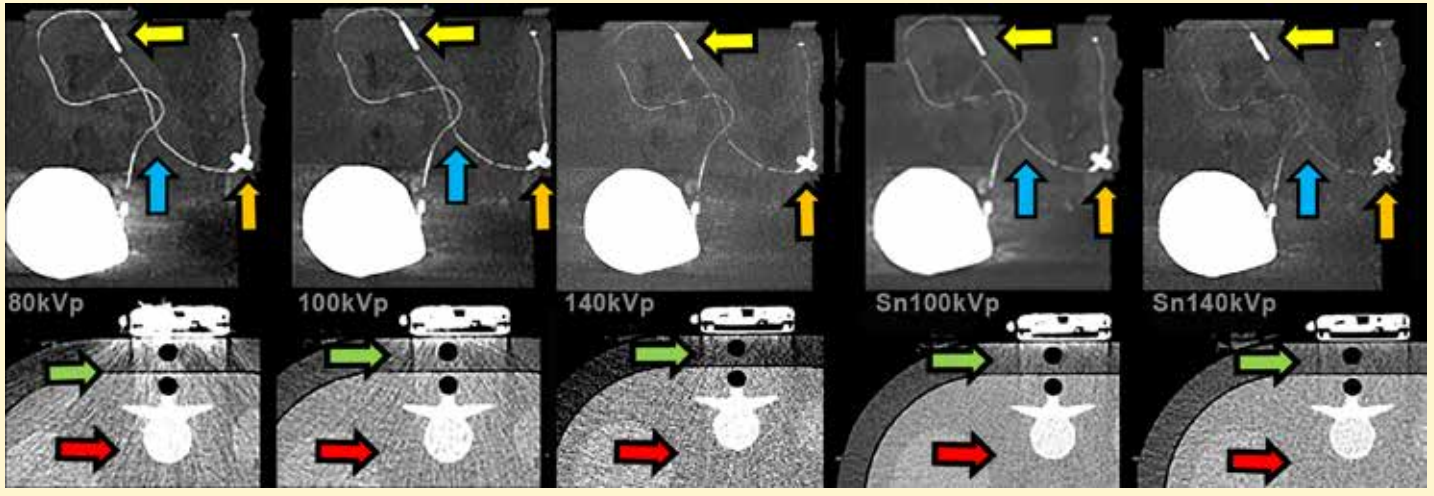

Figure 3. CT imaging of a catheter mounted on a phantom with an extension ring Ascenda intrathecal catheter in a fatty substance, visible catheter (blue arrow) with fixation anchor (orange arrow), and catheter–catheter connector on CT 2D MIP images (yellow arrow). A dose of 80 kVp showed most artifacts (beam hardening [green arrow] and noise of phantom body [red arrow]); 100 kVp: fewer artifacts, but still present; 140 kVp: reduced beam hardening, noise still present; Sn100 kVp: strongly reduced artifacts; and Sn140 kVp: minimum artifacts, but more noise visible and less catheter visibility.

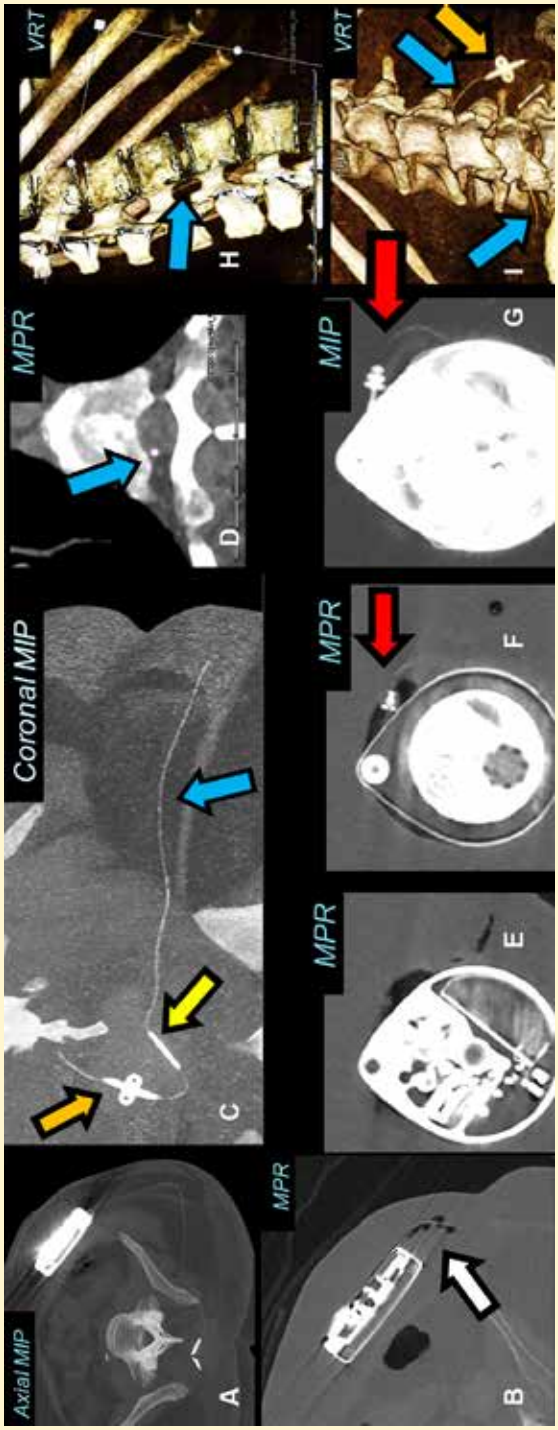

Figure 4. Low-dose SECT 2D/3D imaging Sn100 kVp scan with an effective dose of 0.8 mSv. A combination of MPR, MIP & VRT is used to follow the Ascenda catheter (blue arrow), pump–catheter connection (red arrow), catheter–catheter connection (yellow arrow), fixation anchor (orange arrow) and pump. Postoperative air visible with MPR (B, white arrow), invisible with MIP (A) and is a potential cause of artifacts in MIP and VRT which may mimic a pump–catheter disconnection.

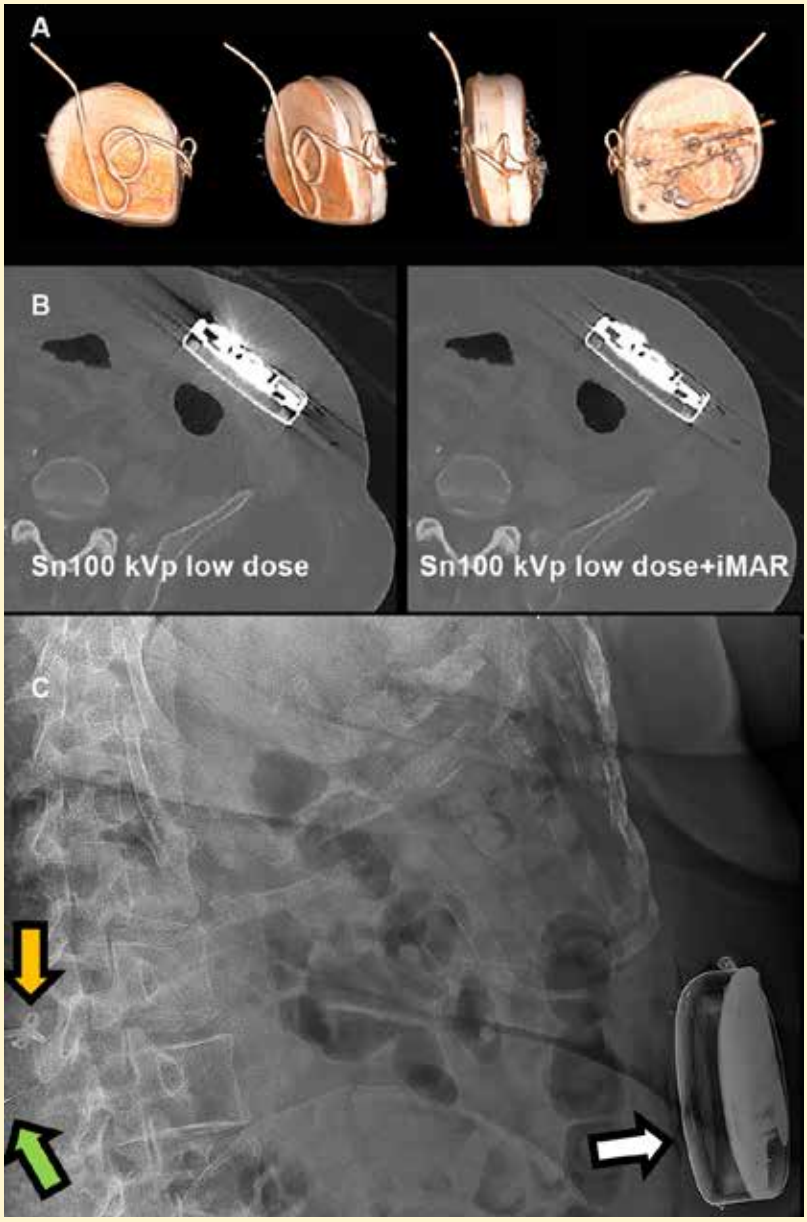

Figure 5. Surplus catheter behind the pump 3D VRT reconstruction (A) with iterative metal artifact reduction reconstruction algorithm (B) showing a normal course of surplus catheter length behind the pump, which is invisible on plain radiography (C, white arrow) and CT (B). The Ascenda catheter cannot be followed along its track on plain radiography (C); The only structures visible are the catheter–catheter connector (green arrow) and the fixation anchor (orange arrow).

radiation exposure of 1.1 mSv for a scan range of 50 cm, which is close to the dose of plain radiography images. The dose of plain radiography in our center was approximately 0.7 mSv, although a value of 3.6 mSv for at least six needed plain radiography images has been reported.[12] We prefer the use of 100 kVp with the Sn filter. The benefit of the filter use is the reduction of beam-hardening artifacts originating from the metal pump, but not all metal-related artifacts that obscure adjacent tissues can be suppressed. Application of a metal artefact reduction algorithm can thereby be of help. When Sn filter is used the obtained narrowed, and increased mean energy level of the X-ray tube spectrum will create an improvement in the overall image quality.[13] The choice for an increase in kVp resulted in a decrease in the contrast between the catheter and the surrounding tissue, which is accompanied by a reduction in artifacts.

Furthermore, the choice for Sn filtering resulted in an additional decrease in the contrast between the catheter and the surrounding tissue, which is accompanied by an increased signal-to-noise ratio. Another disadvantage is the need for higher mAs settings, which may limit the increase of scan speed if the patient is moving, and which is not uncommon in our spastic patient group. In the relatively small phantom, we could omit the beam hardening with Sn100 kVp (Fig. 2). In obese patients or with the hindrance of upper extremity contractures, higher radiation dose values may be needed. This objective could be automatically realized with the automatic mA exposure modulation setup of a CT scanner. For a definite conclusion and the application of CT in vivo using CT scanners from different vendors, imaging protocols per scanner should be developed.

Conclusion

The positive findings of our phantom study in correctly identifying the catheter components supports the in vivo evaluation and a side-by-side comparison with plain radiography. If found superior, then this technique may be able to replace plain radiography while providing better visualization and acceptable radiation exposure.

Comments

Whilst it is easy to diagnose there is a problem with an intrathecal pump/catheter unit (increased pain, increased spasticity) it can sometimes be far from easy to separate underdosing from treatment more reliably and reduce complications. These CT techniques may very well do that.

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Short article but very clear in defining the problem of not being to visualize catheter continuity without additional expense and has- sle of doing a pump side port myelogram.

Timothy Lubenow, MD
Chicago, IL, USA

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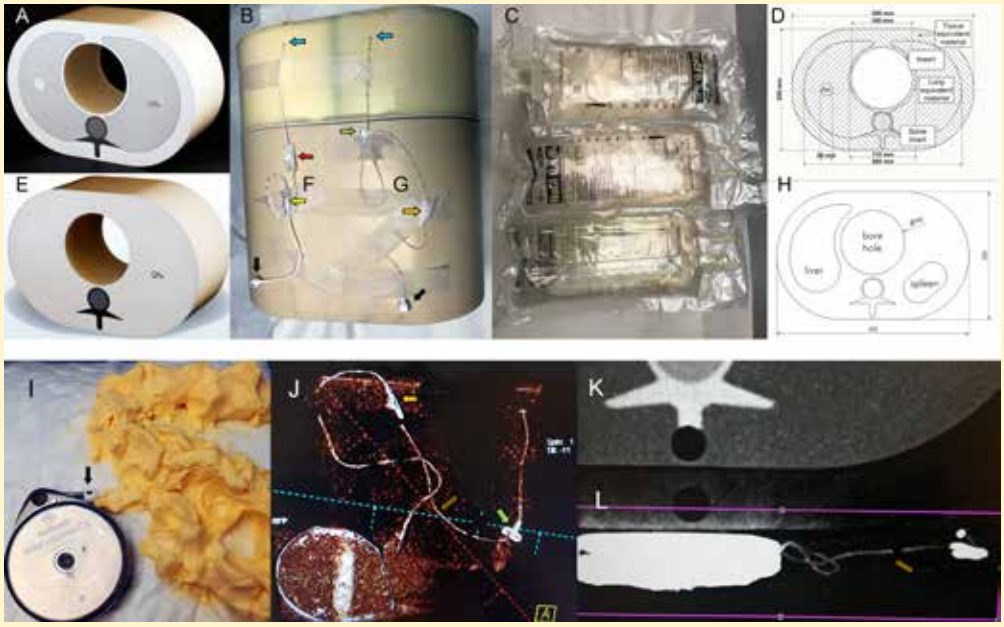
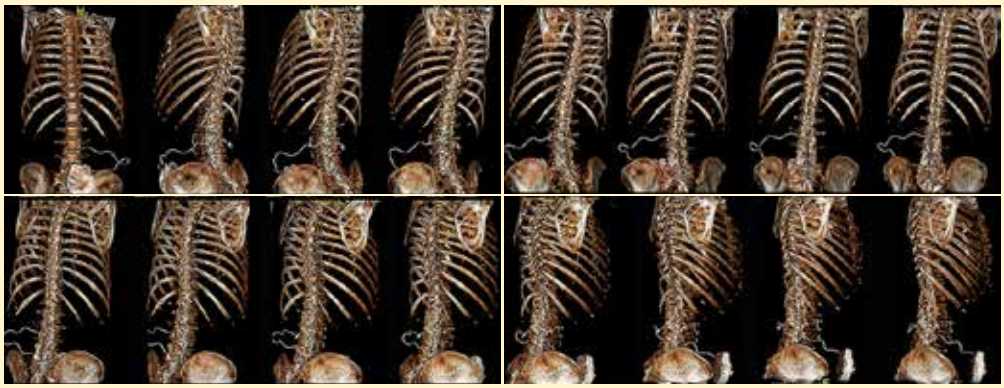
Supplementary Appendix



eFigure 1 Phantom study. Thoracic phantom (A,B), Coverage with saline sacs (C), Thoracic schematic view (D), Abdominal phantom (E), Coverage with intrathecal catheters (8731 and Ascenda), Abdominal schematic view (H), Pump connected with catheter and coverage with fatty substance (I), low-dose single-energy CT scan images (J-L).



eFigure 2 In vivo non-contrast low-dose single-energy CT scan images (360°).

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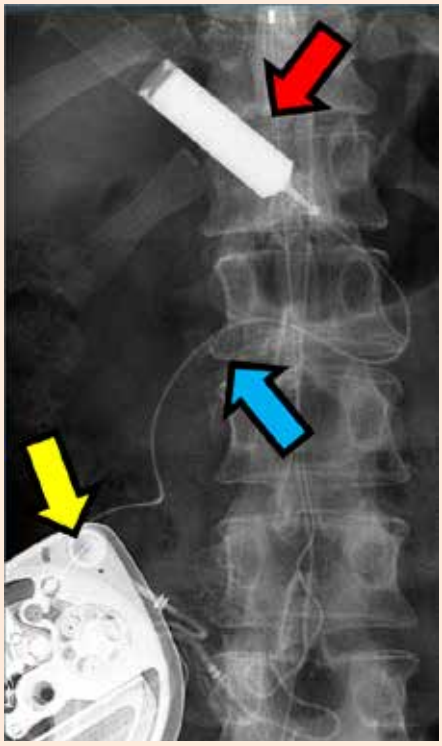
Catheter access port (computed tomography) myelography in intrathecal drug delivery troubleshooting: A single institution case series



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ABSTRACT

Objectives

Intrathecal drug delivery is used for the treatment of intractable spasticity, dystonia, and pain. When the symptomatology is not responding to the therapy, the cause could be a failure of the medication infusion. The purpose of this study was to assess the value of the pump catheter access port (CAP)-myelography and CAP-CT-myelography as an advanced imaging method in treatment failure.

Materials and Methods

We analyzed observational routinely collected data of 70 CAP procedures with 2D and 3D reconstructions in 53 adult patients between November 2013 and November 2018 in whom the cause of failure was unclear. CAP-myelography and CAP-CT-myelography were performed with 2D/3D image reconstructions. When myelography could not be performed or when the study did not reveal the cause, addition procedures such as non-contrast CT, MRI, lumbar puncture CT myelography, and ^{111}Indium-DTPA SPECT CT were performed.

Results

CAP fluid aspiration contrast medium injection was not possible (n=17). In one case contrast was injected in de the pump pocket unintentionally. The remaining examinations CAP myelography (n=52) had limited value for the diagnosis. CAP-CT myelography (n-50) was normal (n=31). The abnormal results were: dorsal dural leak (n=5), subdural catheter position (n=2), limited rostral flow of contrast material (n=4), limited and abnormal contrast distribution (n=3), obstruction of rostral flow (n=2), a leak at the pump-catheter connection (n=1), and a sheared catheter localized in the pump pocket (n=2). A limited contrast distribution turned out to be false positive findings (n=2). CAP-CT myelography was normal in 31 procedures. Four normal CT-CAP myelographic procedures were false negative as the reference tests revealed a cause of ITDD failure. The CAP-CT procedures resulted in a sensitivity of 81% (17/21) and in a specificity of 93% (27/29).

Conclusion

CAP-CT myelography with 2D/3D reconstructions is an essential step in the diagnostic algorithm for patients with ITDD failure.

Keywords

intrathecal treatment failure, pump, catheter access port, computed tomography, myelography

Introduction

Several observational studies demonstrate the value of intrathecal drug delivery (ITDD) for therapy-resistant spasticity, dystonia, and pain.[1-3] Older data show a high complication rate, mainly related to the intrathecal catheter, which varied widely among the treating specialists.[4-7] Current complications are related to the handling of the delivery system itself, as well as to its implantation or to the underlying condition of the patient. As result of catheter improvements, the complication rate seems to be considerably reduced.[8, 9]

Algorithms for troubleshooting and the involved diagnostic procedures are under debate. One topic in the discussion is the role of catheter access port (CAP) computed tomography (CT) myelography as an advanced diagnostic

procedure. Saulino et al.[10] stated that the CAP-CT procedure should be part of the standard approach. However, it was recently suggested that the use of this procedure should be limited to emergencies and should not be considered as a routine examination.[11] The aspiration failure rate of the CAP puncture, the non-physiological flow of contrast material in the intrathecal space, the probable lower costs, and the lower radiation dose of ^{111}Indium-diethylene-triamine-penta-acetic acid scintigraphy (^{111}In-DTPA) single-photon emission CT (SPECT-CT) were presented as arguments.[11]

The CAP procedure is not always easy to perform, which could be one of the reasons for its omission from the standard diagnostic approach. In ITDD failures, advanced imaging procedures are frequently not performed or performed inadequately, which can lead to undertreatment, unnecessary surgery, or even unjustified termination of the therapy. Over the last few years, we routinely used CAP myelography and fluoroscopy in troubleshooting, combined with CT and two-dimensional (2D) multiplanar reformation (MPR),[12] 2D maximum intensity projection (MIP),[12] and three-dimensional (3D) volume-rendering technique (VRT)[12] reconstructions. The intended use of the CAP-CT procedure was to diagnose catheter leaks or obstruction or abnormal rostral distribution of the injected contrast material. With this retrospective observational study focused on routinely collected data, we aimed to assess the value of CAP (CT) myelography as a first-line advanced imaging method in ITDD troubleshooting.

Materials and Methods

Patients

We included all routinely collected data from 70 CAP (CT) myelography and additional related imaging procedures in 53 adult patients who were evaluated for ITDD failure between November 2013 and November 2018. Fifty-two of the patients were referred to our hospital for ITDD troubleshooting. A SynchroMed II pump model 8637 with the associated intrathecal catheters (Type 8731SC or Ascenda 8780/8781) (Medtronic Inc., Minneapolis, MN, USA) was used for the drug delivery. The indication used was, depending on the particular patient's underlying etiology, either morphine-HCl, a morphine-HCl/baclofen mixture, or baclofen prepared by the hospital pharmacy according to the existing regulations. CAP-(CT) myelography was considered when the ITTD failure could not be managed with dose adaptations in combination with conservative non-pharmaceutical treatment and the cause was not identified as being related to the patient's history, a pump readout, the presence of medication fluid in the pump reservoir, or plain radiography. ITDD failure was defined as the presence of one or more of the following criteria: a decrease in effectiveness of the treatment, a discrepancy between the volumes that the pump device calculated and the residual volumes obtained by the refill procedure, manifest- or occult-drug cerebrospinal fluid (CSF) leakage, repeated dosage increases without clinical improvement, and extremely high dosages with an insufficient clinical result. The first and last author reexamined the images, taking all clinical features into consideration. Their assessments were focused on the distribution of the contrast medium injected via the CAP, the pump shape, catheter-pump connections, the course of the catheter, catheter-catheter connection, the dural insertion, and the intrathecal distribution. The study was approved by the medical ethics committee of our center (MEC-2017-326), and the requirement to obtain informed consent was waived.

CAP myelography

CAP insertion using a 24-G non-coring Huber needle was performed under fluoroscopy. We found that, with the template provided with

the CAP kit (Model 8540, Medtronic Inc., Minneapolis, MN, USA), the CAP funnel position could not be recognized in all cases. During fluoroscopy, we use a metal object (e.g., a surgical clamp or a pair of tweezers) to determine the CAP funnel's location. We positioned the C-arm fluoroscopy device such that the beam was parallel to the CAP axis, which allowed perpendicular needle insertion into the funnel. To prevent an injection overdose caused by the flushing of the highly concentrated catheter content into the intrathecal space, we first aspirated 2 ml of fluid.[13] When we could not aspirate, we omitted the contrast material injection and terminated the procedure or performed, when not already present, a non-contrast CT (NCCT) scan. After successful fluid aspiration, we injected 10 ml of contrast material (iohexol, Omnipaque™ 300, GE Healthcare B.V., Eindhoven, Netherlands). Due to the high viscosity of the contrast material and the small needle diameter, we had to apply significant force during the injection. To reduce the force required, the contrast material was injected at body temperature. To ensure an optimal distribution of the contrast material in the CSF, we turned the patient to the left and to the right and placed him or her in the Trendelenburg position. Under fluoroscopy, we controlled the catheter pathway and the intrathecal distribution of the contrast material. Next, we flushed the catheter with 2 ml of NaCl 0.9% fluid to remove the contrast material from the catheter. To prevent a withdrawal syndrome, we programmed the pump for a catheter-priming bolus injection, which was calculated based on the catheter length.

CAP-CT myelography

Following CAP myelography, we performed a CT scan. The first, and largest, group of patients were evaluated with a single-energy CT (SECT) scanner. To optimize the CT results, we recently switched from SECT to dual-energy CT (DECT).[14] Therefore, we used the twin beam dual-energy CT scan (Siemens Healthcare GmbH, Erlangen, Germany) with gold (Au) and tin (Sn) filters in combination in front of the 120 kVp x-ray beam.[15] The filters split the beam into a high- and low-energy X-ray spectrum before it reaches the patient. The different x-rays give DECT an additional advantage over SECT by obtaining better information when metal implants (e.g., the pump or osteosynthesis material) are present in the scanned area. With a metal artifact reduction algorithm (iMAR), further image improvement could be obtained. Originally, we limited the reconstructed scan field of view (FOV) to the spine. To obtain information concerning the entire implanted drug delivery system, we extended the FOV to the extra-vertebral abdominal region. For the imaging of the intrathecal catheter and the distribution of the contrast material above the catheter tip, we applied a lumbar–cervical spine scan range. A breath-holding command was given to avoid pump movement during breathing. The scan parameters for DECT included the following: collimation: 300 x 0.6 mm; rotation time: 0.5 s; and slice thickness: 0.8 mm.

On a workstation, we reconstructed 12 mm MIPs,[12] which enables the imaging of highly intensive structures with respect to the surrounding structures, and 1.5 mm MPRs,[12] whereby thin-slice axial data were converted into coronal, sagittal, oblique, or curved planes, which allow one to follow the course of the implanted catheter. Using VRT,[12] we transformed the axial data into 3D images.

Additional imaging procedures

When CAP(-CT) myelography was impossible or when additional confirmation of the result was needed, we performed supplementary imaging with NCCT, magnetic resonance imaging (MRI), lumbar puncture (LP) CT myelography, or optimized ^{111}In-DTPA scintigraphy combined with SPECT-CT examination. To be certain of a normal rostral intrathecal activity distribu-

tion over time, we optimized the scintigraphy by standardizing the pump flow rate, as result of which the tip of the intrathecal would be reached after 24 hours.

Statistical analysis

The sensitivity and specificity of the different procedures were calculated, comparing the imaging assessment outcome as the index test, while the gold standard reference test was based on all performed imaging procedures, and clinical and surgical information. A true positive result was thereby defined when an abnormality could be demonstrated with the index test and the reference revealed indeed a cause of ITDD failure, a true negative when no abnormality was found with the index test and the reference test, a false positive when an estimated abnormality could not be confirmed by the reference, and a false negative when the abnormality was missed. Due to the limited number of NCCT scan procedures, we omitted the calculations of accuracy.

Sex Age	Disorder	Sympto-matology	Medi-cation	CSF aspi-ration	CAP myelography	CAP-CT myelography (spine)	CAP-CT myelography (extra-vertebral)	Other diagnostic examinations	Standard reference	Final Diag-nosis	Treatment	CAP mye-lo	CAP-CT myelo	Figure
68/ f	spinal cord lesi-on C6	spasticity	B	no				NCCT (spine): cath. epidural; NCCT (extra-vert.): normal, LP-CT myelography: cath. epidural	LP-CT myelo	catheter epidural	passed away			1C, 1D
41/ m	multiple sclerosis	spasticity	B	no				NCCT (spine): cath. epidural; NCCT (extra-vert.): normal	NCCT	catheter epidural	catheter revision			
55/ m	multiple sclerosis	spasticity	B	no				NCCT (spine): catheter epidural	NCCT	catheter epidural	catheter revision			
67/ m	multiple sclerosis	spasticity	B	no				NCCT (spine): catheter epidural	NCCT	catheter epidural	catheter revision			
70/ f	failed back surgery	pain	M	no				NCCT (spine): cath. curved downwards; scintigraphy: normal	scintigraphy	normal, ca-theter curved downwards	dose adaptation			
59/ m	spinal cord lesion T5	spasticity	B	no				NCCT (spine): normal; scin-tigraphy: catheter leakage + catheter obstruction	scintigraphy	catheter leak-age, catheter obstruction	catheter revision			
58/ m	spinal cord lesion T5	spasticity	B	no				NCCT (spine): normal; scinti-graphy: normal	scintigraphy	normal	dose adaptation			
48/ f	multiple sclerosis	spasticity	B	no				NCCT (spine): normal; scinti-graphy: normal	scintigraphy	normal	dose adaptation			
65/ f	failed back surgery	pain	M	no				LP-CT myelography: gra-nuloma	LP-CT myelo	granuloma	removal system, terminati-on therapy			
67/ m	failed back surgery	pain	M	no				MRI: normal	MRI	normal	dose adaptation			

77/ f	failed back surgery	pain	M	no				MRI: normal	MRI	normal	dose adaptation			
36/ m	spinal cord lesion T4	spasticity	B	no				scintigraphy: obstruction rostral tracer distribution	scintigraphy	CSF flow obstruction	catheter revision			
57/ m	spinal cord lesion T5	spasticity	B	no				scintigraphy: normal	scintigraphy	normal	dose adaptation			
66/ f	failed back surgery	pain	M	no				scintigraphy: normal, catheter curved downwards	scintigraphy	normal, catheter curved dornwards	dose adaptation			
68/ m	failed back surgery	pain	M	no					clinical	catheter obstruction?	terminati-on therapy			
20/ m	cerebral palsy	spasticity	B	no					clinical	normal	dose adaptation			
53/ f	stroke	spasticity	B	no					clinical	normal	dose adaptation			
61/ f	multiple sclerosis	spasticity	B	yes	injection contrast material in pocket	failed procedure	contrast material in pocket	scintigraphy: normal, caudal tracer distribution	scintigraphy	normal	dose adaptation			2A
58/ f	spast. spin. syndr.	spasticity	B	yes	limited and abnormal contrast distribution	not performed		MRI: intrathecal cyst	MRI	intrathecal cyst	removal cyst	TP		3B
60/ f	multiple sclerosis	spasticity	B	yes	catheter leakage	not performed			CAP myelo	catheter leakage	catheter revision	TP		3A
58/ f	multiple sclerosis	spasticity	B	yes	catheter leakage	normal			CAP myelo	catheter leakage	catheter revision	TP	FN	

Sex Age	Disorder	Sympto-matology	Medi-cation	CSF aspi-ration	CAP myelography	CAP-CT myelography (spine)	CAP-CT myelography (extra-vertebral)	Other diagnostic examinations	Standard reference	Final Diag-nosis	Treatment	CAP mye-lo	CAP-CT myelo	Figure
18/ m	cerebral trauma	spasticity	B	yes	limited and abnormal contrast distri-bution	catheter subdural			CAP-CT myelo	catheter subdural	catheter revision	TP	TP	
81/ m	spinal cord lesi-on T11	spasticity	B	yes	limited and abnormal contrast distri-bution	catheter subdural			CAP-CT myelo	catheter subdural	catheter revision	TP	TP	1E 3C
50/ m	spinal cord lesi-on C6	spasticity	B	yes	limited contrast distri-bution	limited contrast distribution		scintigraphy: limited rostral tracer distribution	scintigraphy	CSF flow limited	dose adaptation	TP	TP	1B
39/ m	spinal cord lesion T4	spasticity	B	yes	limited and abnormal contrast distri-bution	limited and abnormal contrast distribution		scintigraphy: obstruction rostral tracer distribution	scintigraphy	CSF flow obstruction	restoration CSF flow	TP	TP	
62/ m	spinal cord lesi-on T11	spasticity	B	yes	limited and abnormal contrast distri-bution	limited and abnormal contrast distribution	normal	scintigraphy: obstruction rostral tracer distribution	scintigraphy	CSF flow obstruction	restoration CSF flow	TP	TP	
46/ f	spinal cord lesi-on T10	spasticity	B	yes	stop in contrast distri-bution	stop in contrast distribution		scintigraphy: obstruction rostral tracer distribution	scintigraphy	CSF flow obstruction	restoration CSF flow	TP	TP	
70/ m	cervical myelitis	spasticity	B	yes	limited and abnormal contrast distri-bution	limited and abnormal contrast distribution		scintigraphy: obstruction rostral tracer distribution	scintigraphy	CSF flow obstruction	restoration CSF flow	TP	TP	
44/ m	spinal cord lesi-on C5	spasticity	B	yes	limited contrast distri-bution	limited contrast distribution		scintigraphy: obstruction rostral tracer distribution	scintigraphy	CSF flow obstruction	catheter revision	TP	TP	
36/ m	spinal cord lesion T9	spasticity	B	yes	stop in contrast distri-bution	stop in contrast distribution			CAP-CT myelo	CSF flow obstruction*	terminati-on therapy	TP	TP	3D

16/ m	cerebral damage	spasticity	B	yes	limited contrast distri-bution	limited contrast distribution	normal		clinical	normal	dose adaptation	FP	FP	3E
16/ m	cerebral damage	spasticity	B	yes	limited contrast distri-bution	limited contrast distribution	normal		clinical	normal	dose adaptation	FP	FP	
65/ f	compl. reg.pain syndr.	dystonia	B	yes	limited contrast distri-bution	normal	normal		CAP-CT myelo	normal	dose adaptation	FP	TN	
37/ f	compl. reg.pain syndr.	dystonia	B	yes	catheter curved downwards, reduced flow	normal, ca-theter curved downwards	normal	scintigraphy: normal, cathe-ter curved downwards	scintigraphy	normal, ca-theter curved downwards	dose adaptation	FP	TN	
59/ m	failed back surgery	pain	M	yes	normal	normal	catheter leakage		CAP-CT myelo	catheter leakage	catheter revision	FN	TP	4A
63/ f	multiple sclerosis	spasticity	B	yes	normal	normal		scintigraphy: normal, caudal tracer distribution	surgery	catheter leakage (in-trathecal)	catheter revision	FN	FN	2B
48/ f	cerebral palsy	spasticity	B	yes	normal	normal, retained intrathe-cal-epidural catheter	catheter leakage with fluid in pocket		CAP-CT myelo	catheter leak-age with fluid in pocket	catheter revision	FN	TP	
57/ m	spinal cord lesi-on C5-6	spasticity	B	yes	normal	normal 10		scintigraphy: catheter ob-struction	scintigraphy	catheter obstruction	catheter revision	FN	FN	
62/ f	spast. spin. syndr.	spasticity	B	yes	normal	dura leakage			CAP-CT myelo	dura leakage	blood patch	FN	TP	
52/ f	compl. reg.pain syndr.	dystonia	B	yes	normal	dura leakage		scintigraphy: normal	CAP-CT myelo	dura leakage	blood patch	FN	TP	

Sex Age	Disorder	Sympto-matology	Medi-cation	CSF aspi-ration	CAP myelography	CAP-CT myelography (spine)	CAP-CT myelography (extra-vertebral)	Other diagnostic examinations	Standard reference	Final Diag-nosis	Treatment	CAP mye-lo	CAP-CT myelo	Figure
44/ m	spinal cord lesion T6	spasticity	B	yes	normal	dura leakage	normal		CAP-CT myelo	dura leakage	blood patch	FN	TP	4C
52/ f	compl. reg.pain syndr.	dystonia	B	yes	normal	dura leakage	fluid in pocket		CAP-CT myelo	dura leakage, fluid in pocket	blood patch, aspiration pocket fluid	FN	TP	2C 2D 4B
52/ f	compl. reg.pain syndr.	dystonia	B	yes	normal	dura leakage	fluid in pocket	scintigraphy: dura leakage, tracer in pocket	scintigraphy	dura leakage, fluid in pocket	blood patch, aspiration pocket fluid	FN	TP	
48/ f	cerebral palsy	spasticity	B	yes	normal	normal, retained intrathe-cal-epidural catheter	pump-catheter disconnection with fluid in pocket	scintigraphy: tracer in pocket	scintigraphy	pump-ca-theter disconnection with fluid in pocket	catheter revision	FN	TP	
64/ m	stroke	spasticity	B	yes	normal, retained intrathecal catheter	normal, retained intrathecal catheter		scintigraphy: abnormal cau-dal tracer distribution	scintigraphy	retrograde caudal flow via retained catheter	dose adaptation	FN	FN	
47/ m	spinal cord lesion T7	spasticity	B	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
55/ m	multiple sclerosis	spasticity	B	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
55/ m	multiple sclerosis	spasticity	B	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
18/ m	cerebral trauma	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	

62/ m	cerebral trauma	spasticity	B	yes	normal	normal		scintigraphy: normal	scintigraphy	normal	dose adaptation	TN	TN	
62/ m	cerebral trauma	spasticity	B	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
63/ m	cerebral trauma	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
47/ f	multiple sclerosis	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
45/ f	compl. reg.pain syndr.	dystonia	B	yes	normal	normal		scintigraphy: normal	scintigraphy	normal	dose adaptation	TN	TN	
56/ f	stroke	spasticity	B	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
45/ f	failed back surgery	pain	M	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
72/ m	spinal cord lesi- on T11	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
75/ m	cerebral trauma	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
31/ m	cerebral palsy	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
35/ f	compl. reg.pain syndr.	dystonia	B	yes	normal	normal	normal	scintigraphy: normal	scintigraphy	normal	dose adaptation	TN	TN	
67/ f	spinal cord lesion T6	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
29/ m	cerebral palsy	spasticity	B	yes	normal	normal	normal	scintigraphy: normal	scintigraphy	normal	dose adaptation	TN	TN	

Sex Age	Disorder	Sympto-matology	Medi-cation	CSF aspi-ration	CAP myelography	CAP-CT myelography (spine)	CAP-CT myelography (extra-vertebral)	Other diagnostic examinations	Standard reference	Final Diag-nosis	Treatment	CAP mye-lo	CAP-CT myelo	Figure
31/ f	compl. reg.pain syndr.	dystonia	B	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
56/ f	multiple sclerosis	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
37/ f	multiple sclerosis	spasticity	B	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
37/ f	compl. reg.pain syndr.	dystonia	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
58/ f	failed back surgery	pain	M	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
46/ m	cerebral trauma	spasticity	B	yes	normal	normal	normal		CAP-CT myelo	normal	dose adaptation	TN	TN	
31/ f	cerebral palsy	spasticity	B	yes	normal	normal			CAP-CT myelo	normal	dose adaptation	TN	TN	
61/ f	multiple sclerosis	spasticity	B	yes	normal	normal			CAP-CT myelo	normal, intra-thecal caudal flow	dose adaptation	TN	TN	

Table 1 Patient characteristics

B = baclofen
M = morphine
a,b,c = same patient

CAP = catheter access port
NCCT = non-contrast CT
LP-CT = lumbar puncture CT

TP = true positive
FP = false positive
TN = true negative
FN = false negative

*No further diagnostic procedures

Results

CAP procedures

Table 1 summarizes the patient characteristics. We performed 70 procedures in 53 patients. No adverse events were reported as a result of the procedures. In 13 patients, the method was conducted several times, which resulted in 17 additional procedures, when the patient's spasticity was insufficiently under control and another after two years for again an exacerbation of her spasticity (n=2), for a persistent leak (n=2) for an unexplained reoccurrence of treatment failure (n=2), for a persistent treatment failure (n=8), after the performed surgical intervention was found to have had a limited effect (n=1), for control of a surgical intervention (n=1), and four years after the successful microsurgical removal of an intradural cyst, when a broken catheter was replaced which resulted in a persistent dorsal dural leak at the original catheter insertion site (n=1).

CAP CSF aspiration

In 17 procedures, we could not aspirate the CSF, and therefore, contrast material was not injected via the CAP. In eight of them NCCT scans were performed, showing an epidural catheter position in four examinations (Fig. 1C), which was confirmed by LP-CT myelography in one case (Fig.1D), a downwards curved intrathecal catheter in one examination, whereby with additional ^{111}In-DTPA SPECT-CT, a normal ros-

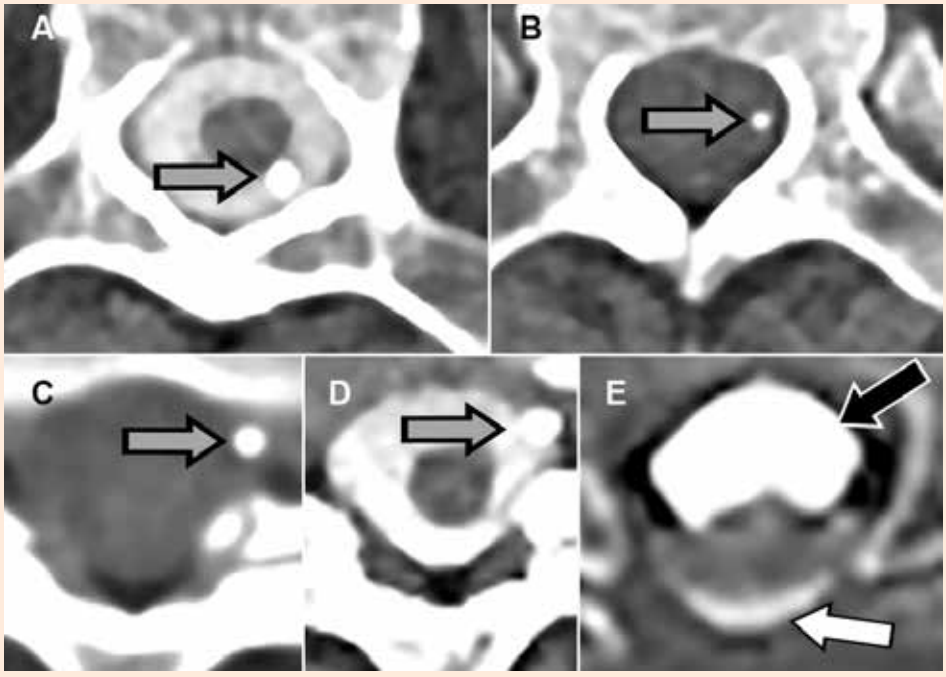

Figure 1. CAP-CT MPR myelography revealed a normal intrathecal 8731SC catheter tip position (A, gray arrow) and a regular small-diameter Ascenda catheter tip position (B, gray arrow). The NCCT MPR image fostered suspicion of an epidural tip position of the 8731SC catheter (C, gray arrow). LP CT myelography confirmed the epidural position (D, gray arrow). CAP-CT MPR myelography showed extensive subdural (E, black arrow) and minimal intrathecal (E, white arrow) contrast material, which explained the irregular contrast material distribution found with CAP myelography (Fig.3C).

tral CSF flow was identified, and normal findings in three examinations in which ^{111}In-DTPA SPECT-CT confirmed normal findings (n=2) or detected catheter obstruction (n=1). In the other nine patients, we performed LP-CT myelography (n=1) showing a granuloma, MRI (n=2) revealing normal findings, ^{111}In-DTPA SPECT-CT (n=3) demonstrating CSF flow obstruction (n=1), or normal results (n=2), and three patients refused further diagnostic procedures. In nine of the seventeen patients (53%) in which CSF aspiration was not possible scintigraphy revealed normal tracer distribution (n=5) and MRI revealed no abnormalities (n=2), dose adaption was successful, indicating a functional catheter.

CAP myelography

In 53 procedures, we injected the contrast medium via the needle in the CAP. Myelography could not be performed due to an unintended injection into the pump pocket (n=1, Fig. 2A). The reference standard (Table 1) was CAP myelography (n=2), MRI (n=1), CAP-CT myelography (n=31), ^{111}In-DTPA SPECT-CT (n=15), clinical outcome (n=2) and surgical findings (n=1). Sixteen of 52 CAP myelography's revealed a suspected pump-catheter related cause of ITDD failure including catheter leak (n=2, Fig. 3A), a downwards curved catheter with possible reduced flow (n=1), limited abnormal contrast distribution (n=6, Figs. 3B–C), an acute stop in the contrast distribution (n=2, Fig. 3D), a limited contrast distribution (n=5, Fig. 3E). In 12 of these 16 CAP myelographic procedures, the reference tests revealed a cause of ITDD failure, while in 4 procedures the limited contrast distribution (n=3) and a downwards curved catheter with possible reduced flow (n=1) turned out to be a false positive finding. Eleven normal CAP myelographic procedures were false negative as the reference tests revealed a cause of ITDD failure. The calculated sensitivity of CAP myelography was 52% (12/23) with a specificity of 86% (25/29).

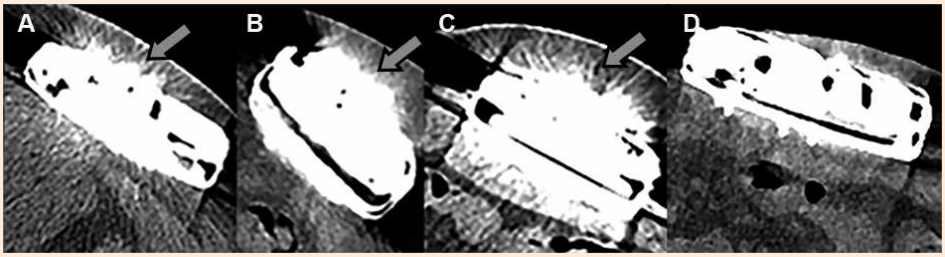

Figure 2. Scattering on CAP-CT MPR (gray arrow) images caused by contrast material in the pump pocket. At the procedure, 7 ml of contrast material was unintentionally injected into the pump pocket (A). A sheared catheter located in the pump pocket caused contrast material accumulation (B). Severe CSF and contrast material appearance in the pump pocket (C) as a result of a dorsal dural leak at the previous catheter insertion, where CSF passed retrograde along the implanted catheter, and a normal pump appearance after aspiration of the fluid and dural leak treatment with an epidural blood patch (D).

CAP-CT myelography

We carried out 50 CAP-CT myelography procedures in which images of the spinal column were reconstructed. In 24 of the procedures, the FOV of the image reconstruction was enlarged to the extra-vertebral region, including the abdominal pump position and the extra-spinal catheter tract. The reference standard (Table 1)

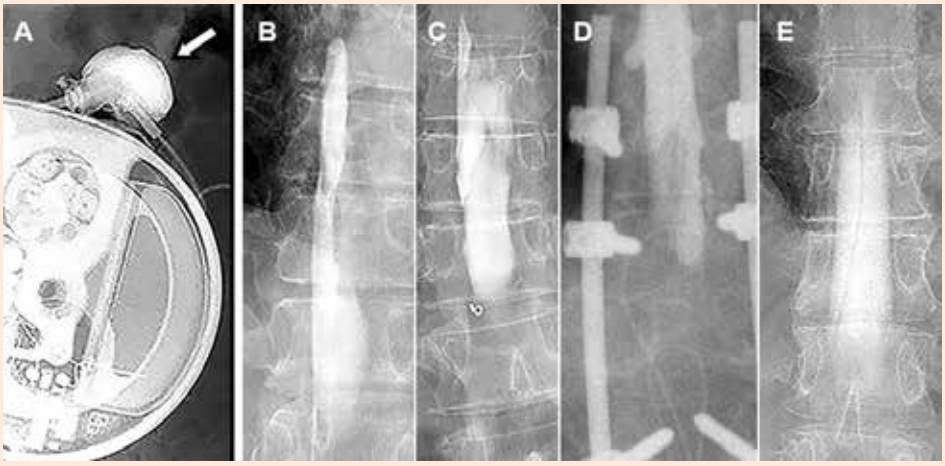

Figure 3. CAP myelography revealed a pump-catheter connector leak (A, arrow), irregular distribution of the contrast material, caused by an intradural cyst (B), subdural catheter position (C), CSF flow obstruction (catheter tip position above the obstruction) (D), and an inadequate Trendelenburg maneuver (E).

was CAP myelography (n=1), CAP-CT myelography (n=31), ^{111}In-DTPA SPECT-CT (n=15), clinical outcome (n=2), and surgical findings (n=1). CAP-CT myelography revealed 16 suspected causes of ITB failure including dorsal dural leak (n=5, Figs. 4F-G), subdural catheter position (n=2, Fig. 1E), limited rostral flow of contrast material (n=4), limited and abnormal contrast distribution (n=3), obstruction of rostral flow (n=2). The extra-vertebral image reconstructions revealed 3 causes of ITDD failure including contrast media around the pump owing to a leak at the pump-catheter connection (n=1), a sheared catheter in the pump pocket (n=1, Fig. 2B), contrast material in the abdominal soft tissue due to a catheter leak (n=1, Fig. 4B-C), which was not identified by CAP myelography (Fig. 4A). Dural leaks (n=5) were caused by a previous catheter insertion site (n=4, Figs. 2C, 4D-E), and after a reinsertion of a catheter (n=1, Figs. 4F–G). In two cases the dural leak which was visible on the spinal CAP-CT myelography was accompanied by retrograde flow to the pump pocket, visible on the extra-vertebral image reconstruction (Fig. 2C).

In two procedures, a limited contrast distribution was found which turned out to be false positive findings. CAP-CT myelography was normal in 31 procedures. Four normal CT-CAP myelographic procedures were false negative as the reference tests revealed a cause of ITDD failure, including one examination in which only the spinal region was evaluated while a catheter leak was present in the extra-spinal region, one examination in which the follow-up scintigraphy was normal, but an intrathecal catheter leak was found during surgical intervention, one examination in which scintigraphy revealed catheter obstruction and one examination in which scintigraphy revealed retrograde tracer distribution via a retained catheter. The CAP-CT procedures resulted in a sensitivity of 81% (17/21) and in a specificity of 93% (27/29).

Discussion

Based on the analysis of the observational collected data of CAP and CAP-CT myelography during for troubleshooting, we confirmed the importance of CAP-CT myelography in diagnosis the causes of ITDD failure. The procedure

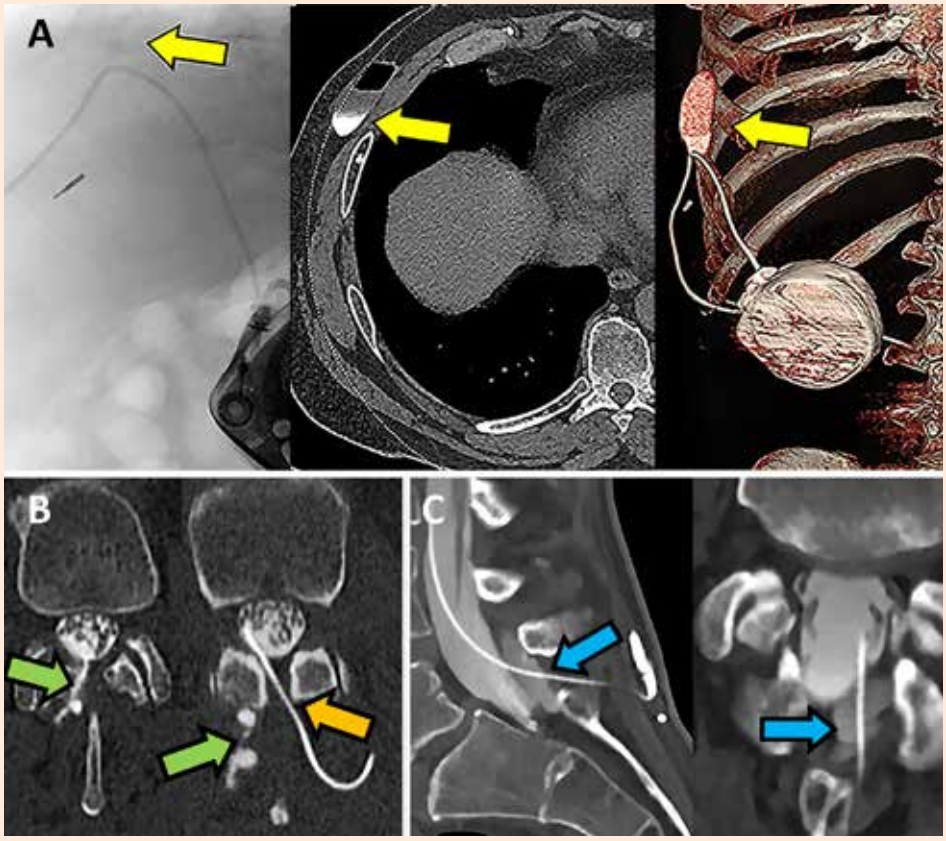

Figure 4. A: The tiny catheter leak was not recognized with CAP fluoroscopic myelography (left, yellow arrow). CAP-CT MPR myelography revealed abnormal subcutaneous contrast material accumulation (middle, yellow arrow). The 3D VRT reconstructions demonstrated minor catheter leak (right, yellow arrow). B: CAP-CT MPR myelography showed dural leak at the original insertion of a migrated catheter (green arrow), with at the opposite site the newly inserted catheter (orange arrow). C: CAP MIP myelography showed minor extradural contrast accumulation, which was caused by a small dural leak (blue arrow).

could be performed safely. CAP-CT myelography exhibited better sensitivity and specificity than CAP myelography. Finally, NCCT could be helpful for the diagnosis of epidural catheter position when fluid cannot be aspirated via the CAP and CAP-CT myelography is therefore not possible.

CAP procedure

When fluid cannot be aspirated from a pump, it does not always indicate a catheter obstruction or a disconnection[16], as we confirmed in nearly half of the cases. We initially terminated the CAP procedure if the fluid could not be aspirated. To diagnose an epidural catheter position, an NCCT scan could be performed. This finding underscores the relevance of replacing standard plain radiography as a postoperative procedure with low-dose CT,[17] which could result in an earlier detection of ITDD failure.

CAP myelography

This study confirmed that an appropriate diagnosis, or identifying an abnormality, can often not be made with CAP fluoroscopy and myelography only, which limits their value when not followed routinely by CAP-CT myelography. Therefore, the use of only CAP-CT myelography has been suggested.[18] However, fluoroscopy provides a screening overview that makes it possible to identify sufficient intrathecal distribution of contrast material, which is crucial for an optimal diagnostic CT myelography examination. An optimal distribution of contrast material can be achieved through rotation and turning of the patient in different directions, including the Trendelenburg position. An inadequate distribution of contrast material could result in false-positive examinations, as the limited distribution may be interpreted as a CSF flow obstruction. Therefore, when fluoroscopy reveals insufficient contrast material distribution in the intrathecal space, the Trendelenburg maneuver should be performed or repeated.

CAP-CT myelography

Through the use of CT myelography extended with 2D MPR/MIP and 3D VRT post-processing reconstructions, we achieve substantial improvement in diagnostic accuracy. The found sensitivity and specificity of the spinal CT myelography examinations indicated the usefulness of the proposed procedure. However, the extra-vertebral parts of the ITDD system should be included in the reconstructed FOV to detect rare catheter leaks or dural leaks that only become manifest as a result of accumulations of contrast material in the pump pocket. This unexpected finding was caused by retrograde flow of CSF and contrast material along the implanted catheter to the pump pocket in catheter and dural leaks. This means that, when fluid accumulation in the pump pocket is detected, a dural leak should be considered.

The reduction of beam-hardening artifacts on DECT facilitated the identification of fluid in the pump pocket and leaks at the metal catheter–catheter connection. However, beam-hardening reduction should be used carefully when one suspects a leak in the pump pocket, which can cause more irregular scattering that resembles beam hardening. The diagnosis of a leak could be overlooked when a strong beam-hardening reduction algorithm is applied.

The observed accumulation of the contrast material in the subdural space, with a faint distribution in the intrathecal space, due to a subdural location of the catheter is rare. The subdural cavity between the meningeal layer of the dura mater and the inner arachnoid mater of the leptomeninges that are adherent to each other usually does not exist.[19] One of the explanations is unintentional separation during puncture.[20, 21]

In all of the patients with an unintended epidural catheter, the cause was not a dural perforation at the tip of the catheter but an epidural position starting at the dural insertion. Despite the epidural location, aspiration of 2 ml via the CAP was possible. It seems that, despite low-volume infusion, epidural fluid accumulation occurs when tissue absorption is insufficient, which is likely related to epidural fibrosis as a result of long-term infusion.[22-24]

After identifying normal rostral distribution with scintigraphy, we accepted the finding of the curved catheter in the intrathecal space as normal in the absence of further complications.[25] Although an intracranial subarachnoid hemorrhage can occur as a result of the intrathecal catheter migration of a retained catheter,[26] the standard approach in the absence of clinical symptomatology is not to remove it.[25] However, the situation is different when the retained catheter creates a fistula in the surrounding tissue that leads to a CSF leak, which was fortunately not present in our series.

Additional imaging procedures

When we cannot assess the cause of ITDD failure with CAP-CT myelography, we normally proceed with other imaging modalities, such as MRI and/or lumbar puncture CT myelography. In particular, when we needed dynamic information concerning catheter flow or the distribution of intrathecal contrast material, we performed ^{111}In-DTPA SPECT-CT scintigraphy. Owing to the high accuracy of ^{111}In-DTPA SPECT-CT, it is open to discussion whether the primary choice for ITDD troubleshooting should be CAP-CT myelography or ^{111}In-DTPA SPECT CT scintigraphy.[11] We prefer our modified (DE) CT-CT myelography, as it offers excellent possibilities in terms of identifying flow obstruction, catheter kinking, and leak. Further advantages are that puncturing the CAP provides an opportunity to aspirate CSF for diagnostic microbiological and pharmacological examinations. For therapeutic purposes, the intrathecal catheter content can be aspirated after an overdose or for complex dose concentration changes. Moreover, a bolus dose of the current medication, an additional drug, or contrast material for controlling the ITDD can be injected via the CAP. CAP-CT myelography generally provides more local information, than low-dose ^{111}In-DTPA SPECT-CT. In dural and catheter leaks, the more detailed images of CAP-CT myelography are essential in the treatment. However, ^{111}In-DTPA SPECT-CT is of value when no fluid can be aspirated via the CAP. In addition, when a normal-shaped limited flow is identified and there is no certainty that the Trendelenburg position has been appropriately performed, scintigraphy can be used to visualize the physiologic fluid distribution. In both methods, however, identifying fluid in the pump pocket can be an issue. In CAP-CT myelography, pump scattering can mask the presence of fluid, although the irregular scattering of fluid differs from that of beam hardening caused by the pump. The problem can be overcome by reducing the scattering via advanced CT techniques like DECT. We found that, in ^{111}In-DTPA SPECT-CT, the intense tracer activity in the pump is not an obstacle to assessing aberrant fluid in or nearby the implanted pump with the use of image scaling and the progression of the fluid accumulation during multiple imaging sessions. Hence, we disagree with those who advocate reserving the CAP-CT procedure only for emergencies and using ^{111}In-DTPA in all non-acute situations.[11] As the first line of advanced imaging in troubleshooting, the advantages of scintigraphy do not outweigh the convenience and accuracy of a CAP(-CT) myelographic procedure, even when one not consider the burden placed on the patient, the costs, and the low likelihood of availability in every center.

Study limitations

The analysis of the observational routinely collected data was intended to evaluate the diagnostic role of CAP-CT myelography in ITDD failure and to improve the procedure and the evaluation of its results. A limitation is that the data analysis could not be addressed using existing reporting guidelines such as STrengthening the Reporting of OBservational studies in Epidemiology (STROBE).[27] Nevertheless, routinely collected data are frequently used to improve patient care and health care efficiency. To our knowledge, our study is the most extensive analysis; however, the sample size is small. In addition, the retrospective character of this research presents a chronology bias;[28] how this might have influenced our conclusions must be considered. To reduce misclassification bias, all images were reassessed. The most important limitation is the unstructured approach to data collection, which resulted in the absence of a standardized reference test based on a second imaging modality or surgery to determine the real cause of ITB failure. Instead, we composed the reference based on all available data, including the index test, additional imaging mo-

dalities, surgery, and wait-and-see results. Despite the bias in the design of this study, the data suggest that CAP myelography followed by CAP-CT myelography are indispensable steps in determining the causes of ITDD treatment failure.

Conclusions

In our view, the main contributions of this article are as follows:

- After plain radiography, CAP-(DE)CT myelography with image reconstructions of the spinal and extra-vertebral regions in combination with 2D MPR/MIP and 3D VRT reconstructions is a first-line advanced imaging procedure for cases involving ITDD failure and can serve as the standard in the majority of the cases on which treatment decisions can be based. However, we experienced a substantial overlap with ^{111}In-DTPA SPECT-CT in the final diagnosis.
- Failure to aspirate CSF via the CAP does not indicate a catheter failure in all cases. When aspiration is not possible, an NCCT-scan should be performed to exclude an epidural catheter position.
- Solely conducting CAP myelography is insufficient for the diagnosis of ITDD but it has value in facilitating needle insertion of the CAP and as a screening method determining sufficient distribution of the contrast material, which is crucial for a diagnostic CAP-CT myelography.

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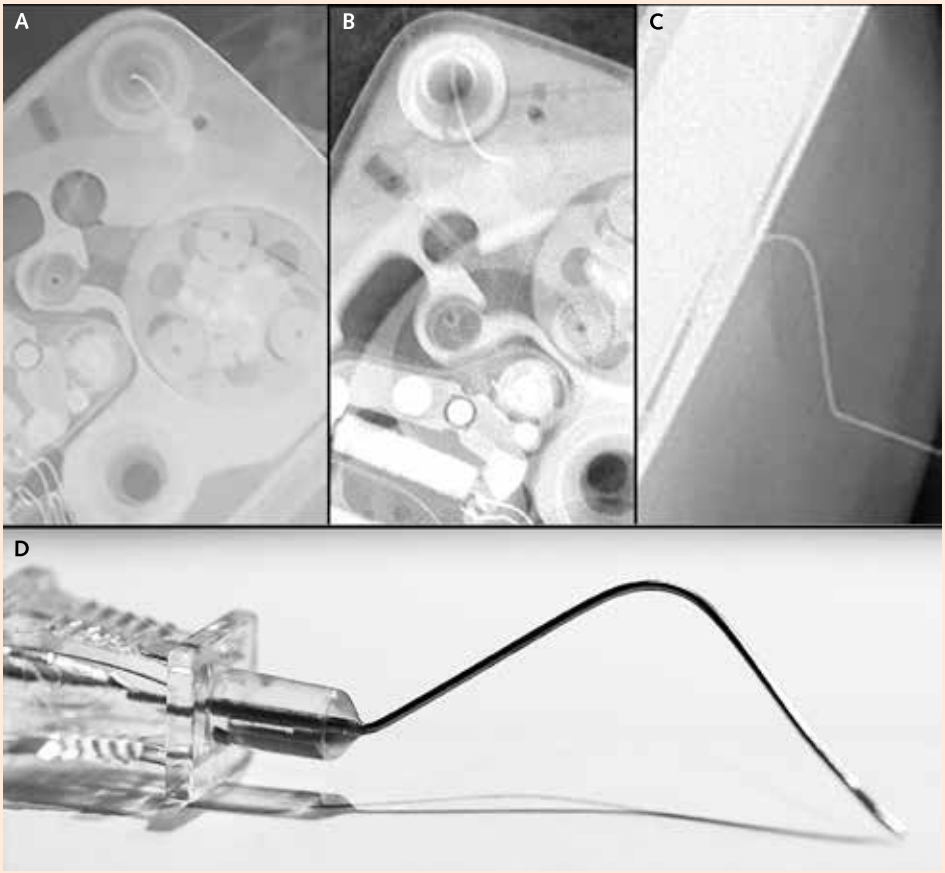
Supplementary Appendix

CAP needle insertion

In 65 of the 70 procedures, we could retrieve data about the needle insertion in the CAP funnel. In 40 cases, we had a regular needle insertion, and in 19 and 6 cases the needle insertion was associated with mild and severe needle bending, respectively (eFig.1).



eFigure 1: Needle insertion of the catheter access port (CAP) funnel with mild (A) and severe needle bending (B–D).

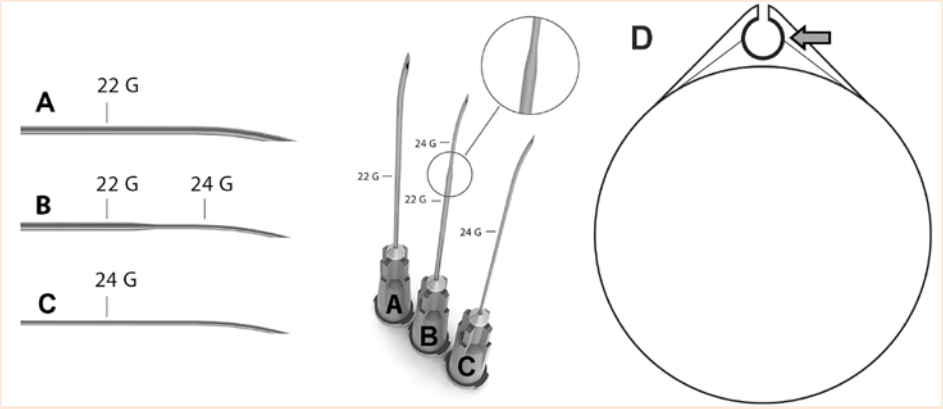
Discussion

For puncturing the CAP, a nearly perpendicular approach to the funnel-shaped opening is required to recognize and pass the built-in silicone septum. We experienced a tendency of bending and distortion of the thin needle—in particular, in a more deeply positioned pump, or in the presence of rigid fibrotic scar tissue—which causes the procedure not to be easy. When the extended fibrotic reaction is present around the pump, the recognition of the stiff fibrotic tissue or the CAP silicone membrane

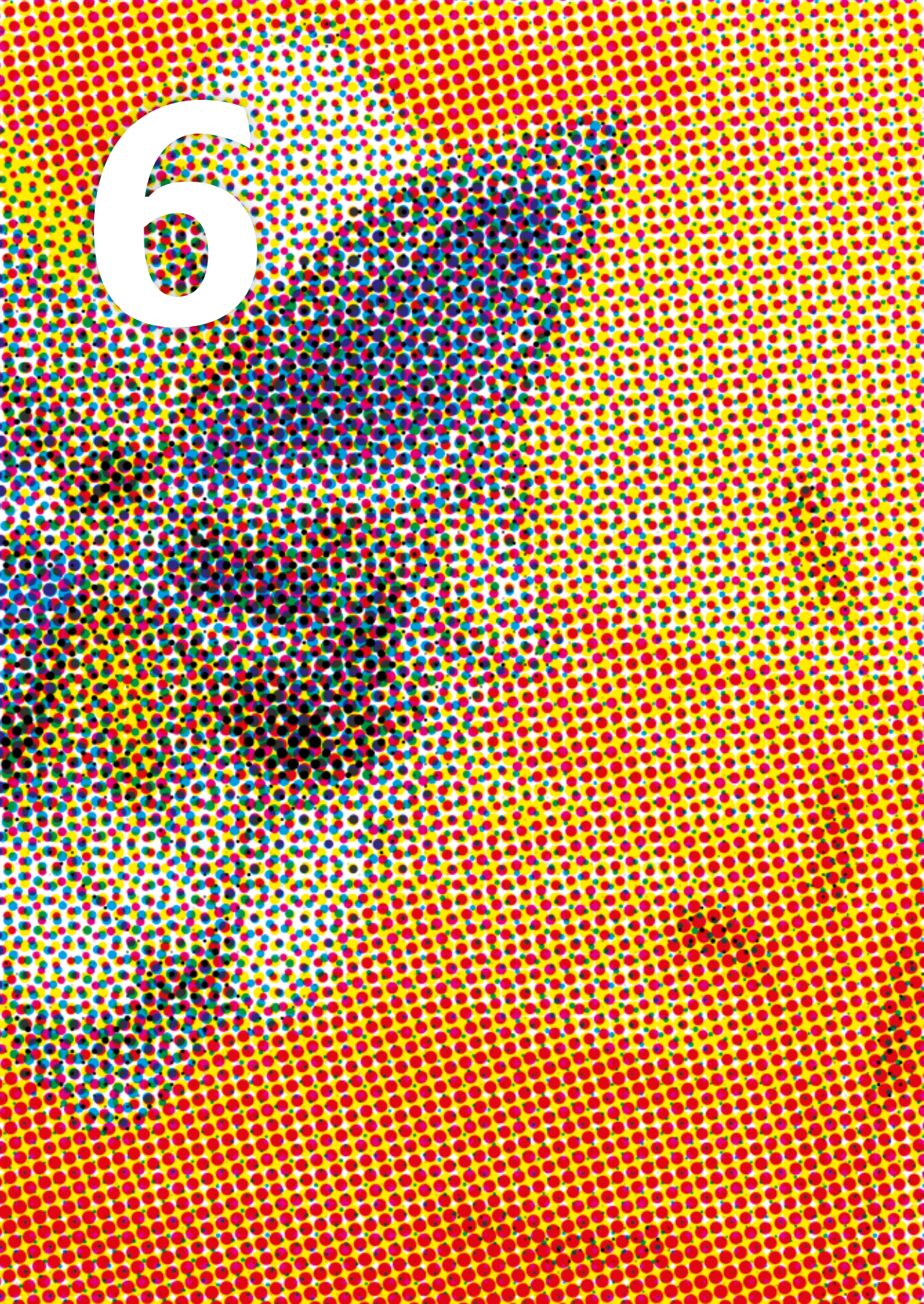
can be problematic. This occurrence plays a role when we cannot aspirate fluid. In our opinion, there is, therefore, an urgent need for improvement of the insertion with the vulnerable 24G Huber needle. We are convinced that the complexity of the CAP needle insertion plays an essential role in omitting the procedure mentioned in the literature.[15]

Proposal

A solution for the vulnerable 24G Huber needle could be the use of a conical 20G–24G one (eFig.2). We have (as of yet) been unable to find a manufacturer of such a needle.



eFigure 2: Huber needle for pump reservoir refill (A). A conical-shaped Huber CAP needle with a proximal diameter of 22G, and a distal one of 24G, is suggested to prevent needle distortion (B). Current Huber needle for CAP insertion (C). Another improvement would be a template of the CAP kit with a partially open ring (D, gray arrow).


6

Isotopic scintigraphy in intrathecal drug delivery failure: A single institution case series

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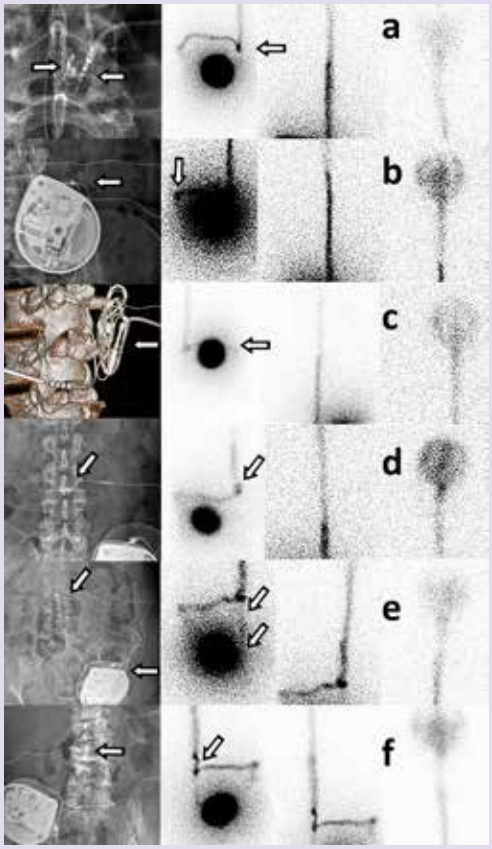

Submitted

ABSTRACT

Objective

To assess the feasibility and diagnostic accuracy of an optimized ^{111}Indium-diethylenetriamine-penta-acetic-acid Single Photon Emission Computed Tomography (^{111}In-DTPA SPECT-CT) examination in patients with intrathecal drug delivery (ITDD) failure.

Design

Retrospective analysis of observational, routinely collected data from a case series of patients.

Setting

University Center for Pain Medicine and Department of Radiology & Nuclear medicine.

Participants

Twenty-seven patients participated between January 2014 and January 2019. Thirty-six examinations were performed.

Methods

Standardized pump flow rate with additional SPECT-CT imaging was performed. Ten ml mixture of the treatment medication and 20 MBq ^{111}In-DTPA was injected in the pump reservoir. Planar and SPECT-CT images were acquired at 24, 48, and 72 h after injection, and at 96 h and/or 7 days, if needed. Reassessment of all images by the first two authors according to a conventional analysis on planar imaging and to optimized analysis with evaluation of SPECT-CT images, taken into account a standardized pump flow rate and with a stepwise standardized interpretation.

Results

Twenty-two abnormalities in twenty-one examinations were identified, 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. CSF flow obstruction turned out to be false a positive finding at follow-up (n=1). In the 15 normal examinations one false negative finding was encountered. The sensitivity was 95% (20/21) and the specificity 93% (14/15). A a significant difference ($p < 0.000$) was found between the accuracy of the conventional analysis and optimized analysis.

Conclusions

The optimized ^{111}In-DTPA SPECT-CT examination is a powerful diagnostic to detect the cause of ITDD failure.

Keywords

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

Introduction

Intrathecal baclofen or analgesic drug delivery (ITDD) using an implanted pump system is a well-established treatment with approximately 30,000 implants per year. Despite advancements in manufacturing technology and implantation techniques, a high incidence of adverse events and therapy failure is reported.[1-4] For many years, consensus guidelines for troubleshooting in ITDD were lacking, which may increase the risk of underdiagnosis, undertreatment, unneeded surgical interventions, or even

unjustified termination of therapy. ITDD failure has an enormous impact on the patients' quality of life, because it is the last-resort therapy for many patients. Tolerance for treatment,[5] exacerbation of the underlying disorder or comorbidity as a cause of the failure should therefore be concluded after extensive diagnostic procedures only. Recently, an expert panel developed an algorithm to reach consensus on the optimal diagnostic approach in ITDD failure,[6] and a guideline for the interpretation of the plain radiography was published.[7] The indications for more advanced diagnostic procedures are 1) a decrease in the effectiveness of ITDD; 2) a discrepancy between obtained residual volumes by the refill procedure and those calculated by the pump device; 3) manifest or occult drug and cerebrospinal fluid (CSF) leakage, or 4) a repeated and sometimes extremely high dose increase without a sufficient clinical response.[6,8,9] In suspected ITDD failure, the initial steps in the diagnostic approach are clinical history taking[9], a readout of the pump programming, a check for the presence of medication fluid in the pump reservoir, and plain radiography examinations.[7] However, when this approach is inconclusive, there is no consensus on the further evaluation. The possible next steps could be the aspiration of CSF from the intrathecal space via the catheter access port (CAP)[6,9], contrast material injection via the CAP combined with computed tomography (CT) myelography,[6,10,11] high-resolution CT with two-dimensional (2D) and three-dimensional (3D) reconstructions[12], or a surgical catheter or pump revision (without diagnostic procedures before surgery). When the first three steps do not reveal the cause, ^{111}Indium-diethylenetriamine-penta-acetic-acid (^{111}In-DTPA) scintigraphy could be performed.[5,8-10,13-18] Some clinicians even bypass the CAP procedure and use ^{111}In-DTPA imaging as the next step after plain radiography.[19] With its long radioactive half-life time of 2.8 days, ^{111}In-DTPA offers unique possibilities for dynamic imaging studies. After injecting into the pump reservoir images can be acquired for several days following the radiotracer distribution in the spinal catheter system and the subarachnoid space, without interrupting drug treatment.[13-15,17] ^{99m}Technetium-DTPA has also been used for this purpose[5,13], but due to ^{99m}Technetium's limited half-life time of six hours, the pump 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.[5]

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.[15] In this retrospective study of observational, routinely collected data, we intend to assess 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, performing additional single-photon-emission low-dose computed tomography (SPECT-CT) imaging and the use of a standard evaluation format for image interpretation. We hypothesize that an optimized ^{111}In-DTPA scanning protocol and analysis including evaluation according to a standard format is needed and that SPECT-CT is a useful addition to planar imaging.

Materials and methods

We included all adult patients who underwent ^{111}In-DTPA scintigraphy for ITTD failure evaluation between January 2014 and January 2019. All patients except one were referred from other centers for ITTD troubleshooting. In all patients, conventional diagnostic modalities including clinical history, a readout of the pump programming, accurate aspiration volume ver-

sus interrogated, or plain radiography did not reveal the diagnosis. In 2014, the optimized ^{111}In-DTPA protocol and analysis (OP, Table 1) was implemented in our center. Standardization of the pump flow rate allows the evaluation of tracer transit time which is crucial for a correct interpretation of the images. From cerebral fluid flow studies[20, 21], it is known that the upward flow from caudally up to the cerebral cisterns takes 2 to 2.5 h, with a steady state reached after 8 h. With the infusion rate we used, in which the catheter tip is reached in 24 h, the cerebral cisterns should be visible at 48 h after the filling of the pump, due to both CSF flow as well as passive tracer diffusion in the CSF. The additional SPECT-CT is intended to obtain more detailed information about the location of a potential flow disorder. This retrospective study has been approved by the Medical Ethics Committee of the EMC, 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 for information on the catheter properties and the medication concentration was performed. The expected transit time for reaching the catheter tip was calculated. When the catheter end would not be achieved in 24 h, the pump was programmed for a bridge bolus. 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 placed into the reservoir[22,23], which usually takes one to several days. At the nuclear medicine department, 10 ml of the 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 h and/or 7 days after pump filling using a Siemens Symbia T16 SPECT-CT scanner (Siemens Healthcare, Erlangen, Germany). Planar images (256 x 256 matrix, medium-energy limited purposes (MELP) collimator) were acquired from anterior and posterior of the pump/abdomen region, the thorax, and the head/neck region with an acquisition time of 10 minutes per view (and 20 minutes at 7 days post-injection). After that, SPECT-CT was acquired for verification, attenuation correction and anatomical localization. SPECT parameters were 128 x 128 matrix, 60 views/detector, 30-second time per view. Low-dose CT parameters were: 110 kV, 40 mAs, a 0.6-second tube rotation, 0.8 mm pitch, and a 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 be pump malfunction, leakage at the pump-catheter connection or the connection of 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 (ED, DvA) evaluated the planar images according to the conventional analysis (CA) which was distilled from six case studies in literature[13-17] In these studies imaging is performed after 4 to 72 h[14-18]. In some publications, progression time of tracer through the catheter was calculated, and - if needed - the time for imaging was customized.[17,18] When the tracer progressed along the subcutaneous and intrathecal catheter part and the tracer was distributed[14] evenly throughout the cerebral cisterns, without any signs of leakage, the examination was regarded as normal (Table 1).[17] All previous studies were done without a standardized pump flow rate, without SPECT-CT[18] except in one study, and without a standardized stepwise imaging interpretation. Thereafter they reanalyzed the images based

on the optimized ^{111}In-DTPA scanning protocol (OP) and analysis with evaluation of SPECT-CT images, taking into account a standardized pump flow rate and with a stepwise standardized interpretation (Table 1).

Conventional analysis (CA) - Planar imaging assessment
Optimized practice (OP) - Planar imaging assessment - SPECT-CT assessment - Standardization pump flow rate - Stepwise standard interpretation

Table 1. CA versus OP.

The stepwise and standardized interpretation of the images included the following:

- Step 1. Is the pump flow rate standardized?
- Step 2. Is access to patient's file and previous other imaging procedures available?
- Step 3. Is the pump visibility, is tracer activity around the pump visible, and has the tracer activity a normal shape?
- Step 4. Are the abdominal horizontal catheter segments visible, is normal tracer spread in the subcutaneous part of the catheter from anterior to posterior present?
- Step 5. Is the tracer activity at the horizontal/vertical catheter transition, normal or enhanced?
- Step 6. Is caudal spread of tracer activity visible, if yes, is the tracer activity normal, enhanced or broadened? When visible, is tracer activity already present at the catheter tip?
- Step 7. Is tracer activity present in kidneys/bladder/elsewhere in abdomen? When visible, is tracer activity already present at the catheter tip?
- Step 8. Is the distribution of tracer activity spread in the lumbar and thoracic catheter segment in the spinal canal, normal? Is the intensity of tracer activity increased or has it a broader aspect? Is increased tracer activity accumulation present at catheter tip?
- Step 9. Is tracer activity visible in the spinal canal above the level of the catheter tip, and in the cerebral cisterns. Has the tracer activity a normal intensity? Do we have relative differences in tracer activity?

Data analysis

The sensitivity and specificity were calculated, comparing the results of the imaging assessment (conventional analysis and optimized analysis) as the index test and the final diagnosis after three months as the reference test, which was based on all relevant imaging and clinical and surgical information.

A true positive result was thereby defined when an abnormality could be demonstrated with the index test and the reference test revealed indeed a cause of ITDD failure, a true negative when an abnormality was not found with the index test and the reference test, a false positive when an estimated abnormality could not be confirmed by the reference test, and a false negative when the abnormality was missed. The accuracy of the conventional analysis and the optimized ^{111}In-DTPA procedure were compared with the McNemar Test with IBM SPSS Statistics Version 25.

Results

Patients

Thirty-six ^{111}In-DTPA planar and SPECT-CT examinations were performed in 27 patients. In 7 patients, the examination was performed two times and three times in one patient. Patient characteristics are summarized in Table 2. In all drug delivery standardization procedures with the bridge bolus and in all scintigraphy examinations no adverse events were encountered.

The reference standard (Table 2) was the results obtained with the optimized procedure analysis (n=17), including optimized planar (n=16) and SPECT-CT (n=1) or findings during intervention (n=19). With the conventional analysis 11 of 36

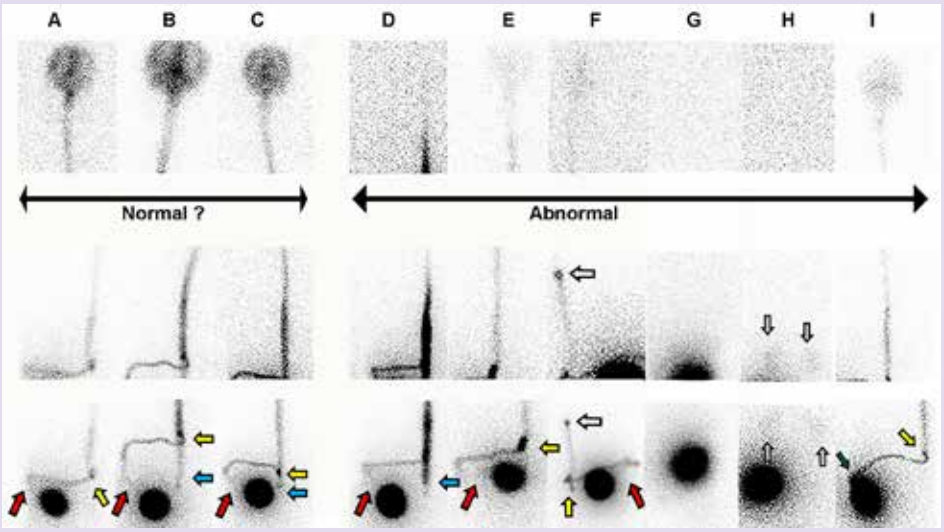

Figure 1. Examples of planar images from 9 examinations with a standardized pump flow rate of the abdomen, thorax and head region (resp. lower, middle and upper row).
Upper row: normal (A, B, C) and reduced (D–I) tracer activity at the cerebral cisterns.
Middle row: enhanced tracer activity at catheter tip (F, white arrow), 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 activity (H, gray arrows), abnormal pump shape (I, dark gray arrow), enhanced tracer activity at catheter tip (F, white arrow).

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 a visible pump only (n=2). With the optimized ^{111}In-DTPA protocol and analysis 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: catheter obstruction and leakage at the pump-catheter connection (Figs. 1E, 2). Fifteen examinations did not reveal the cause of ITDD treatment failure. In 19 of these 21 examinations, interventions confirmed the cause of ITDD failure, while after 1 positive examination no surgical intervention was performed. In one examination the diagnosis of CSF flow obstruction based on limited rostral tracer distribution turned out to be a false positive finding at follow-up. In the 15 normal examinations one false negative finding was encountered.

	Age Sex	Disorder	Symptomatology	Medication	Cath. tip	Planar results	TP/ TN/ FP/FN	Planar results	SPECT-CT results	TP/ TN/FP/ FN	Best standard reference	Final diagnosis	Treatment	Clinical result	Figure
						convential analysis		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	1H, 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 blood-patch	improved	
7	50/f	CRPS	dystonia	B	T2	normal	FN 2	normal	leakage dorsal	TP 5	intervention	dural leakage	epidural blood-patch	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 blood-patch + puncture pocket	dystonia under control	

	Age Sex	Disorder	Symptomatology	Medication	Cath. tip	Planar results	TP/TN/FP/FN	Planar results	SPECT-CT results	TP/TN/FP/FN	Best standard reference	Final diagnosis	Treatment	Clinical result	Figure
						convential analysis		optimized practice							
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	FBS	pain	M	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	SCl 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	
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	SCl C5	spasticity	B	T7-8	normal	FN 6	obstruction rostral tracer distribution	obstruction rostral tracer distribution	TP 8	intervention	CSF flow obstruction	replacement catheter	spasticity under control	5
25	51/m	SCL C6	spasticity	B	T8	obstruction rostral tracer distribution	TP 4	obstruction rostral tracer distribution	obstruction rostral tracer distribution	TP 9	intervention	CSF flow obstruction	replacement catheter	spasticity under control	
26	64/m	SCL T12	spasticity	B	T9-10	normal	FN 7	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 5	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	normal	FN 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 6	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 7	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	normal	FN 9	obstruction catheter	obstruction catheter	TP 15	intervention	obstruction catheter	replacement catheter	spasticity under control	

	Age Sex	Disorder	Symp-tomatol-ogy	Medi-cation	Cath. tip	Planar results	TP/ TN/ FP/FN	Planar results	SPECT-CT results	TP/ TN/FP/ FN	Best standard reference	Final diagnosis	Treatment	Clinical result	Figure
						convential analysis		optimized practice							
32	59/m	SCL T5-6	spasticity	B	T8	normal	FN/FN 10(11)	obstruction catheter	obstruction catheter + leakage pocket	TP/ TP 16 (2x)	interven-tion	obstruction catheter (dorsal, lumbar transition) + leakage catheter (part in pocket)	replace-ment catheter	spastici-ty under control	1E, 2
33	46/f	SCL C6-7	spasticity	B	T10	obstruction catheter	TP 8	obstruction catheter	obstruction catheter	TP 17	OP	obstruction catheter	replace-ment catheter scheduled	passed away	
34	43/m	SCl C7	spasticity	B	T8	obstruction catheter	TP 9	obstruction catheter	obstruction catheter	TP 18	interven-tion	obstruction catheter	replace-ment catheter	limited im-proved	
35	37/m	SCL T4	spasticity	B	T7	obstruction catheter	TP 10	obstruction catheter	obstruction catheter	TP 19	interven-tion	obstruction catheter	replace-ment catheter	only im-proved spastici-ty lower extremi-ties	
36	66/f	FBS	pain	M	T9	obstruction catheter	TP 11	obstruction catheter	no tracer distribution in spinal canal	TP 20	interven-tion	obstruction catheter	removal system, termi-nation treatment	un-changed	1F

Table 2. Patient characteristics.
CP=cerebral palsy, CRPS=complex regional pain syndrome, FBS=failed back surgery, MS=multiple sclerosis, SCL=spinal cord lesion (C=cervical, T=thoracic), CSF=cerebrospinal fluid, TP=true positive, TN=true negative, FP=false positive, FN=false negative.

Leakage

Seven examinations revealed leakage. Only two were clearly recognized on planar images, which showed only tracer activity In the pump or an abnormal pump shape (n=1, Fig.1I, dark gray arrow), and additional SPECT-CT confirmed the presence of tracer activity outside the pump in the pump pocket. The remaining cases of leakage were found with SPECT-CT (n=5): leakage in the pump pocket (n=1) caused by a sheared catheter located in the pump pocket (Fig.2G-J), retrograde leakage 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 them the dorsal leakage was also 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 the persistent ITB failure, a catheter replacement was performed, whereby minor catheter damage of the intrathecal catheter part was found.

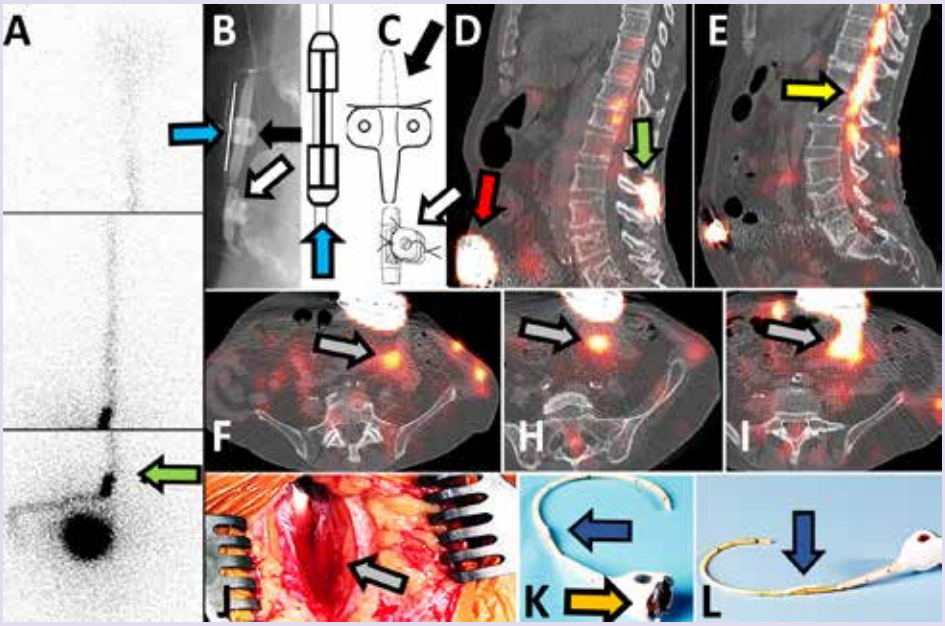

Figure 2. Sheared catheter and leakage in the pump pocket in a 59-year-old male with spasticity with a spinal cord lesion at T5. Dorsal tracer accumulation in the drug delivery system parts (A, green arrow) including needle-shaped catheter-catheter connector (B,C, blue arrows), anchor (B,C, black arrow) and retained old-type anchor (B,C, white arrow). Enhanced tracer activity at the abdominal/lumbar transition (A, lower row) with limited tracer activity in the cerebral cisterns (A, upper row) was suspicious for catheter obstruction. SPECT-CT fusion images show enlargement of the pump shape (D, red arrow) and some fluid outside the pump pocket (F-I, gray arrows). At surgery fluid in the pump pocket was identified (J, gray arrow) caused by a sheared catheter. Also, at surgery a catheter obstruction was found. Post-explantation image of the system showed a catheter-pump connector distortion (K, orange arrow) and a sheared catheter (K,L, purple arrow).

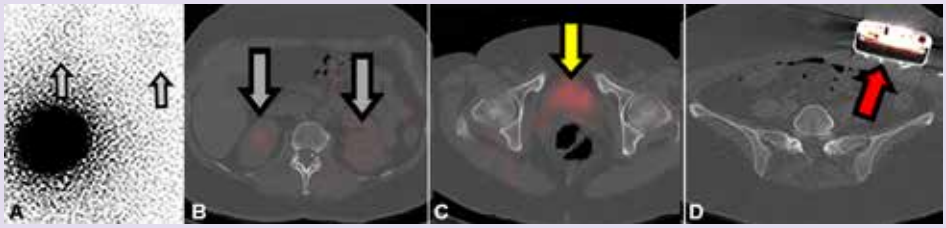

Figure 3. A 54-year-old woman with pain caused by failed back surgery, in which a readout of the pump revealed a normal pump delivery rate. Planar image (A) revealing a normally shaped pump, with subtle tracer activity in the kidneys (A, gray arrows), and no tracer activity in the catheter segments. SPECT-CT (B-D) confirmed tracer activity in the kidneys (B, gray arrows) and in the bladder (C, yellow arrow), and no signs of tracer activity around the pump in the pump pocket (D, red arrow). The subtle tracer activity outside the pump (in kidneys and bladder) means that the tracer passed the inner pump tubing and has 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) makes leakage at the pump catheter-connector also very unlikely. A subtotal catheter obstruction was therefore considered, alt-hough the lack of tracer activity in the catheter segments could not be fully explained. MRI revealed a granuloma at the tip of the catheter which was confirmed at surgery.

Catheter obstructions

Seven catheter obstructions were found. Five were recognized at planar imaging with conventional analysis with augmented tracer activity at the catheter tip with a minimal rostral spread (n=3, Fig.1F), increased tracer activity at the abdominal horizontal-vertical lumbar catheter transition (n=1, Fig.1E) , and with tracer activity in the pump only (n=1, Fig. 1G), and associated with tracer activity in the kidneys and bladder (n=1,Fig.1H,3A-C). In the latter patient a granuloma at the catheter tip was detected during surgery. Two examinations were considered normal with conventional analysis, but optimal analysis interpreted increased activity at the abdominal horizontal-vertical lumbar catheter transition as obstruction (n=2, Fig.1E).

CSF flow obstruction

In eight examinations CSF flow obstruction was diagnosed and one of them was a false positive finding. Four of the remaining seven diagnoses could be based on planar imaging with conventional analysis. Planar and SPECT-CT images of the optimized protocol and analysis indicated CSF flow obstructions (n=8). One of them was a false positive finding. The remaining seven showed lumbar broadening and extended caudal activity in combination with invisible or limited visible cerebral cisterns (n=5, Fig.1D,4), gradually increasing caudal activity in combination with reduced rostral flow (n=1, Fig. 5), or only limited rostral flow (n=1).

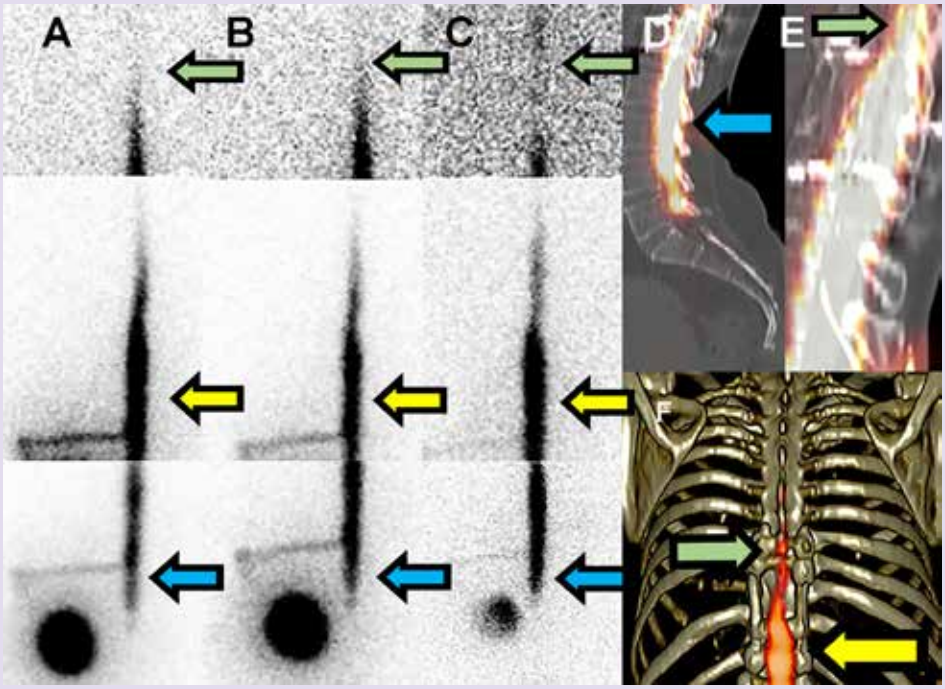

Figure 4. CSF flow obstruction in a 47-year-old female with spasticity with a spinal cord lesion at T10. Planar imaging at 48 h (A), 72 h (B) and 7 days after injection (C) revealed increased lumbar-caudal tracer activity (yellow and blue arrows) and tapering of tracer activity with reduced rostral tracer activity spread (green arrows) without tracer activity at the cerebral cisterns. SPECT-CT images (D,E) also showed increased tracer activity at the lumbar-caudal 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.

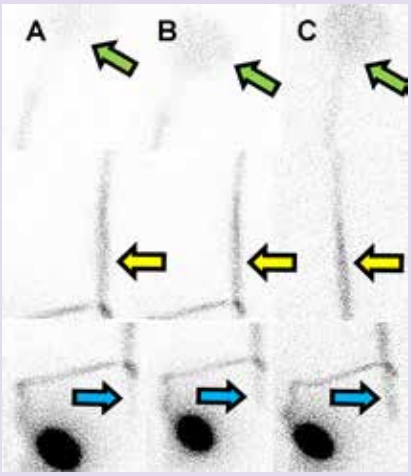

Figure 5. CSF flow obstruction in a 46-year-old male with spasticity with a spinal cord lesion at C5. Planar images at 48 h (A), 72 h (B) and 7 days after tracer injection (C) show increasing caudal tracer activity (blue arrows) over time, pronounced tracer activity at lumbar level (yellow arrows), a thoracic gradient above the catheter and insufficient rostral tracer distribution with reduced tracer activity at the cerebral cisterns (green arrows). Images are suspicious for a CSF flow obstruction.

Accuracy of conventional and optimized analysis

The conventional analysis data showed true positives (n=11), false positives (n=0), true negatives (n=15), and false negatives (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 true positives (n=20), false positives (n=1), true negatives (n=14) and false negatives (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 analysis and optimized analysis.

Discussion

Based on the analysis of this retrospective study on observational routinely collected data, we confirmed the importance 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 in ITDD failure when conventional diagnostic modalities do not reveal the cause. In most of the examinations with the optimized analysis, we were able to correctly diagnose the cause of ITTD failure, which was an improvement compared to the conventional analysis. Our study indicate that planar imaging combined with SPECT-CT is an adequate technique to identify and localize functional alterations resulting in a correct diagnosis. In chronic ITTD treatment, the penetration of tracer activity into surrounding tissue can be hindered by a fibrotic layer around the pump, which impedes the diagnosis of leakage. The very intense tracer activity in the implanted pump itself could be an obstacle for the detection of aberrant fluid around the pump, however, image scaling of both planar and SPECT-CT images could facilitate separation of fluid inside the pump reservoir and in the surrounding pump pocket.

To be certain that imaging is performed after tracer activity reaches the catheter tip and preventing potential misinterpretations, we implemented a standardized pump flow rate and changed the timing of scanning to 48 h, 96 h, and seven days after pump filling. Without the standardization of the pump flow rate, the timing of tracer activity to reach the tip is unclear. As a result, the diagnosis of a partial obstruction characterized by a delayed and/or reduced rostral visibility will be missed. Therefore, the published statement that the presence of any amount of tracer activity in the intrathecal space[14] and the cerebral cisterns[17] indicates absence of an abnormality is not justified.

Also, imaging should not be limited to a single time point, as leakage and partial obstruction can become more and more apparent over time. Increased tracer activity at the horizontal and vertical catheter transit position should be evaluated for possible overprojection of catheter parts, connector and/or fixation anchor. Another concern is visible tracer activity below the level of the tip of the catheter when the tracer has already reached the cisterns. We experienced that in the majority of the normal cases intrathecal tracer activity is not found below the level of the tip. This could be related to the extremely low-volume pump infusions in contrast to large volume of contrast material bolus injections in radiographic examinations. 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.[24] The catheter tip in this reported case was positioned at level L5 for surgical reasons. Scintigraphy showed stagnation of the tracer activity at that low lumbar level and did not transit upwards, which was interpreted as the cause of the ITDD failure.

To identify stagnation in the drug delivery, it is crucial to observe the amount of tracer activity in the cerebral cisterns. A blockage of the ros-

tral tracer distribution with broad caudal, lumbar, and thoracic tracer activity is suspect for an obstruction in rostral CSF flow. The analysis demonstrates that with the optimized procedure, we could not only estimate normal functioning or a malfunction of the delivery system, but with the standardized pump flow rate we could easier 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 could also localize the problem.

Study limitations

Routinely collected data are frequently used to improve patient care and health care efficiency. In our study, we intended to evaluate the diagnostic role of ^{111}In-scintigraphy in ITDD failure and to improve the procedure and the evaluation of its results. However, the retrospective nature of the study hampers the application of reporting guidelines such as STrengthening the Reporting of OBservational studies in Epidemiology (STROBE).[25] Although, to our knowledge, the analysis is the most extensive the sample size is small. In addition, a chronology bias[26] is presented by the retrospective character of the study, and this might have influenced our conclusions must be considered. We reassessed all images to reduce a misclassification bias. However, the most critical limitation is the unstructured approach to data collection, which resulted in the absence of a harmonized reference standard to determine the real cause of ITDD failure. Instead, we composed the reference based on all available data, including the index test, additional imaging modalities, surgery, and clinical information such as the result 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 procedure and analysis is a powerful diagnostic tool in cases of ITDD failure when previous conventional examinations do not reveal the cause for failure. The method is crucial not only for determining suspected infusion system malfunction but also for examining possible hindrance in the rostral intrathecal distribution of medication. Sizable, prospective, multicenter cohort studies are needed to develop consensus criteria for the role of isotopic scintigraphy in ITDD troubleshooting.

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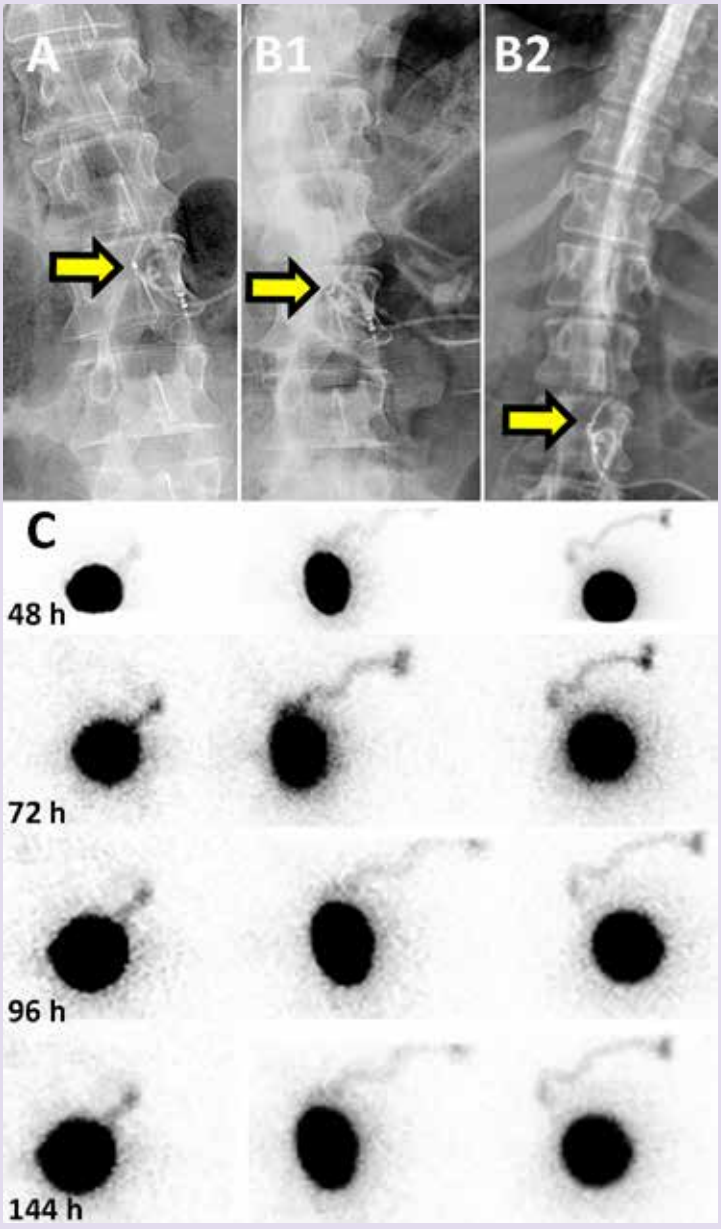
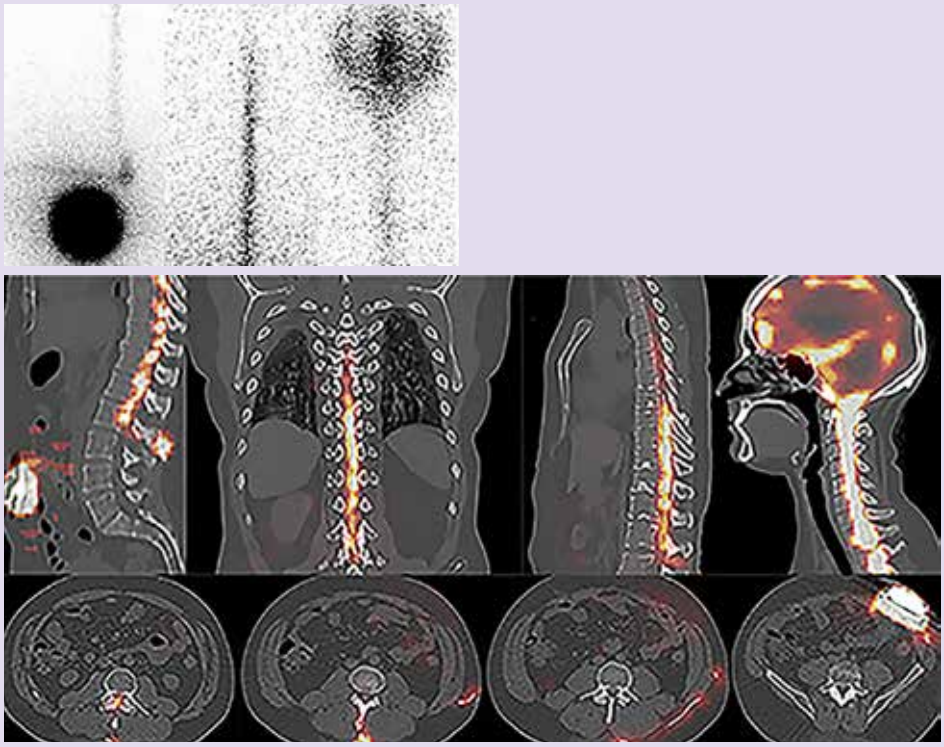
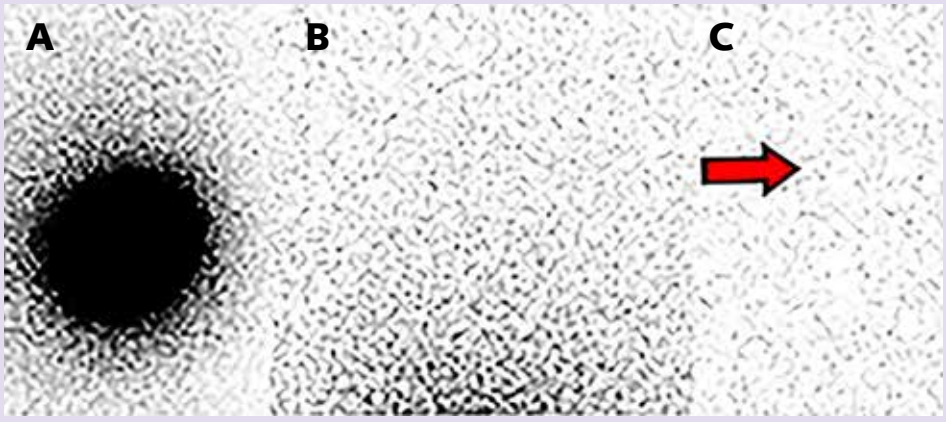
Supplementary Appendix



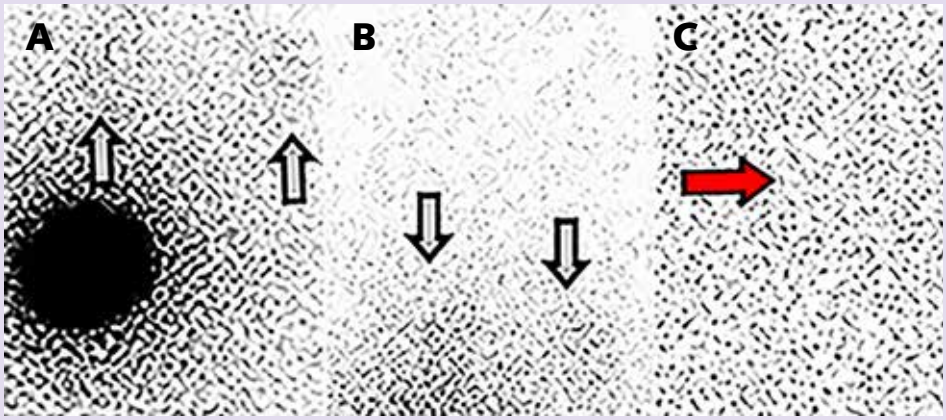
Several paroxysmal baclofen withdrawal events. Plain radiography revealed a curled catheter just after the catheter fixation anchor (yellow arrow). CAP myelography revealed a normal myelogram. Based on this patient was considered ITB-tolerant. ^{111}Indium-DTPA scintigraphy performed at the referral for a second opinion showed a catheter obstruction at the curled catheter. After catheter revision, spasticity was entirely under control.



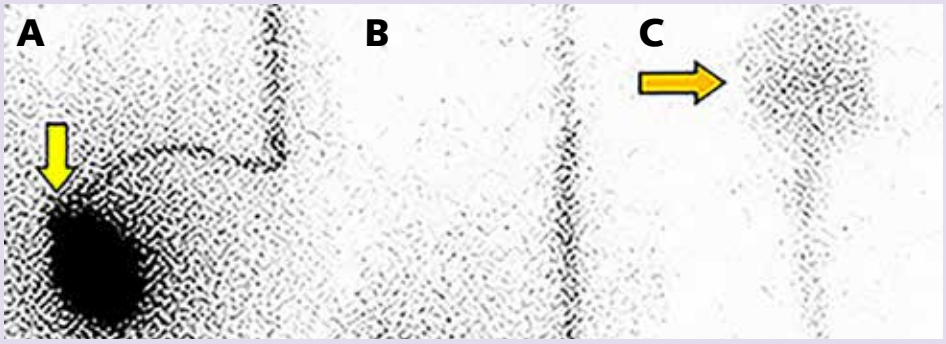
Normal pattern of activity spread on planar (upper row) and SPECT CT images (lower row) 48 h after injecting ^{111}Indium-DTPA in the pump reservoir with standardized pump flow rate of reaching the catheter tip at 24 h.



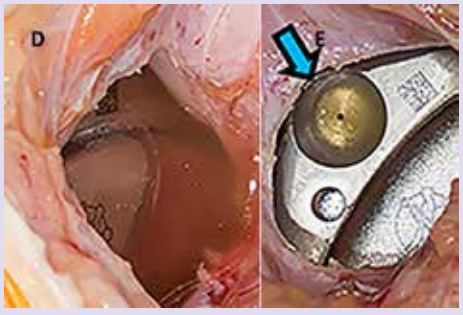
Planar image revealed visible pump (A), no activity in catheter (B) and cerebral cisterns (C, red arrow). The cause could be pump failure, activity had not passed the inner tubing of the pump, or complete catheter obstruction.



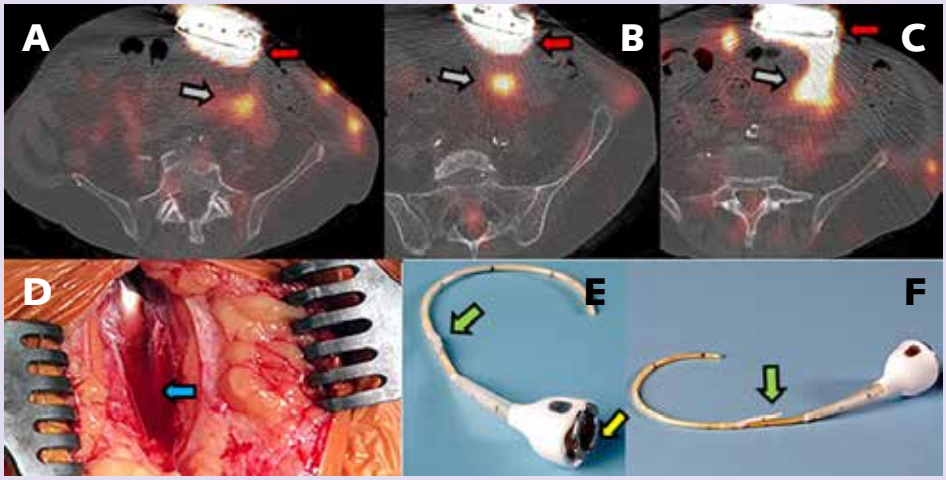
In this case, planar image revealed activity in pump (A) and in kidneys (A,B, gray arrows), no activity in catheter (B), and cerebral cisterns (C, red arrow). Possible cause could be disconnection of pump/catheter or leakage of pump/catheter. A pump failure is not likely.



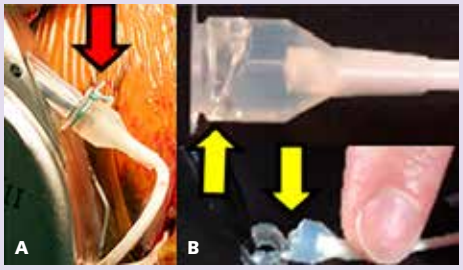
Planar images (left) revealed abnormal pump shape (A, yellow arrow), activity in catheter and thoracic subarachnoid space, and limited activity in cerebral cisterns (C, orange arrow).



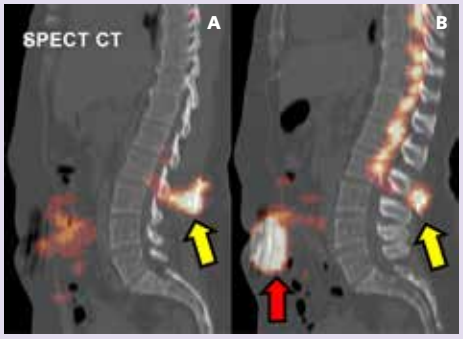
In vivo images during surgery (D), revealed fluid in pump pocket (green arrow), and activity in catheter access port funnel (E, blue arrow), which explained the abnormal shape (A, yellow arrow). Causes could be leakage somewhere in the drug delivery system or at dura insertion of catheter.



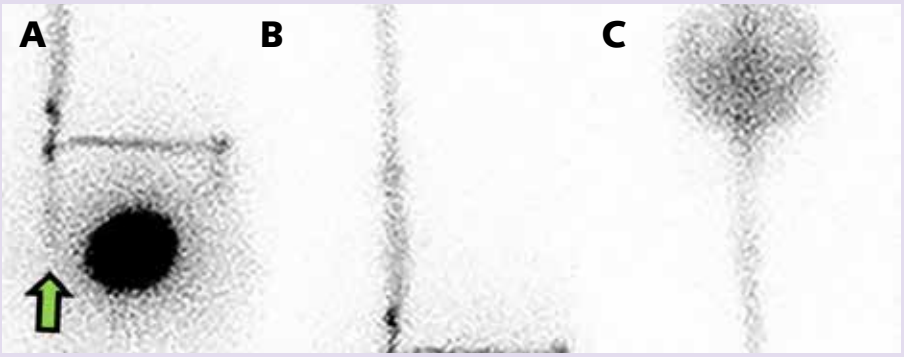
SPECT-CT images revealed remarkably increased pump activity (A–C, red arrow) and gradually increasing activity outside the pump (A–C, gray arrow). In vivo image during surgery (D, blue arrow) revealed fluid in pump pocket, which was caused by sheared Ascenda catheter (E,F, green arrow), and distortion pump–catheter connection (E, yellow arrow).



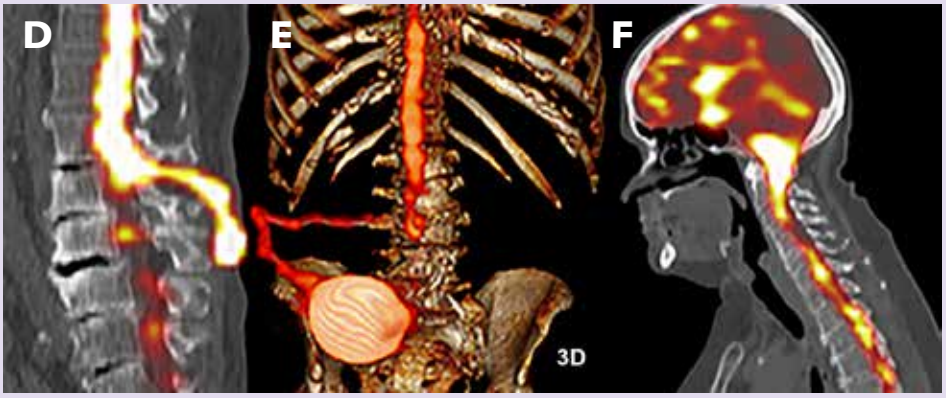
In vivo images during surgery revealed old type sutured pump–catheter connector (A, red arrow), and by suture sheared catheter (B, yellow arrow) (suture removed), which caused leakage.



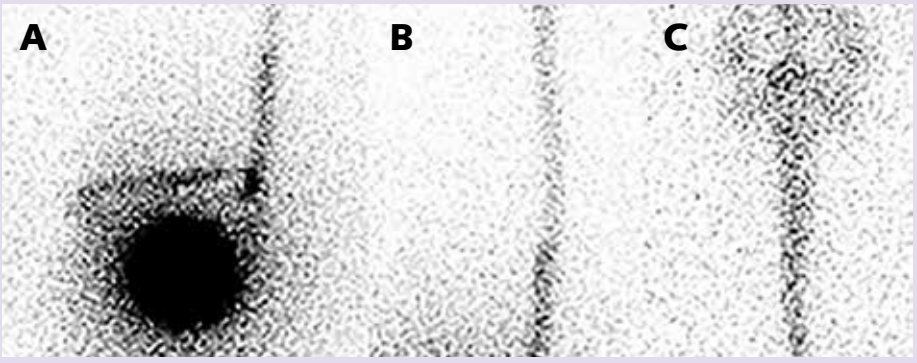
SPECT-CT revealed leakage at dorsal connector of the catheter segments (A,B, yellow arrow). Fluid passed along catheter to the pump pocket resulted in deformed pump shape (B, red arrow). At physical examination (C), in deeply implanted pumps, fluid in the pump pocket often cannot be recognized, whereas in other cases, it can be found easily (red arrow). In this particular case, the migration of a previously implanted intrathecal catheter resulted in dura leakage. A repeated homolog epidural blood patch solved the problem (Page 134).



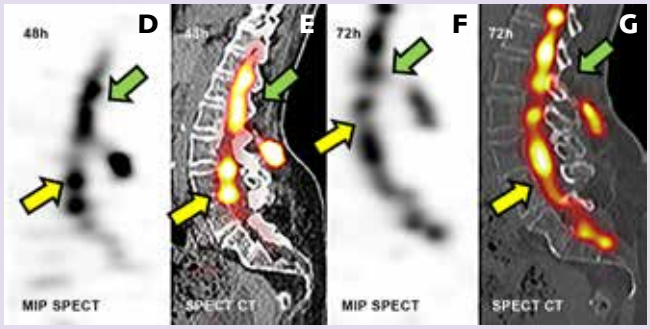
Planar images (A–C) revealed normal activity in pump, catheter, thoracic space, and cerebral cisterns. There was limited caudal activity (A, green arrow), which could be normal or limited CSF leakage.



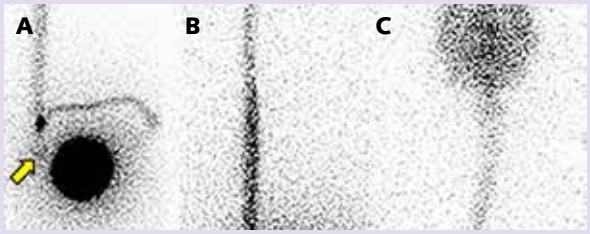
SPECT CT images (D–F) revealed a normal pattern, probably with minimal caudal activity. Clinically, signs of post-spinal headache were not present, and an explanation of treatment failure was not found.



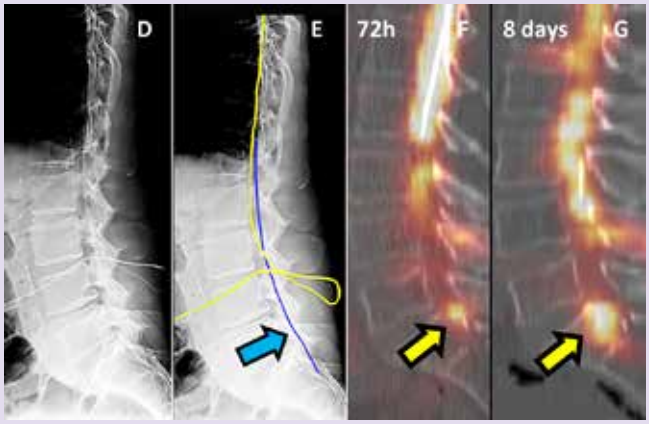
Planar images (A–C) revealed normal activity in pump, catheter, thoracic space, and cerebral cisterns. Question: increased caudal activity (A, yellow arrow)?



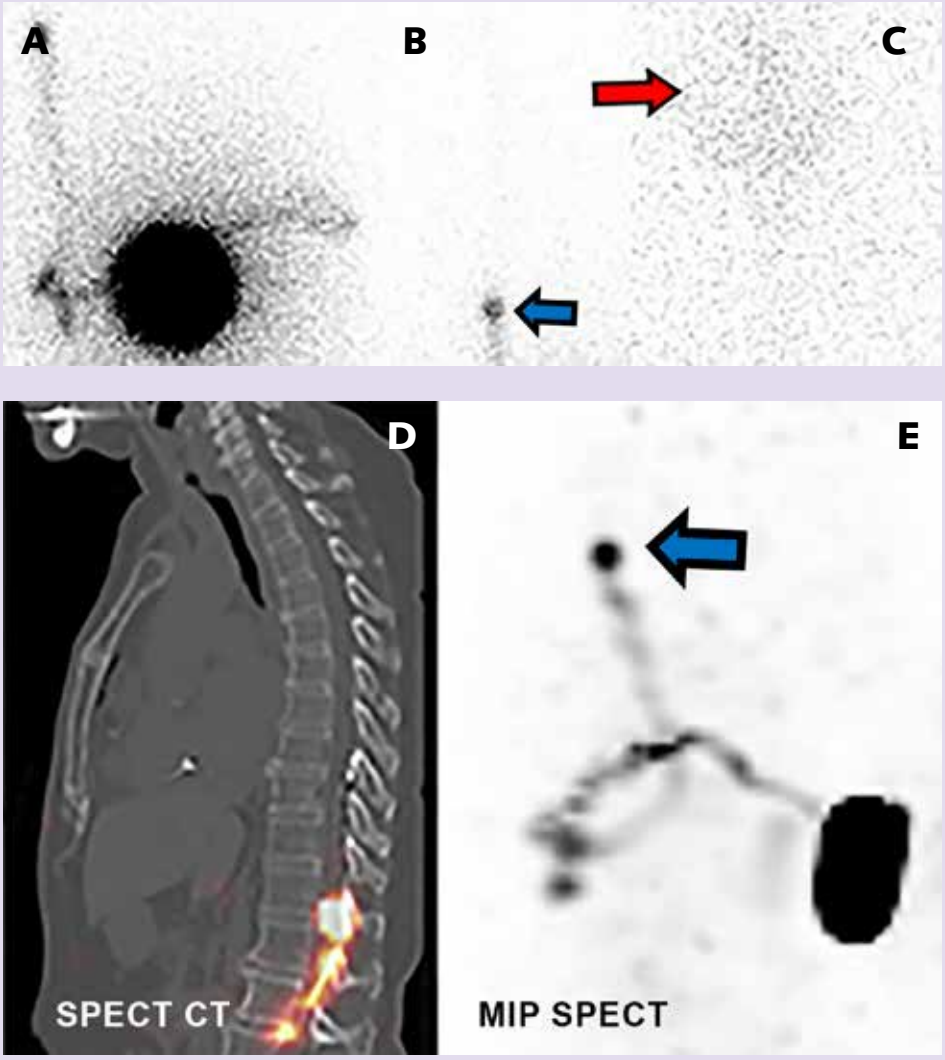
SPECT CT images (D–G) revealed intrathecal activity spread (green arrow) and remarkable increasing caudal activity (yellow arrows). Diagnostic dilemma: Normal or abnormal caudal activity spread? The initial conclusion was a normal variant; however, because of persistent treatment failure, revision of the intrathecal catheter segment was performed, whereby an intrathecal catheter leak was found.



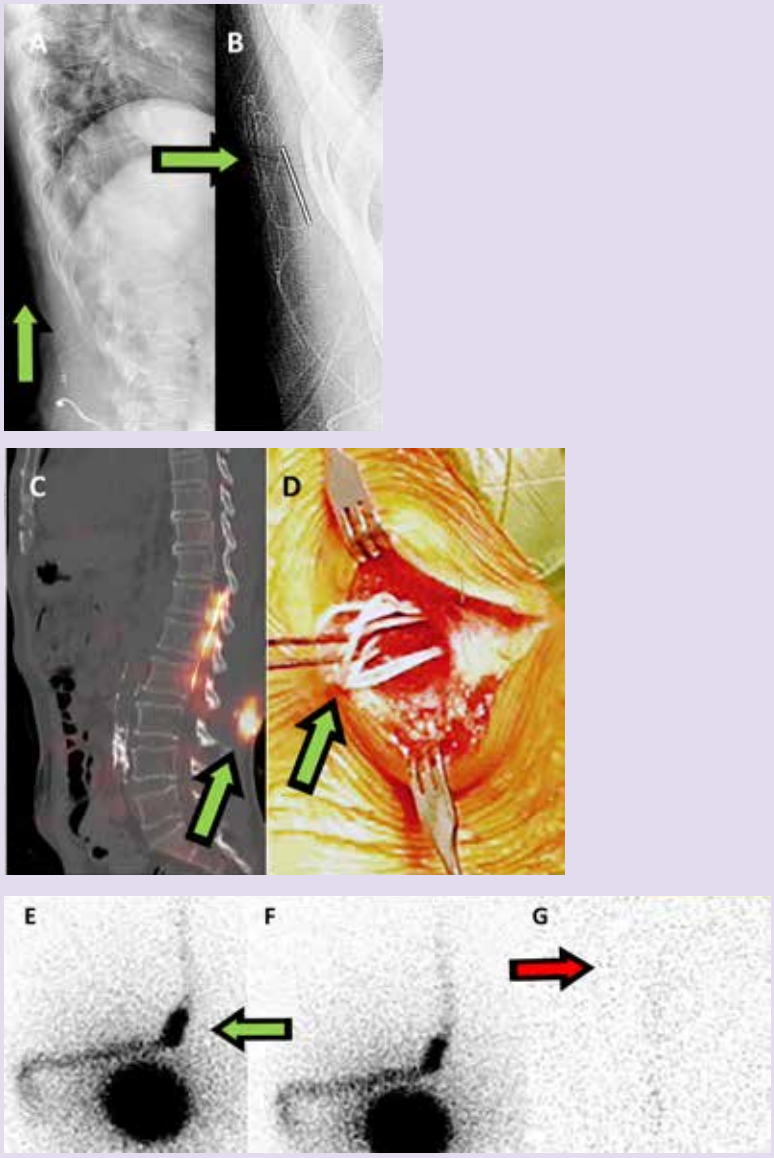
Planar images (A–C) revealed normal activity in pump, catheter, thoracic space, and cerebral cisterns. Limited caudal activity (A, yellow arrow): Normal or abnormal?



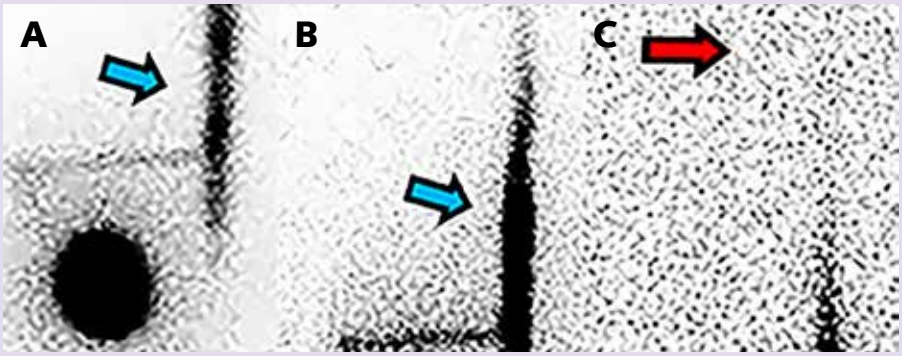
Plain X-ray (D), and artist rendering (E, blue line and blue arrow) revealed a retained catheter. SPECT-CT images (F,G) revealed remarkable increasing caudal activity (yellow arrows), caused by backflow via retained catheter segment (E, blue arrow).



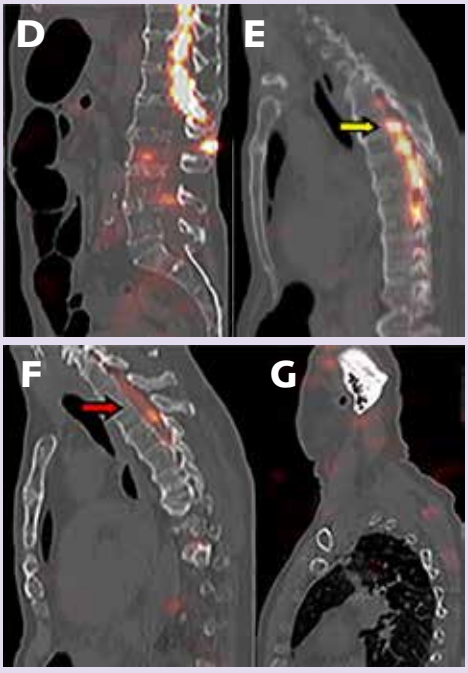
Planar images (A–C) revealed normal activity in pump and catheter, and stagnation of activity at the level of the catheter tip (B, blue arrow), with very limited activity cranial of the catheter tip in the thoracic/cervical space, and in the cerebral cisterns (C) (red arrow). SPECT-CT (D) and MIP-SPECT (E) images revealed stagnation of activity at catheter tip level (blue arrow), which created suspicions of a granuloma.



Plain radiography (A) + magnification (B) revealed a dorsal coiled catheter (green arrows). SPECT-CT showed abnormal dorsal tracer activity accumulation (C, green arrow) with limited intrathecal tracer activity distribution suspect for a catheter obstruction. Planar scintigraphic images (E-G) revealed activity in pump and catheter, with remarkably intense tracer activity at the level of the abdominal/lumbar transition (green arrow), and limited tracer activity distribution in the spinal canal. In vivo (D, green arrow) showed a dorsal coiled catheter as the cause of the obstruction.



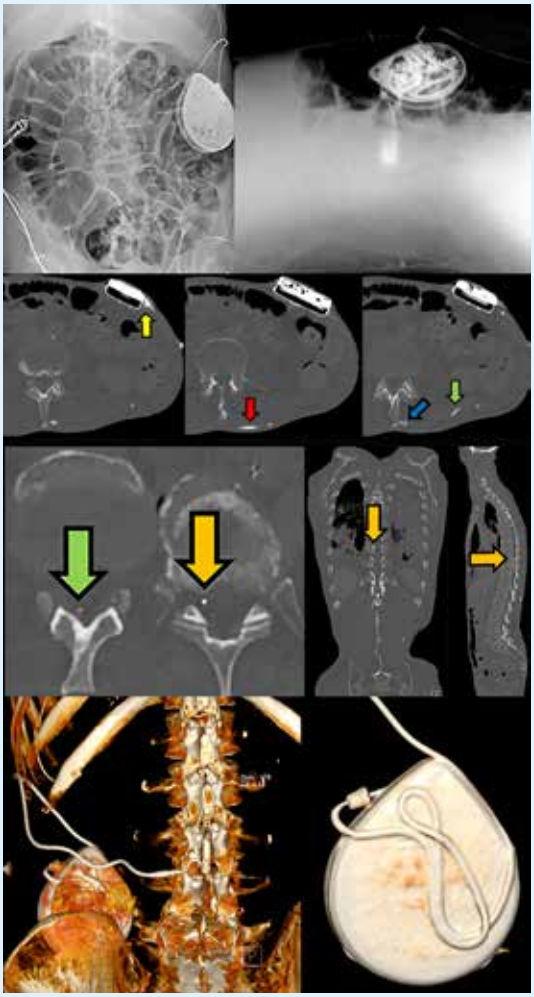
Planar images revealed remarkably wide aspect of activity at lumbar and thoracic level, also remarkable caudal activity (A,B, blue arrows), and almost no activity in cerebral cisterns (C, red arrow).



SPECT-CT images (D–G) revealed stagnation of activity at the T10 spinal cord injury level (E, yellow arrow), minimal activity at high thoracic/cervical level (F, red arrow), and no activity in cerebral cisterns (G), which was caused by subarachnoid obstruction.

7

Complications associated with intrathecal drug delivery systems



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Invited Review. Additional podcast

Learning objectives

By reading this article, you should be able to:

- Describe the consequences of failure of an intrathecal drug delivery system
- Explain the choice of diagnostic procedures available to determine the cause of failure
- Describe the management of intrathecal drug delivery system failure

Key points

- Device failures and human errors related to intrathecal drug delivery systems can lead to fatal complications as a result of withdrawal or overdose.
- Health professionals often fail to recognise complications of intrathecal drug delivery failure because of lack of awareness.
- Opioid-induced intrathecal granulomas can cause spinal cord compression and radicular symptoms.
- Non-pathogenic microorganisms can cause meningitis with minor clinical symptoms.

Keywords
Intrathecal drug delivery, complications

Introduction

Intrathecal drug delivery is an invasive treatment for the management of therapy-resistant pain, spasticity, and dystonia that is not controlled by oral administration. This form of delivery is based on the premise that effective treatment can be achieved by administering a low volume of drugs near the site of action, thus reducing the incidence and severity of adverse effects. High systemic doses of drugs are required to achieve the same concentrations. On-label drugs used include morphine, baclofen, and ziconotide, but the use of off-label drugs such as hydromorphone, clonidine, fentanyl, and mixtures of different drugs are used frequently. Errors and treatment failures can have life-threatening consequences. Health professionals are often unaware of potential complications of intrathecal drug delivery and their management due to a lack of exposure to these systems. This article aims to provide an overview of the management of complications and diagnostic procedures for troubleshooting drug delivery devices.

Drug delivery device-related complications

Device-related complications can be caused by malfunction of the pump or catheter, which will lead to therapy failure.

Intrathecal catheter-related complications

Problems associated with intrathecal catheters are migration, laceration, occlusion, or disconnection.[1] The Ascenda intrathecal catheter (Medtronic Inc., Minneapolis, MN, USA) seems to perform significantly better than earlier models.[2]

Pump-related complications

Pump failure is uncommon despite the high implantation rate.[3] Failures of the Synchromed II (Medtronic Inc., Minneapolis, MN, USA) pump are rare. Pump stall caused by rotor corrosion can occur in earlier pump generations that are still in use. Programmable pumps have an electric power source, the failure of which can result in pump failure. Low battery life can result in pump failure, but this is indicated by the programmer device.

Magnetic resonance imaging-related complications

Programmable pumps can fail temporarily during use of MRI because of rotor stall induced by the magnetic fields. A pump should automatically restart after the termination of the scan, but it can sometimes take a few hours to do so. A reboot can be attempted by programming a bolus delivery; an emergency pump replacement must be performed should this process fail.

The use of MRI in patients with the programmable Prometra pump system (Flowonix Medical Inc., Mount Olive, NJ, USA) is complicated. The device is MRI-compatible after its medication reservoir has been entirely emptied and refilled with a 0.9% NaCl solution and the system programmed at a zero-flow rate. These steps are required because the magnetic field opens the pump valves, which results in an immediate discharge of the contents of the drug reservoir, the inner tubing, and the catheter into the patient, thus causing an overdose. Removing the medication from the entire system is not easy and can only be entrusted to experienced clinicians, who may not be always accessible. Fixed-rate delivery devices operate mechanically and are powered by a gas pressure chamber surrounding a flexible inner reservoir, both made of titanium. An increase in temperature induced by MRI temporarily increases the delivery rate. In our view, the potential complications of termination of therapy outweigh the risk posed by the transient increase in delivery rate, particularly in patients receiving intrathecal baclofen (ITB) therapy.

Human factors

Human factors include refill schedule mistakes, miscalculations of the dead space of the inner pump tubing or catheter content, programming mistakes, and incorrect refill and access port procedures. Such errors can be mitigated by creating a prescription system in advance and adhering to it. Drug admixtures and pump program prescriptions should be double-checked by competent clinicians. Refill procedures should only be performed by clinicians who are familiar with the technique required, and aware of the symptoms and signs of overdose or failure of therapy and the significance of neurological signs and symptoms. Suitable arrangements must be in place for 24/7 medical cover because of the risk of life-threating complications. For reasons of safety, dose changes in an outpatient setting should not exceed more than 10–15% of the daily dose.

Complications

Early referral to a specialist centre is essential as treatment options in a non-specialist setting are limited to supportive measures.[4]

Overdose

An overdose is usually the result of incorrect pump programming, pump failure, or, in the case of the Prometra pump, failure to empty the reservoir prior to MRI. Rarely is an overdose a consequence of an error related to preparation of the drug solution.

Intrathecal baclofen overdose

Intrathecal baclofen overdose is characterised by ascending hypotonia, hypotension, hypothermia, nausea, vomiting, respiratory depression, seizures, and decreased conscious level from somnolence to coma.[5] Intrathecal analgesic overdose of opioids can present with nausea, vomiting, hyperalgesia, double vision, nystagmus, itching, myoclonus, respiratory depression, seizures, and somnolence to coma, and even death.[6]

Intrathecal clonidine overdose

Overdose of clonidine can present as severe hypertension, confusion, unconsciousness, profuse sweating, dysarthria, and respiratory depression.[7]

Intrathecal ziconotide overdose

Overdose with intrathecal ziconotide is relatively common, even during dose titration, due to its narrow therapeutic window and the delayed onset and offset of analgesia.[8] The drug is cleared from the CSF relatively quickly but remains bound within tissues.[9] Adverse effects include dizziness, confusion, memory impairment, ataxia, abnormal gait, somnolence, asthenia, headache, nausea, vomiting, and diarrhoea. Less frequent adverse effects include postural hypotension, impaired vertebral expression, abnormal thought processes, dry mouth, anxiety, peripheral edema, nystagmus, and elevated creatine phosphokinase.[9] The adverse outcomes of ziconotide are reversible within 4 days[10] to two weeks.[9]

Management

The management of an overdose includes supportive treatment with close monitoring. In severe cases, lumbar puncture with the aspiration of 30 ml of CSF and reinjection of the same volume of saline should be considered. Intravenous naloxone is required for the management of an opioid overdose.[6] To prevent damage to the pump, a programmable pump that has been stopped should be restarted within 48 h. Reducing the flow rate may not be adequate to manage symptoms of overdose. In such cases, the reservoir should be emptied and rinsed several times with saline to ensure that it is entirely free of the highly concentrated drug. The next step is to fill the reservoir with the medication at a lower concentration. The refill is followed by emptying the catheter via a catheter access port (CAP) puncture, programming for a bolus volume of the calculated catheter content and

repeat aspiration of the catheter. If the aspirated content is less than the inner pump tubing volume, the programming and the aspiration will have to be repeated. As the final step, the inner tubing and catheter should be filled by bolus pump programming. In a fixed flow device, emptying the internal tubing is impossible. The only solution is then several CAP punctures with aspiration for 24 h.

Withdrawal

Sudden termination of intrathecal drug delivery as a consequence of catheter issues, pump issues, or human factors such as programming errors or manipulation of pump by the patient can result in withdrawal phenomena. Within several to 48 h, abrupt interruption can present varied symptoms, which can result in misdiagnosis and life-threatening delay in treatment. Ziconotide can be discontinued abruptly without withdrawal effects.[9]

Intrathecal baclofen withdrawal

Abrupt ITB interruption presents within several hours or up to 2 days with mild exacerbation of spasticity, fever, excessive sweating, and pruritus.[1] Diagnosis of withdrawal may not be suspected by clinicians unfamiliar with this condition. Neuropsychiatric symptoms such as hallucinations, disorientation and psychosis can occur. Hypotension, tachycardia, and seizures may develop. In the most severe cases, hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, and potentially fatal multi-organ system failure can occur.[11]

Intrathecal opioid withdrawal

Symptoms of intrathecal opioid withdrawal symptoms include lacrimation or rhinorrhea, piloerection ('goose flesh'), myalgia, diarrhoea, nausea/vomiting, anxiety, pupillary dilation and photophobia, insomnia, autonomic hyperactivity (yawning, tachypnea, hyperreflexia, tachycardia, sweating, hypertension), and hyperthermia.[12]

Intrathecal clonidine withdrawal

Intrathecal clonidine withdrawal, which has also been reported in ITB,[13] manifests in the form of hypertension and leads to rapid onset of a sympathomimetic crisis with associated Takotsubo-type cardiomyopathy.[14] In the absence of obstructive coronary artery lesions, this syndrome, also known as left ventricular apical ballooning syndrome and stress-induced cardiomyopathy, is typically characterised by transient systolic dysfunction of the apical and mid-segments of the left ventricle. Patients often present with symptoms and signs of acute coronary syndrome.

Management

Supportive treatment with close monitoring is required. Oral baclofen in combination with intravenous benzodiazepines is required for management of ITB withdrawal.[4,11]

Intravenous supplementation may be required in patients with opioid and clonidine withdrawal. Externalised intrathecal catheters can be used if supplementation therapy is not sufficient. The disadvantage of this approach is that a larger volume needs to be delivered by an external device. In patients with pump explantation caused by infection, withdrawal can be overcome by the temporary use of the explanted pump as an external device, whereby the original spinal catheter is externalised with replacement of the proximal catheter part.[15]

Cerebrospinal fluid leak

Cerebrospinal fluid leaks can be caused by persistent dural opening at the catheter insertion site, catheter-pump disconnection, a damaged catheter-pump connector, a perforated or sheared catheter, or an interruption of the catheter-catheter connector. Older catheter systems that are still in use have a sutured catheter-pump fixation. The suture can cut the connector, leading to CSF leak.

A severe CSF leak can result in withdrawal syn-

drome, but this outcome is unusual with a minor leak. Limited leakage is detected based on treatment failure, spinal headache, or inadvertently during the percutaneous refill procedure (Fig. 1).

More pronounced leaks lead to local CSF accumulation outside the spinal canal and are recognised by dorsal swelling, ventral swelling, or both, but visible swelling may be absent.

In some cases, the passage of CSF along the catheter to the pump pocket leads to abdominal swelling (Fig. 2). This swelling, which should be differentiated from a seroma, hematoma, or abscess. Cerebrospinal fluid can be confirmed by puncturing the distention, followed by examination of the fluid for beta-2-transferrin.

A severe CSF leak is associated with intracranial hypovolemia, which can cause a subdural hematoma. Typically, a CSF leak is characterised by postural headache, but this is often absent. Nevertheless, a severe CSF leak should be considered an emergency. The origin of a leak is determined by CAP CT myelography or ^{111}Indium-diethylenetriamine-penta-acetic-acid (^{111}In-DTPA) scintigraphy.

Management

The treatment for leakage is to identify the cause and, if it is device-related, to perform a surgical restoration. In contrast to dural leaks as result of lumbar puncture, treatment with bed rest only is frequently insufficient when a leakage is related to inserted intrathecal catheters. In such cases, one or more homologous blood patches and bed rest are then the treatment of choice. Cerebrospinal fluid accumulation in the pump pocket being passed through along the catheter is treated by percutaneous fluid aspiration. The needle is introduced above the pump and remains in contact with it to prevent accidental catheter puncture.

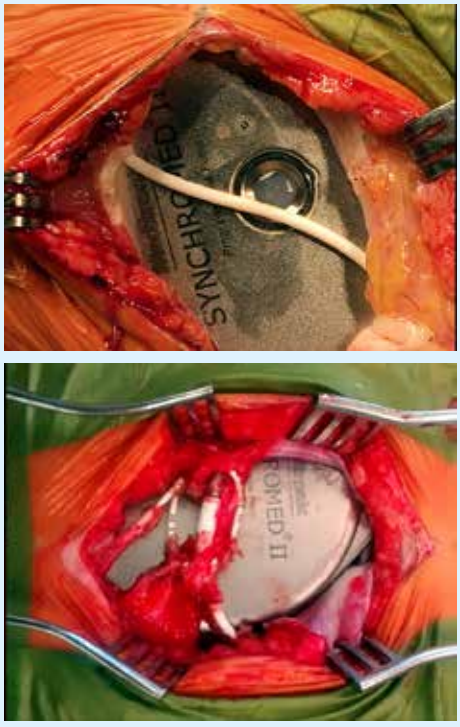

Figure 1. Overlying catheter above the refill membrane.

Figure 2. Dorsal dura leakage leading to abdominal pocket protrusion.

Granuloma formation

Granuloma formation at the thoracic catheter tip is an uncommon complication of intrathecal opioid administration[16] and is rare with ITB.[17] An association between granuloma and the dose of the intrathecal medication remains unclear.[18] Opioid-induced granulomas can cause spinal cord compression and radicular pain in the thoracic or lumbar regions. There is exacerbation of pain despite dose increments, as drugs are unable to reach the target neural tissue. Diagnosis is based on MRI showing an abnormal tissue formation at the catheter tip (Fig. 3).

Management

Catheter replacement at another level or termination of the infusion with monitoring may be appropriate, as the mass could resolve on its own.[16] Surgical removal of the granuloma is indicated in cases that involve neurological deficits.

Obstruction of cerebral spinal fluid flow

Cerebrospinal fluid flow obstruction can be caused by focal arachnoiditis with fibroconnective adhesions, which will result in accumulation of the infused medication. The accumulation gives rise to a high local concentration, which can lead to a vicious cycle of chronic arachnoiditis.

Management

In cases of limited CSF flow obstruction, catheter replacement can be attempted. However, multiple revisions are not indicated. Preliminary results show that restoration of the CSF flow by microsurgical adhesiolysis or percutaneous balloon fenestration appears to solve the problem.[19]

Infection

Implantable device infections can be attributed to the surgical procedure or the refilling of the percutaneous pump reservoir. They can be caused indirectly via hematogenous seeding

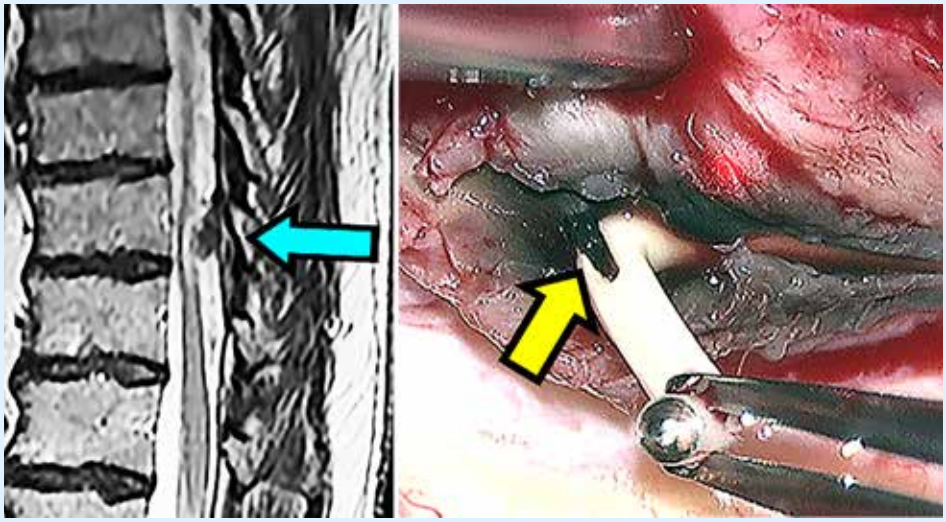

Figure 3. A granuloma (A, blue arrow). Tremendous in vivo ingrowth with an abnormal black colouring (B, yellow arrow). The patient complained of exacerbation of pain in his legs without neurological signs. The causes can easily be overlooked when MRI is limited to the lumbar area.

from a distant source. The clinical manifestations of local infection include localised pain, protrusion, erythema, and fever. In a progressive infection with pus formation, the swelling is more pronounced, and the skin has a shiny appearance. A striking observation is that a device infection is not invariably accompanied by fever. The causative microorganisms can be identified on cultures of the local pus, blood, and CSF.

Pump pocket infection can spread to the central nervous system, leading to meningitis.[20] Isolated meningitis can occur even should the pump pocket appear to be normal. The clinical symptoms of meningitis are highly dependent on the causative microorganism. Symptoms such as fever, headache, stiff neck, vomiting, and change in consciousness occur inconsistently. There is a risk of missing the diagnosis of meningitis. Staphylococcus aureus meningitis presents with high-grade fever. In contrast, Staphylococcus capitis meningitis can be missed, as it does not present with high grade fever.

Treatment

Superficial infection is treated with oral antibiotics.[21] In more severe infections, explantation of the implanted device is necessary to mitigate the risk of meningitis.[20] In ITB and intrathecal clonidine, the dose should be reduced gradually over 5 days, as sudden termination can lead to a potentially life-threatening withdrawal syndrome. Patients with cerebral damage or a spinal cord injury at the T6 level or higher who are implanted with an ITB device are at risk of autonomic dysreflexia upon sudden withdrawal. Broad-spectrum antibiotics such as meropenem and vancomycin should be administered until the causative microorganism is identified.

Anecdotal information suggests that pump explantation may not always be necessary.[22-24] System salvage should be considered in infection with a non-pathogenic microorganism, minor clinical symptoms, and in patients at high risk of sympathetic crisis.[22,24] Antibiotic treatment with meropenem and vancomycin delivered intravenously combined with vancomycin in the pump[24] and oral rifampicin is an option. Successful pump salvage by wrapping the pump in two gentamicin-impregnated collagen sheets has been described in a patient with S. aureus infection of the pocket site.[23] The patient had previously experienced life-threatening autonomic dysreflexia after ITB termination, which precluded temporary discontinuation of ITB. Major concerns of this method are the potential for the developing antibiotic resistance with long-term gentamicin administration and the risk of recurrence.

Diagnosis of intrathecal drug delivery system failure

We used an algorithm in our institution to determine the cause of intrathecal drug delivery failure (Fig. 4). The primary diagnostic steps are estimating the amount of fluid in the pump reservoir and a low-dose single-energy CT (SECT) scan.[25]

Computed tomography with post-processing two-dimensial (2-D) and (3-D) reconstructions allows visualisation of the entire drug delivery pathway as opposed to plain radiography (Fig. 5). Catheter access port myelography can be used should CT fail to determine the cause. Fluid should be aspirated from the CAP before injection of contrast material to prevent overdose, as the catheter is filled with a high concentration of drugs. The highly viscous contrast material should then be flushed with normal saline. The catheter should subsequently be refilled with a precisely calculated amount equaling to the catheter volume by either pump bolus or manual injection.

Information concerning a catheter's diameter and length is essential in calculating its volume. This information should be recorded in the clinical records and in the memory of the programmable pump during implantation. By

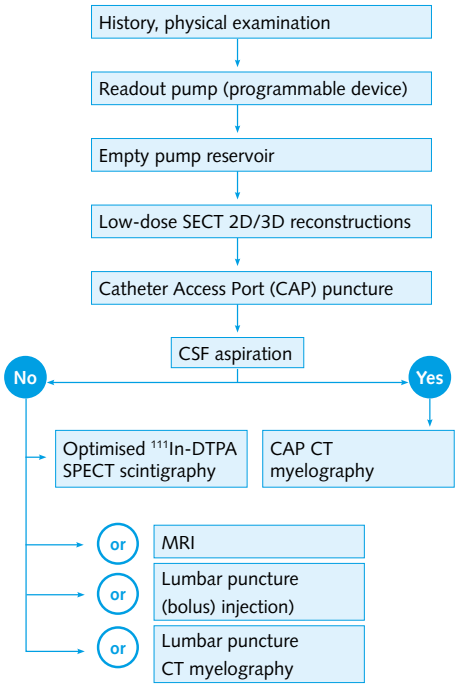

Figure 4. Overview (aetiology, diagnostic algorithm) of intrathecal drug delivery troubleshooting
CSF = cerebrospinal fluid; SECT = single-energy computed tomography; DECT = twin-beam dual-energy computed tomography; ^{111}In-DTPA SPECT = ^{111}Indium-diethylene-triamine-penta-acetic-acid single-photon emission computed tomography.

combining CAP myelography with CT and 2- and 3-D reconstructions, failures associated with drug delivery can be identified. It is crucial to not limit the CT field of view to the spine but rather to extend it to the abdominal region where the pump is implanted. Contrast material should not be injected if it is not possible to aspirate fluid via the CAP, as there will be a risk of overdose. Non-contrast CT can be used to identify an abnormal catheter position. In addition, lumbar puncture CT myelography can be considered if in doubt. ^{111}In-DTPA scintigraphy can be useful when CAP CT myelography fails to identify the cause of failure, and when fluid cannot be aspirated via the CAP or if dynamic

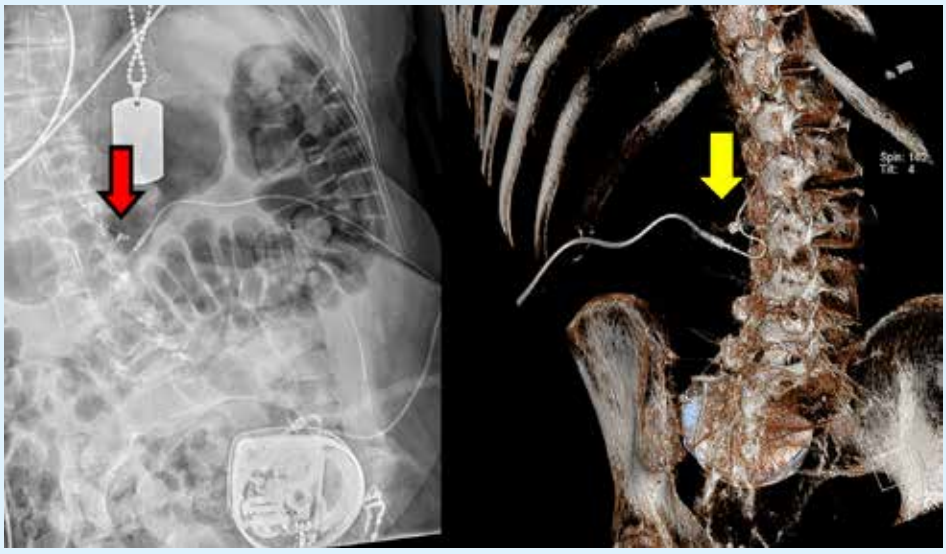

Figure 5. Improved catheter visualization. Plain radiography indicated a possible kinked catheter (red arrow). DECT with 3D volume rendering revealed a regular curved catheter (yellow arrow) with no obstruction.

information regarding catheter flow and the spread of intrathecal medications is required. It can also help to identify minor leakages. ^{111}In-DTPA scintigraphy can be enhanced by adding single photon emission CT (SPECT) and by standardising the flow rate in programmable pump devices. Magnetic resonance imaging is of limited value in intrathecal drug delivery system failure and is used to exclude granuloma, syringomyelia, or intrathecal obstructions.

Summary

Although intrathecal drug administration using an implanted pump system has been used in clinical practice for many decades, awareness of its applications, complications associated with its use and management of complications remains limited. Early diagnosis and management of withdrawal and overdose is essential as they can be potentially life-threatening. Early involvement of clinicians with experience in managing these devices is essential.

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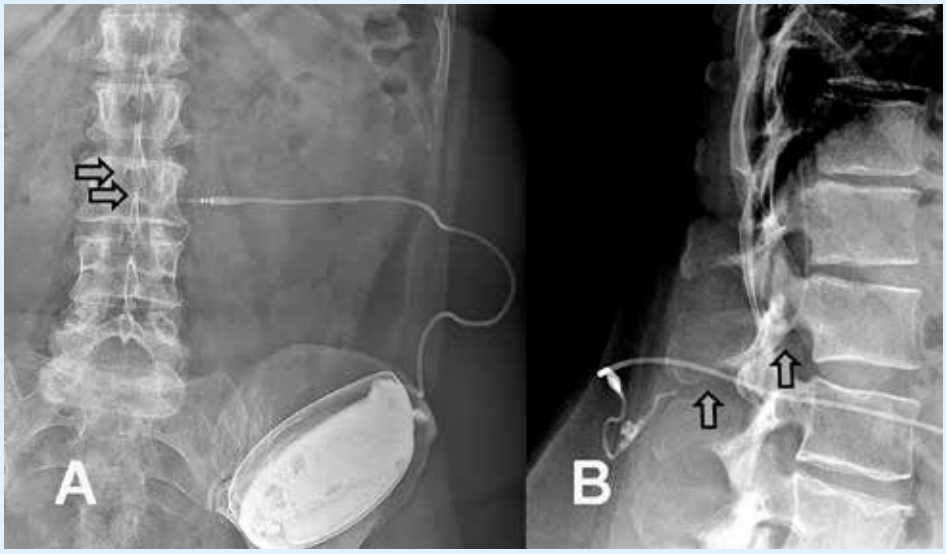
Multiple choice question 1



A 45-year-old woman with therapy-resistant lower back pain was treated with intrathecal morphine for 5 years. She experienced an exacerbation of her pain without other clinical signs. Plain radiography revealed a sheared spinal catheter. The appropriate next step would be the following:

a) Removal of the complete catheter via a laminectomy
b) Surgical disconnection of the catheter parts from the connector and removal of the extra-vertebral broken part, leaving the rest of the catheter in place
c) Non-contrast computed tomography with three-dimensional (3D) volume rendering reconstruction
d) Lumbar puncture CT myelography
e) Scintigraphy, with the pump filled with ^{111}Indium-diethylenetriamine penta-acetic acid (^{111}In-DTPA)

Answers

a) False. Complete removal of the catheter is justified when the retained catheter segment causes leakage of cerebrospinal fluid (CSF) via the extradural end of the sheared catheter. Plain radiography cannot provide information concerning CSF leakage.
b) False. This approach is appropriate in the absence of CSF leakage via the extradural end of the sheared catheter. Information about leakage is not present. The correct approach is to leave the retained catheter in place if it can be determined that CSF leak is absent.
c) False. Non-contrast CT with 2D/3D volume rendering reconstruction can provide clear visualisation of the catheter to determine if the sheared catheter is intradural or extradural. It does not, however, provide information on any potential CSF leak.
d) True. With lumbar puncture CT myelography, CSF leakage can be identified by backflow of the contrast material via the sheared intra-extradural catheter part.
e) False. Pump scintigraphy is unhelpful, as the catheter is completely disrupted, and intra-extradural CSF leakage can therefore not be identified.

Multiple choice question 2

A 52-year-old patient presented with protrusion of the abdominal wall and mild postural headache about 24 hours after implantation of an intrathecal morphine drug delivery system. No other clinical features were present. A puncture of the swollen pump pocket revealed 40 ml of a transparent light-yellow fluid. The appropriate diagnosis include the following:

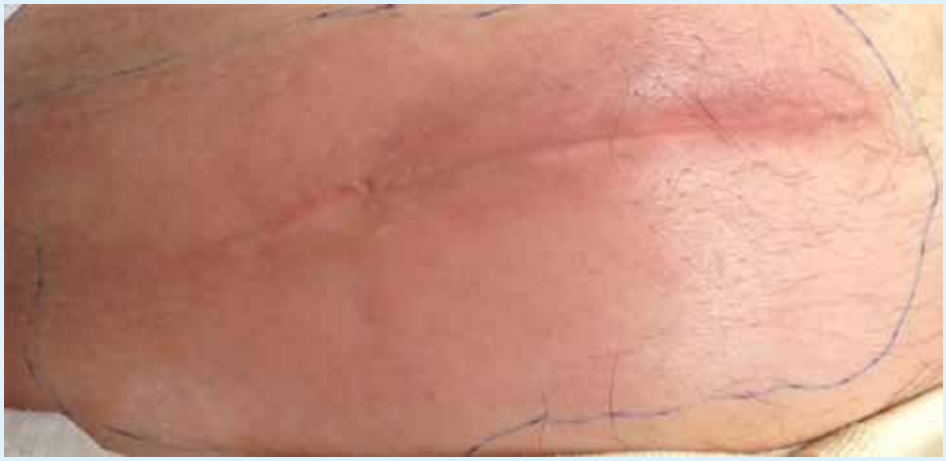
a) Seroma
b) Infection
c) Hematoma
d) Cerebrospinal fluid accumulation
e) Allergic reaction to the pump

Answers

a) False. Although seroma can be yellow in colour, it is not transparent. The accumulation of 40 ml in a day is unlikely.
b) False. Infection within 24 hrs with the accumulation of a large volume of exudate is unlikely. Secondary infection of accumulated fluid is a possibility, but it is unlikely to manifest within a day. Fever should be expected with an on-going infection.
c) False. Haematomas can occur after implantation, but the aspirate is not transparent light yellow.
d) True. Cerebrospinal fluid leakage can manifest within one day as a result of:
   - a sheared catheter segment in the pocket
   - disconnection or sheared pump–catheter connection
   - dural leakage with CSF advancing along the catheter to the pocket.

   The postural spinal headache is associated with the CSF leakage. Cerebrospinal fluid mixed with local wound fluid causes the light yellow colour.
e) False. An allergic reaction to the pump will not result in 40 ml of fluid accumulation in the pocket.

Multiple choice question 3



A 52-year-old man with a cervical spinal cord lesion was treated with intrathecal baclofen for 25 years. He developed Staphylococcus aureus cellulitis at the orifice of the suprapubic catheter, which was successfully treated with an antibiotic medication. He subsequently developed superficial infection of the pump pocket without fever. The appropriate treatment includes the following:

a) Oral antibiotic trial(s)
b) Dose reduction and an intravenous antibiotic treatment
c) Immediate wound drainage
d) Immediate removal of the drug delivery system
e) Explantation of the drug delivery system after a dose reduction

Answers

a) False. The superficial infection of the pump pocket is likely the result of progression of cellulitis. An oral antibiotic treatment trial would not be appropriate.
b) True. Immediate explantation is not indicated, as the infection is superficial, and systemic symptoms such as fever are absent. The drug dose should be reduced in increments to prevent withdrawal. Intravenous antibiotic treatment should be initiated to prevent the development of meningitis.
c) False. Immediate wound drainage is not indicated at this stage.
d) False. Immediate removal of the drug delivery system is not indicated at this stage.
e) True. The preferred treatment is the removal of the entire drug delivery system as soon as the intrathecal medication has been terminated. Biofilm formation on the surface of the drug delivery system makes eradication with antibiotics difficult.

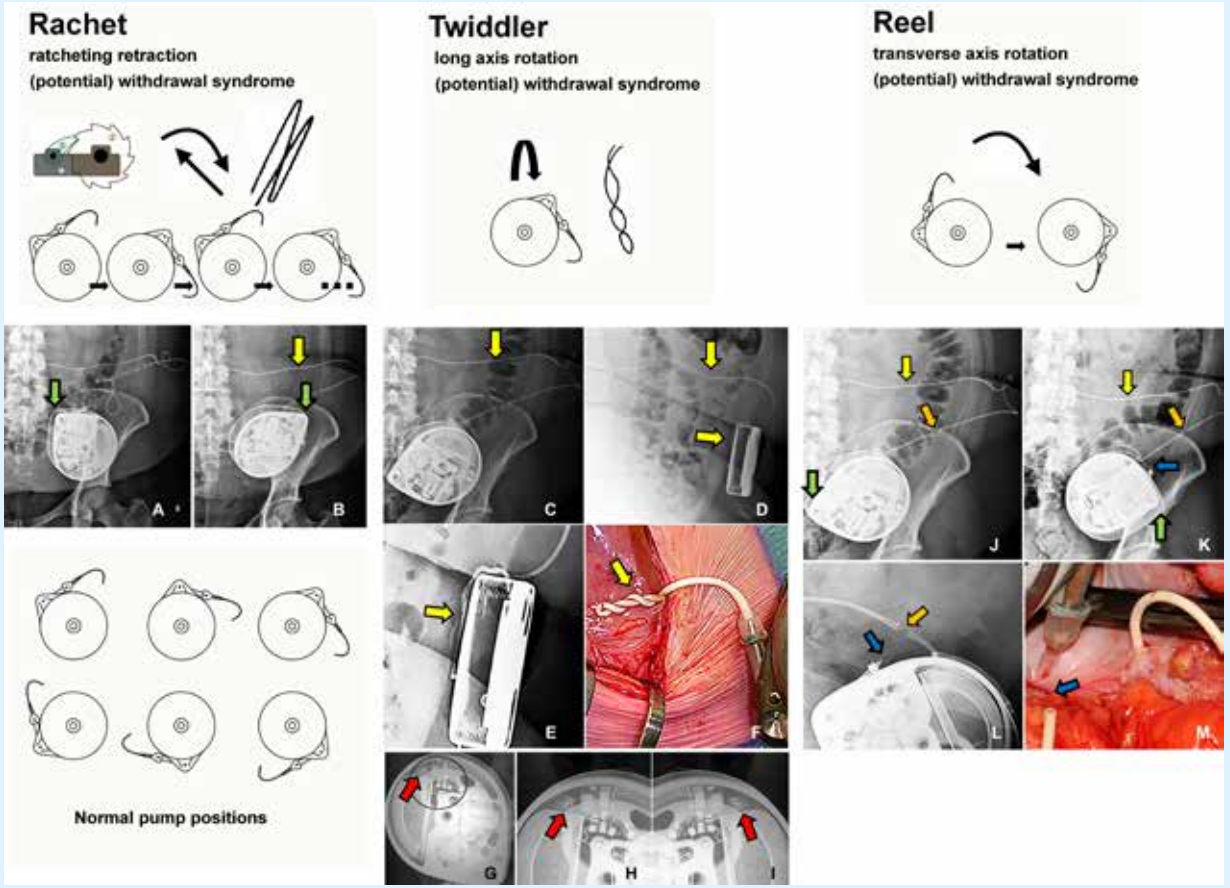
Multiple choice question 4

A 45-year-old patient with an implanted device for ITB 3 months earlier for the management of spasticity presented with mild muscle weakness and mild fever for 4 weeks. No other clinical symptoms were present. The possible diagnosis includes the following:

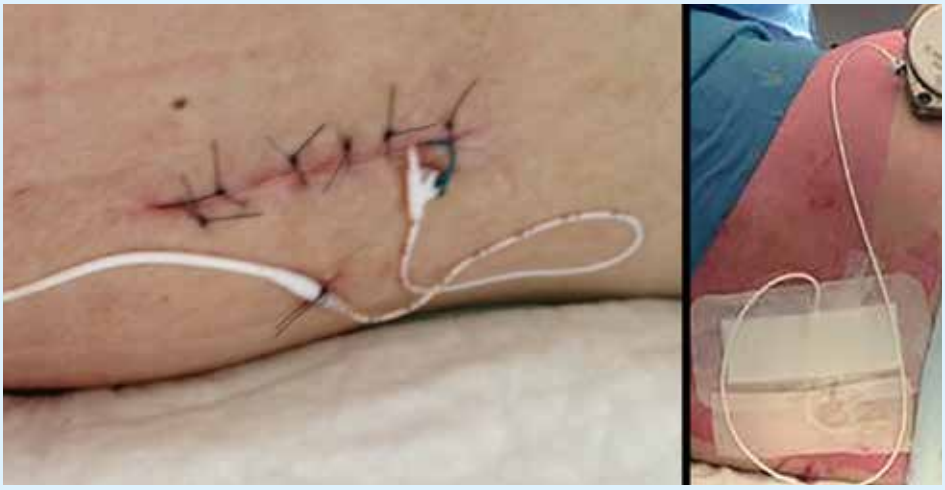
a) Condition unrelated to the drug delivery device
b) Staphylococcus aureus meningitis
c) Staphylococcus epidermidis meningitis
d) Intrathecal baclofen overdose
e) Mild intrathecal baclofen withdrawal syndrome

Answers

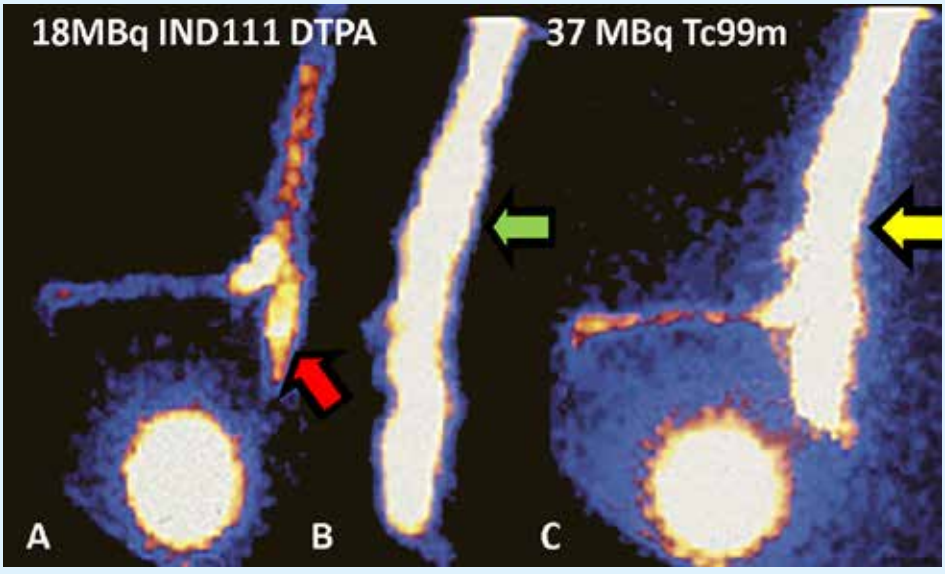
a) True. There is no reason to consider a relation with the drug delivery device.
b) False. Staphylococcus aureus meningitis presents with a high-grade fever.
c) True. Staphylococcus epidermidis can result in treacherous, meningitis that can easily be overlooked
d) False. The mild elevation in temperature with muscle weakness makes an overdose unlikely.
e) False. Intrathecal baclofen withdrawal syndrome is associated with muscle hypertonia, not with muscle weakness.



eFigure 1. Treacherous pump manipulations. The manipulations by the patient will finally result in a complete catheter obstruction or a fracture at the catheter-pump connection or disconnection of the catheter-catheter connector.



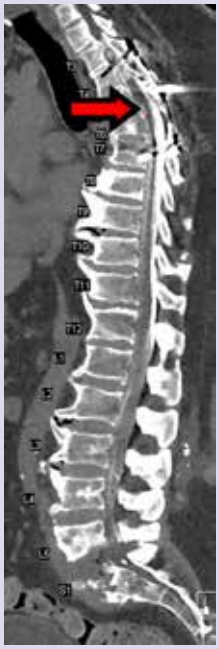
eFigure 2. Temporary external use of an explanted pump.



eFigure 3. Epidural spread. ^{111}In-DTPA scintigraphy (A, red arrow) revealed dorsal dura leakage. The 20ml injected blood marked with 99mTechnetium (B, green arrow; C, yellow arrow) showed an epidural spread up to the high thoracic region (C).

8

Restoration of rostral cerebrospinal fluid flow to solve treatment failure caused by obstruction in long-term intrathecal baclofen administration



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Note:
1. Portions of this work were orally presented at the European Society of Neuroradiology, 41st Annual Meeting, Rotterdam, The Netherlands, September 22,2018.
2. Portions of this work were presented in poster form at the Radiology Society North America, 104th Annual Meeting, Chicago, United States, November 25-30, 2018.

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ABSTRACT

Objects

We describe five traumatic spinal cord injury (SCI) patients with an intrathecal baclofen administration (ITB) failure caused by a rostral CSF flow obstruction referred to our expert center between January 2014 and January 2019. We discuss the diagnostic workup, rostral CSF flow obstruction as the cause of the ITB failure and treatment.

Methods

When we could not determine the cause of the ITB failure through the patient's history, physical spasticity examination, pump readout, absence of fluid in the pump reservoir during aspiration, or plain radiography, we performed pump catheter access port (computed tomography [CT]) myelography. When CT myelography did not reveal the diagnosis, we used scintigraphy. In an obstruction, we aimed for CSF flow restoration. In three cases, we conducted a laminectomy with microsurgical adhesiolysis. In two of these patients, we could not achieve CSF flow restoration; thus, we placed an intradural catheter bypass. Recently, in three patients, we applied a less invasive technique of percutaneous fenestration of the obstruction.

Results

In one case, we performed a successful catheter replacement. In another case using surgical adhesiolysis, spasticity control was complete. In two cases, we could obtain improvement with an additional intradural bypass, followed by a percutaneous fenestration of the obstruction, resulting in further improved CSF flow restoration. In one case, percutaneous fenestration was the first line of treatment. In all cases with percutaneous fenestration, we experienced spasticity control.

Conclusion

Preliminary results showed that the restoration of rostral CSF flow might result in an effective ITB treatment in patients with an intrathecal obstruction.

Keywords

CSF flow, obstruction, neurosurgery, balloon dilatation, restoration

Introduction

Following a spinal cord injury (SCI), 62% to 88% of the patients develop spasticity.[1-4] Nonetheless, the resulting muscle tone might have advantages, such as advantages during transfers or as a clinical indicator of noxious stimuli.[5] In generalized spasticity, the GABA-B receptor agonist baclofen is the most frequently used drug. Since 1984, intrathecal baclofen (ITB) has become an often used therapy in intractable cases.[6] A rostral cerebrospinal fluid (CSF) flow obstruction is a rare cause of long-term ITB failure. In this paper, we describe five adult SCI patients with an ITB failure caused by a rostral CSF flow obstruction. After CSF flow restoration either by microsurgical adhesiolysis, intradural bypass,[7,8] or percutaneous fenestration, we evaluated the ITB treatment effect. CSF flow restoration was attempted based on the following observations: a successful clinical treatment with an intradural shunt in a patient with a CSF flow obstruction (not published); cerebral cistern visualization with ^{111}Indium-diethylene-triamine-penta-acetic acid scintigraphy

(^{111}In-DTPA) in normal cases; the lack of treatment effect when the catheter tip was placed above an obstruction; and cerebral symptomatology, which occurred upon an ITB overdose. Based on these observations, we hypothesized that besides the regional effect of ITB, rostral CSF flow is also needed for effective ITB treatment, and that the restoration of rostral CSF flow in obstructions could be a useful therapy in the case of ITB failure.

Methods

The five patients were referred to our expert center for ITB troubleshooting between January 2014 and January 2019. In four of the five patients, catheter revision(s) had not resolved the ITB failure. All patients used a SynchroMed II delivery system (Medtronic Inc., Minneapolis, MN, USA). Five were treated with baclofen only, and one with a combination of baclofen and hydromorphone. During the diagnostic workup, the rostral CSF flow obstruction was demonstrated and treated via the restoration of the rostral CSF flow. For this retrospective study, we received approval from the medical ethics committee of the Erasmus Medical Center (MEC-2017-326), and the requirement to obtain informed consent was waived.

Diagnostic workup

When we could not determine the cause of ITB failure through the patient's history, physical examination of the spasticity, pump readout, absence of fluid during aspiration of the pump reservoir, plain radiography, or low-dose CT, we performed pump catheter access port (CAP) computed tomography (CT) myelography.[9] Via the CAP, we injected 10 ml of contrast material (iohexol, Omnipaque™ 320, GE Healthcare B.V., Eindhoven, The Netherlands), followed by fluoroscopy and CT. Occasionally, we injected contrast material via a lumbar puncture when we could not perform CAP myelography (Cases 3, 5). To demonstrate the presence or absence of the rostral spread of the injected contrast material, we used the Trendelenburg position immediately after the contrast material injection. The images were evaluated for an inhomogeneous or reduced contrast material distribution. To be informed about the length of the intrathecal obstruction, we added cervical CT myelography to the diagnostic algorithm[9] (Cases 3, 4). When in doubt of an obstruction, we additionally performed ^{111}In-DTPA (Cases 1, 2, 3). We mixed the medication in the pump reservoir with 20 MBq of ^{111}In-DTPA and standardized the pump flow rate for each patient in such a manner that after 24 h the catheter tip would be reached in the case of normal flow. To maintain the same dose, we adapted the drug concentration in advance. A previous radioisotope study showed that the tracer reaches the cerebral basal cisterns from the lowest caudal level in 2–2.5 h.[10] Therefore, basal cisterns should be clearly visible at 111In-DTPA within 48 h. We assumed stagnation in drug delivery due to a rostral CSF flow obstruction when the tracer appearance in the basal cisterns was later than 48 h, limited, or not present (Fig. 1).

Summary of Cases

We summarized the patient's history, the used diagnostic procedures exhibiting a partial or complete CSF obstruction, and the treatment in Table 1.

	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	male	male	female	male	male
Age	44	64	47	60	38
Level of SCI	C5	T12	T10	T2	C6
Treatment somewhere else					
Dose adjustments	yes	yes	yes	yes	yes
Improvement	none	none	none	none	none
Catheter revision			N = 1	N = 3	N = 18
Improvement			no	no	no
Intradural bypass					C6–T6
Improvement					no
^{111}Indium scintigraphy					
At referral					
Spasticity	severe	severe	severe	severe	severe
Pain			severe		
Years of successful ITB	4	3	12	19	<1
Baclofen dose (mcg/24h)	502	1,374	498	483	2,216
Opioid dose (mg/24h)			Hydromorphone 2.2		
Our diagnostics					
Plain radiography	normal	normal	normal	normal	normal
Catheter tip	T7–8	T9–10	T11	T7	T9
Aspiration fluid CAP	yes	yes	yes	yes	no
CAP myelography obstruction	partial T7	partial T11	complete T10–11	complete T5–7	
CAP CT myelography obstruction	partial T7	partial T11	complete T10–11	complete T5–7	
^{111}Indium scintigraphy obstruction	partial T7	partial T11	complete T9–10		complete T9
LP CT myelography obstruction			complete T8–9		extradural catheter
CP CT myelography obstruction			complete T10		
Our treatment					
None					
Catheter revision	yes				yes
Improvement	good				some
Microsurgical adhesiolysis		yes			
Improvement		excellent			
Microsurgical adhesiolysis +			yes		yes
Intradural bypass			T8–L2		T6-10
Improvement			some		some
Percutaneous fenestration			yes	yes	yes
Improvement			good	excellent	good

Table 1. Summary of patient history, diagnostic procedures, obstruction, and treatment.

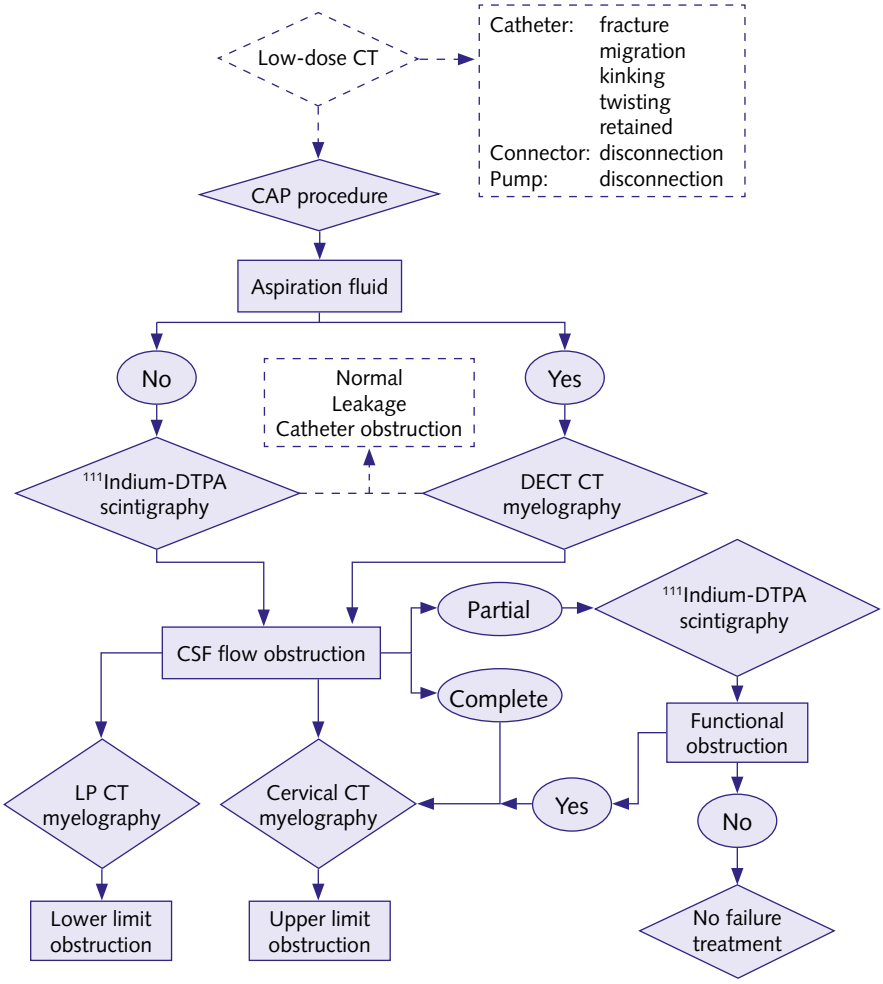

Figure 1. Algorithm imaging of CSF flow obstruction.

Case 1

A 44-year-old man who experienced a traumatic SCI American Spinal Injury Association (ASIA)-A at the C5 level eight years ago developed disabling intractable spasticity of the lower and upper extremities. After a successful ITB bolus injection test two years later, the patient was successfully treated with ITB for four years. However, the spasticity reoccurred gradually despite a daily dose of 502 mcg. Several higher doses did not result in an improvement, and the patient was referred to our center. At the time of referral, the patient had severe spasticity of the lower and upper extremities (a Modified Ashworth Scale [MAS] score of 3). CAP (CT) myelography was suspicious of an obstruction at the T10 level (Fig. 2A, 2B), which was confirmed by ^{111}In-DTPA (Fig. 2C). Because no catheter revisions were performed previously, we first replaced the intrathecal catheter, which resulted in a clinically significant decrease of the spastic symptoms (MAS 1) for, currently, 15 months.

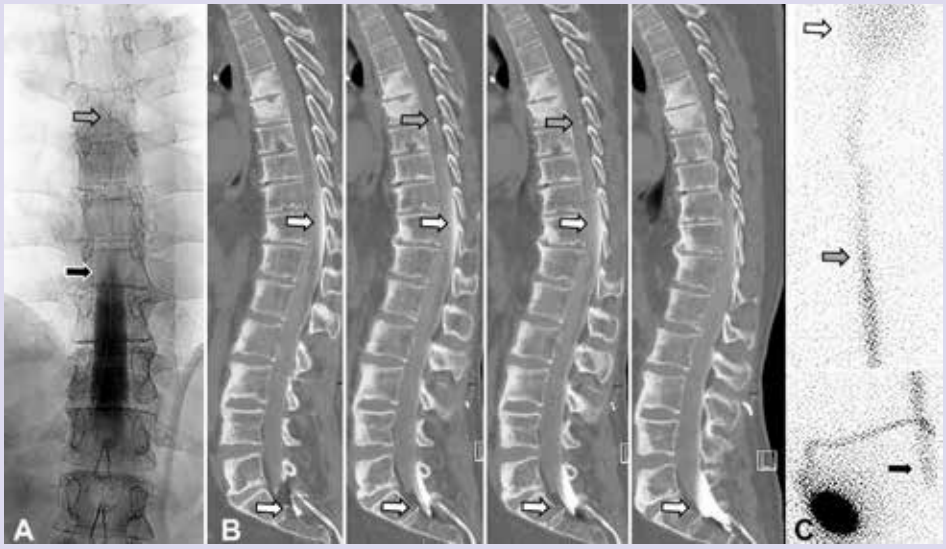

Figure 2. Catheter access port (CAP) myelography (A) showed stagnation of contrast material (black arrow). The catheter tip is located above the contrast material (gray arrow). CAP CT myelography (B) with 4 consecutive sagittal reconstructions revealed a caudal flow of the contrast material (white arrow). Planar ^{111}Indium-DTPA scintigraphy 7 days (C) showed a limited rostral tracer spread, increased lumbar/thoracic gradient (gray arrow), increased caudal spread black arrow), and insufficient cerebral cistern (white arrow).

Case 2

A 64-year-old man experienced a traumatic SCI ASIA-A at the T9–10 level 24 years ago. Over the years, the patient developed disabling therapy-resistant generalized spasticity of the lower extremities, which could be managed by oral spasmolytic medication. Nevertheless, after 20 years, his spasticity could no longer be controlled by this medication. After a positive ITB bolus injection test, the patient was successfully treated with ITB for three years. Gradually, his spasticity worsened, which could be reduced to MAS 3 by increasing to an extremely high daily dose of 1,374 mcg. CAP CT myelography (Fig. 3A) and ^{111}In-DTPA, including Single Photon Emission Computed Tomography (SPECT-CT) (Fig. 3B) and planar images (Fig. 3C), were suspicious of an obstructed spread of contrast material and tracer material, respectively. We performed a laminectomy at T9–10 with a midline dura opening. With a microscope, we observed severe adhesions and crystalloid drug accumulation in several loculations. We conducted adhesiolysis of the fibrotic leptomeninges and removed the crystalloids, which resulted in CSF flow restoration. After finishing the surgery, the ITB dose was reduced arbitrarily by 50%. The next day, the patient was slightly sedated, with completely flaccid legs. We cut the dose further to 550 mcg, which was sufficient to control the patient's spasticity (MAS 0) for two years.

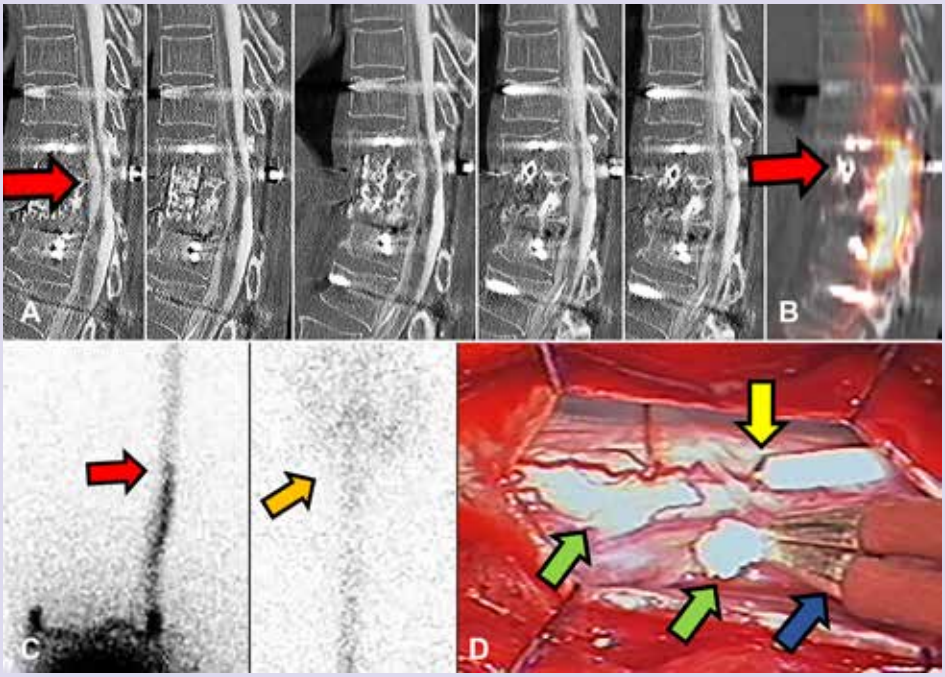

Figure 3. CAP CT myelography (A) with 5 consecutive sagittal reconstructions revealed narrowed contrast material column (red arrow), suspicious for contrast material stagnation. 111In-DTPA SPECT CT at 48 h (B) showed obstruction at the level of the spinal cord lesion (red arrow). 111In-DTPA planar (C) revealed a lumbar/thoracic gradient (red arrow), limited cerebral cistern tracer spread (orange arrow). In vivo microscopic view with opened dura showed intrathecal catheter tip (yellow arrow), forceps (blue arrow), and baclofen medication crystallization (green arrow).

Case 3

A 47-year-old woman experienced a traumatic SCI ASIA-B at the T10 level 18 years ago. The patient's rehabilitation was hindered by severe lumbar and low thoracic pain and disabling generalized spasticity of the lower extremities, leading to a bedridden situation for about 18 months. After a positive ITB bolus injection test, the patient was successfully treated with ITB for 12 years. Gradually, the patient experienced exacerbation of her spasticity and pain. Despite dose adaptations of both baclofen and morphine, and later hydromorphone, her complaints were persistent. A catheter revision did not relieve the pain and spasticity. For troubleshooting, the patient was referred to our center. At the time of referral, the patient had severe spasticity of the lower extremities (MAS 3) with a daily ITB dose of 683 mcg, and high pain scores (a Visual Analogue Scale [VAS] score of 8) in the lumbar region with a daily hydromorphone dose of 4.5 mg. We evaluated her pain and performed local anesthetic lumbar blocks, which did not reveal improvement. CAP (CT) myelography indicated an inhomogeneous stagnation of contrast material just below the SCI level. ^{111}In-DTPA after 48 h showed an abnormal widening of the tracer spread at the lumbar/low-thoracic transition, a narrowed thoracic region, and no tracer activity in the cisterns, suggesting an obstruction (Fig. 4B).

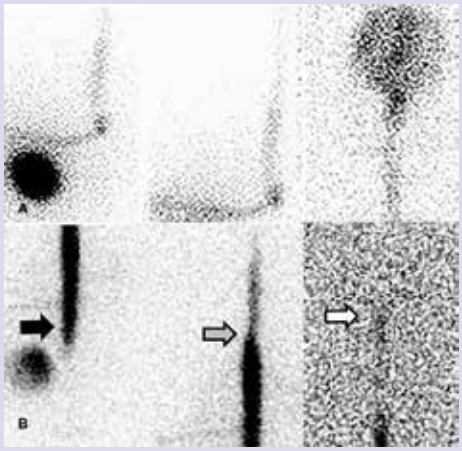

Figure 4. Planar ^{111}In-DTPA at 48 h (A, B). A patient without CSF flow obstruction with normal lumbar, thoracic, and cerebral cistern tracer spread (A). Case 4 with widened tracer activity caudal and at lumbar/low-thoracic transition (B, black arrow), thoracic gradient (B, gray arrow), and no cisternal tracer spread (B, white arrow).

We performed a laminectomy at the T10–11 level. Under microscopic vision, we performed an extensive local adhesiolysis of the fibrotic leptomeninges, but we could not restore the CSF flow. We decided not to enlarge the laminectomy, but to place an intradural catheter bypass[7,8] from T9 to L2. After surgery, the spasticity was under control (MAS 0) with a daily ITB dose of 460 mcg, but the pain remained unchanged despite a daily dose of 3.2 mg of hydromorphone. In the three years following the intervention, severe spasticity with a daily ITB dose of 505 mcg reappeared (MAS 3). The patient underwent several pain treatments elsewhere, but despite these treatments and a daily intrathecal hydromorphone dose of 3.5 mg, the patient had a high VAS score of 8 at the referral. ^{111}In-DTPA including SPECT found identical planar images as before the surgical intervention, consistent with a nonfunctional intrathecal bypass (Fig. 5A).

Based on our experience at the previous laminectomy where we were not aware of the length of the intradural obstruction, we wanted to be informed about the magnitude of the obstruction in advance. Therefore, we performed lumbar dual-energy CT (DECT) myelography with 3D reconstructions (Fig. 5B, 5C), and, in a second session, cervical CT myelography (Fig. 5D, 5E). With the Seldinger technique,[11] we performed a percutaneous fenestration of the obstruction with balloon dilatation. With the patient in the prone position with 5 ml of lidocaine 1% local infiltration, a midline lumbar puncture was performed with an 18G Tuohy needle (B Braun Medical B.V., Oss, The Netherlands). We inserted an Angled Guidewire 0.035 (Terumo Benelux N.V., Leuven, Belgium) into the intrathecal space, and advanced a 5F Brite Tip introduction sheath over the guidewire (Cordis Cardinal Health B.V., Amsterdam, The Netherlands). Via the sheath, we perforated the obstruction with the guidewire. In the next step, we advanced a 5x120 mm 0.038 Admiral Xtreme balloon (Medtronic Trading NL B.V., Eindhoven, The Netherlands) and gradually inflated the balloon until reaching the pain threshold. We deflated and repeated inflation several times to achieve, if possible, optimal balloon expansion at a nominal pressure of 8 bar. We controlled the dilatation results with cervical myelography through the injection of 10 ml of iohexol 300 via the inserted sheet. After each contrast material administration, we aspirated 10 ml of fluid to maintain intrathecal normovolemia. We repeated the balloon inflation and deflation procedure on two lower levels. Immediately after successful dilatation, the patient experienced severe nausea with vomiting, which we explained by the sudden rostral spread of the baclofen/hydromorphone medication. As therapy for this intoxication, we aspirated 30 ml of CSF and injected 1 mg of granisetron intravenously. Within a couple of minutes, the patient's spasticity (MAS 0) and

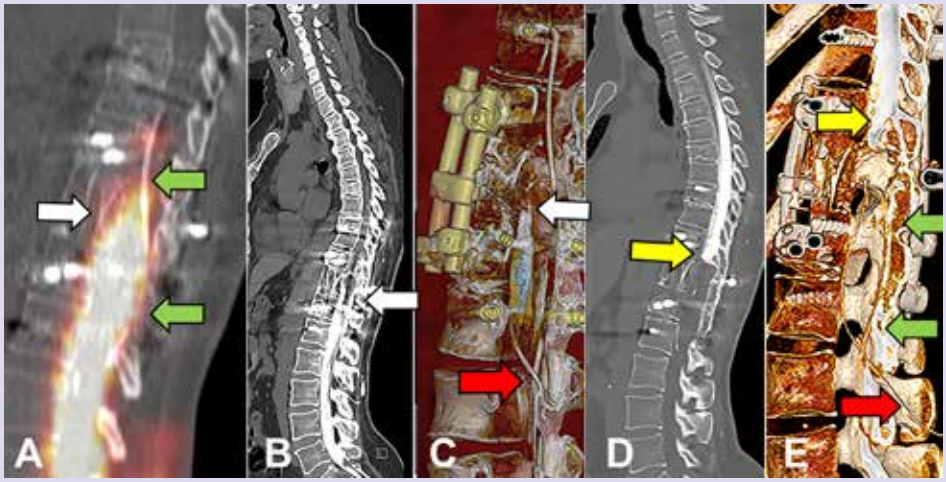

Figure 5. ^{111}In-SPECT CT with stagnation of tracer (white arrow), non-functional intradural shunt (A, E, green arrow), and no tracer activity above the tip of the shunt (A). Lumbar CT (3D) myelography with stagnation of contrast material at Th11 (B, C, white arrow), and with cervical CT (3D) at Th10 (D, E, yellow arrow). Intrathecal catheter (red arrow).

pain (VAS 0) disappeared entirely and have remained absent for, currently, a period of six months with a daily ITB dose of 505 mcg and an intrathecal hydromorphone dose of 3.5 mg.

Case 4

A 64-year-old man experienced a traumatic SCI ASIA-A at the T2 level 25 years ago. The patient developed disabling therapy-resistant spasticity of the lower limbs and the abdominal and thoracic region, which was complicated by autonomic dysreflexia (AD) several times a day, and which could insufficiently be controlled by oral medication. Two years later, after a positive ITB bolus injection test, the patient's spasticity, as well as his AD, was successfully treated with ITB for 15 years. At the time of a pump replacement because of the end of the battery life, the patient's treating physician also decided to replace the intrathecal catheter. From that time onward, the severe spasticity with frequent daily periods of AD could no longer be managed by ITB. To overcome the ITB failure, the patient underwent three catheter revisions without any result. At the time of referral, the MAS score was 2. Nevertheless, the patient had severe spontaneous and intentional spasms of the lower extremities and the abdominal and thoracic region, and AD every hour. CAP CT myelography (Fig. 6A) and cervical CT myelography (Fig. 6B) revealed contrast material stagnation at the SCI level.

With the same percutaneous fenestration procedure (Fig. 6D–6J) as in Case 3, we could restore the rostral CSF flow (Fig. 6C). Immediately after the successful dilatation, the patient experienced nausea and a headache, probably as a result of the sudden rostral spread of the baclofen medication. We drained 30 ml of CSF and injected 1 mg of granisetron intravenously. Within a couple of minutes, his spasticity dis-

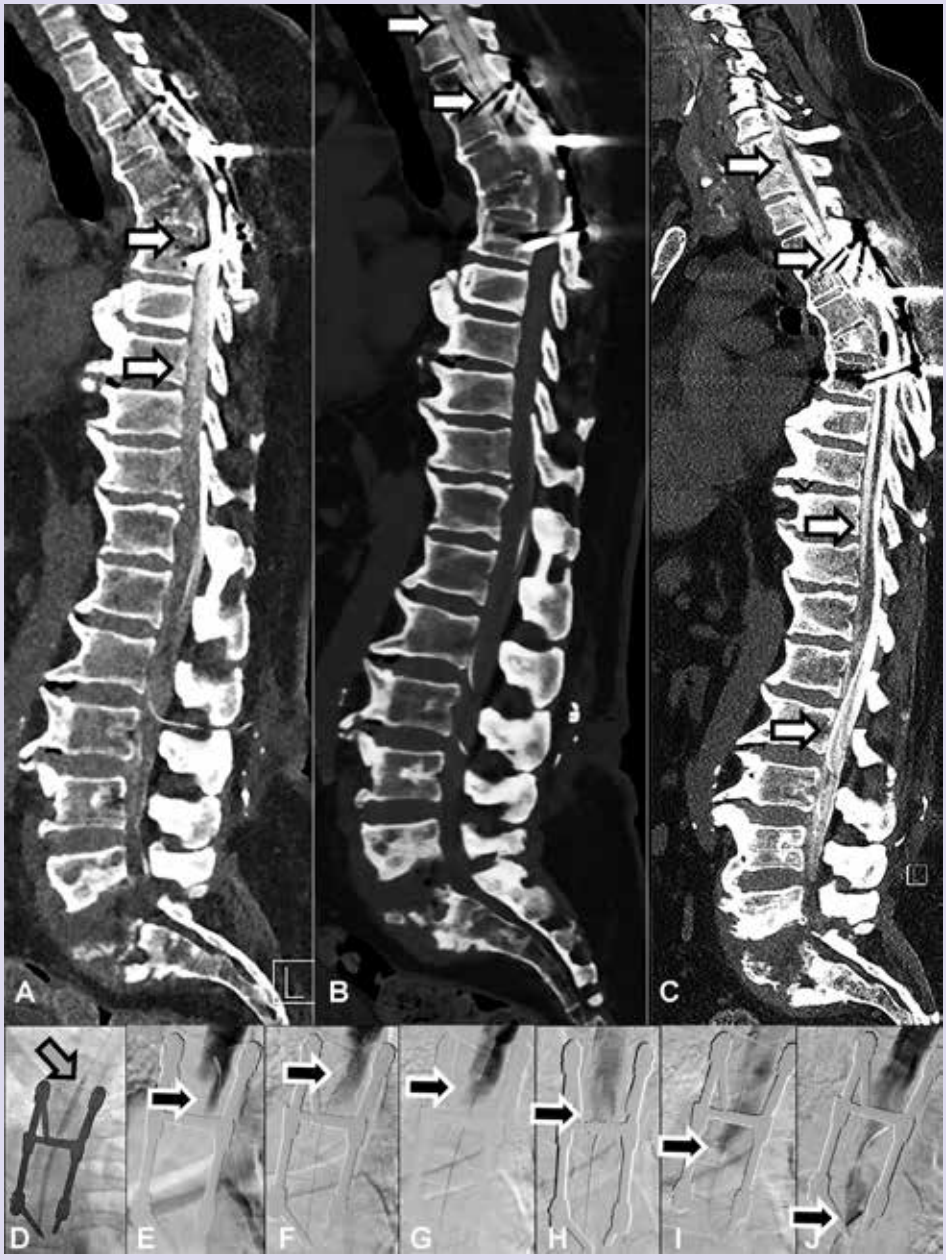

Figure 6. CAP myelography (A) and cervical CT myelography (B) with inhomogeneous stagnation (white arrow). Cervical CT myelography after percutaneous balloon fenestration (C) with restoration of contrast material spread (white arrow). Fluoroscopy during the procedure with inserted balloon (D, gray arrow). Cervical contrast material injection to evaluate the effect of balloon dilatation (black arrow): starting situation (E), some widening on the same level (F, G), and the result of the fenestration (I–J).

appeared entirely. After that, the ITB dose was titrated to 157 mcg, which was sufficient to control his spasticity and AD, and the additional 140 mg of daily oral baclofen medication could be stopped permanently. At this moment, the result has lasted for six months.

Case 5

A 38-year-old man experienced a traumatic SCI ASIA-B at the C6 level 19 years ago. The patient developed disabling therapy-resistant spasticity of the lower extremities, abdominal region, trunk, and right hand, which could insufficiently be managed by oral spasmolytic medication. After a positive ITB bolus injection test two years later, the patient was successfully treated with ITB for less than one year. In particular, spasticity of the abdomen, trunk, and right hand was problematic. Over 14 years, the patient underwent 18 surgical interventions to improve the ITB treatment, but all these procedures did not lessen his complaints. The patient was referred to our center for troubleshooting. At the time of referral, the patient had severe generalized spasticity of the lower extremities and right hand, and severe spontaneous and intentional spasms of the abdominal region and trunk several times a day, despite an extreme ITB daily dose of 2,216 mcg. During CAP myelography, we could not aspirate CSF and, therefore, contrast material was not injected, and we terminated the procedure. ^{111}In-DTPA SPECT at 72 h and seven days via the pump demonstrated tracer accumulation at the lumbar–low thoracic transition, a stagnation of the tracer at T2, and no activity in the cerebral cisterns. CT myelography via L3–4 showed an extradural catheter position. We inserted a new intrathecal catheter with the tip on T10. Postoperatively, with a daily ITB dose of 360 mcg, the spasticity of his lower extremities was under control, but the spasticity of his abdomen, trunk, and right hand was not. Dose increments up to 1,109 mcg did not improve the situation. With magnetic resonance imaging (MRI), a granuloma was excluded. Because of the persistent complaints two months later, an ^{111}In-DTPA was performed, and a tracer stop at the catheter tip and minimal activity in the cerebral cisterns were found, consistent with an obstruction at the catheter tip level. We performed a laminectomy at the T10–11 level and found an intact intrathecal catheter. With a microscope, we observed severe adhesions and crystalloid drug accumulation in several loculations. We conducted extensive local adhesiolysis, but we could not restore the CSF flow. We decided not to extend the laminectomy, but to place an intradural catheter bypass[7,8] from T10 to C6. Following the surgery, the spasticity improved, but the trunk and upper extremity remained problematic, despite the high daily ITB dose of 1,109 mcg. Two years later, we performed a percutaneous fenestration of the obstruction. During a lumbar puncture at the L2–3 level, minimal spontaneous CSF flow was observed. We experienced a hindrance advancing the guidewire at several thoracic levels. By moving the guidewire back and forth, we could overcome the problem. We advanced the sheath over the guidewire and inserted the balloon. With repeated balloon inflation and deflation on the low thoracic level, we could manage several obstructions. When reaching level C7, we observed a massive obstruction. At this moment, the patient was complaining of a severe headache, mild autonomic dysreflexia (only transpiration and piloerection), and exacerbation of the abdominal spasticity. We terminated the procedure, reduced the daily dose to 500 mcg, and treated the headache with paracetamol. After removing the balloon out of the sheath, we observed spontaneous CSF flow, although less than normal. The CT scan immediately after the procedure revealed improvement of the CSF flow; but at the lumbar and cervical levels — and less at the thoracic level — some obstructions were still present. The next day,

his spasticity considerably improved to MAS 1, and the paroxysmal spasms almost completely disappeared. Until now, the result has lasted for four months.

Discussion

Treatment results

This small case series showed that rostral CSF flow restoration could solve ITB failure in SCI patients with an intrathecal flow obstruction. All patients had a previous successful ITB bolus injection test and were, therefore, suitable candidates for long-term ITB. As a consequence, the short benefit duration in one patient was unexpected, while the other four patients had successful ITB for years.

Adhesions

In line with the literature,[8] we identified peroperatively severe adhesions in three patients and, in two, even crystalloid drug accumulation in several loculations. We observed a rostral CSF flow obstruction as the cause of ITB failure only in traumatic SCI patients, and not in other ITB patients. There probably may be a relationship with the original trauma or the previous post-traumatic neurosurgical intervention. It could be assumed that the obstruction existed already at the start of the ITB treatment. However, the experience of excellent treatment for years, which is also reported in the literature,[8] more likely suggests a CSF flow hindrance during the course of the ITB treatment. We had no information about the preexisting arachnoiditis in the referred patients. In our opinion, it is not common practice to evaluate arachnoiditis before starting ITB. Even when arachnoiditis, known or unknown, is present, patients will be treated with ITB after a positive diagnostic ITB bolus test. The observed loculations may develop after focal arachnoiditis resulting in fibroconnective adhesions,[12] whereby the leptomeninges will give rise to loculation formation.[13] This may lead to accumulation of the infused medication, which is what we found (Fig. 3D). The accumulation of drugs will give rise to a high local concentration, which in turn can lead to a vicious cycle of chronic arachnoiditis. It is assumed that the longer the exposure, the higher the probability that a toxic response to the drug will occur.[14] In chronic intrathecal infusion of morphine and hydromorphone, arachnoiditis may result in the formation of space-occupying masses (granuloma) in the intrathecal space.[15,16] This phenomenon was recently supported by a relationship between granuloma formation and local mast cell degeneration in intrathecally administered drugs.[17] Such an association was found for morphine and hydromorphone, but not for baclofen.[17] The difference between the mentioned opioids and baclofen is in accordance with clinical experience, in which granuloma formation is a well-known complication of intrathecally administered opioids,[15,16] but rare when using intrathecal baclofen.[18–20] The extremely low incidence of the reported clinical granuloma formation in chronic ITB and the absence of factors of granuloma development in animals and mast cell cultures[17] make the etiology of obstruction in SCI patients treated with ITB unclear.

Imaging

To be certain of a CSF flow obstruction, the Trendelenburg position is crucial in CAP (CT) or conventional lumbar CT myelography. When in doubt if an obstruction is present, the dynamic ^{111}In-DTPA often revealed the cause of the ITB failure. In a complete obstruction, the observed tracer widening and caudal tracer collection on the images are probably the result of a backflow.

Interventions

After the success of the first case, we also intended to perform an operative adhesiolysis in two other patients. However, despite extensive local adhesiolysis, we could not restore the CSF

flow. We decided not to extend the laminectomy, but to apply an intradural catheter shunt. With the shunt, we could obtain improvement in both cases, although not in the trunk and the right-hand spasticity in one patient. Based on our recent experience with promising results, we now prefer the less invasive percutaneous fenestration as the first step in rostral CSF flow restoration. To prevent a multi-segmental laminectomy, the percutaneous technique also has the advantage in a more extended length obstruction. The method has a potential risk of damage in ASIA-B patients in particular (Case 3). We regarded this as a calculated risk in a severely suffering patient after an insufficient result from visual microsurgical adhesiolysis. This risk was extensively discussed in advance with the patient. During the procedure, we inflated the small diameter dilatation balloon in several steps in such a way that compression on the spinal cord was minimal. All the procedures were performed with a continuous awake monitoring of the patient to recognize potential damage. Before the procedure, we extensively discussed the pros and cons of the treatment. Another issue could be that in the future, epidural stimulation could be of benefit. Traumatic adhesiolysis may interfere with epidural stimulation, as this is reliant on viable axons remaining at the site of the injury. For the moment, we will be confronted with ITB failures with, besides adhesiolysis, no other treatment options. A larger group of patients and basic research are needed for the full elucidation of the effect of the restoration. When the balloon inflation will not meet our expectations, we will consider surgical adhesiolysis with or without a bypass.

Needed rostral CSF flow

We hypothesized that rostral CSF flow is also needed for ITB administration to be effective. This is in contradiction to the current view of a solely local segmental ITB effect.[21–23] With rostral CSF flow restoration either by surgical adhesiolysis, intradural bypass, or percutaneous balloon fenestration, we could obtain improvement in the five treated patients. These preliminary results supported our hypothesis and implied that an intervention to restore the flow could solve an ITB failure caused by a CSF flow obstruction. A recently published case report[8] of the successful use of a subarachnoid-subarachnoid shunt seems to support our results.

Autonomic dysreflexia control

From our own clinical experience with various ITB failures, we know that an ITB failure will not only lead to the reoccurrence of severe intractable spasticity, but in high SCI levels, also to the lack of autonomic dysreflexia control (Case 4),[24,25] a syndrome that can even be life-threatening.[26–29] These features justify extended diagnostic procedures and attempts to find a solution for ITB failure, and not merely to accept ITB tolerance as an exacerbation of the underlying disorder.

Duration of the clinical effect

How long the achieved result will last and whether we can repeat the procedure in the case of recurrent failure are uncertain. A larger group of patients and basic research are needed for the full elucidation of the effect of the restoration of CSF flow.

Conclusion

Preliminary results showed that the restoration of the rostral CSF flow might result in an effective ITB treatment in patients with an intrathecal obstruction.

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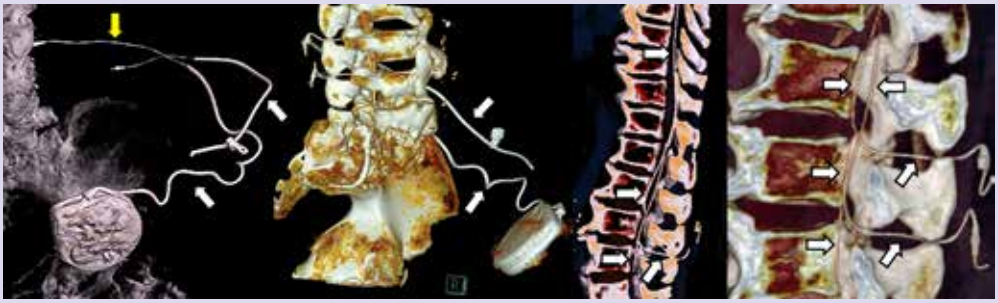
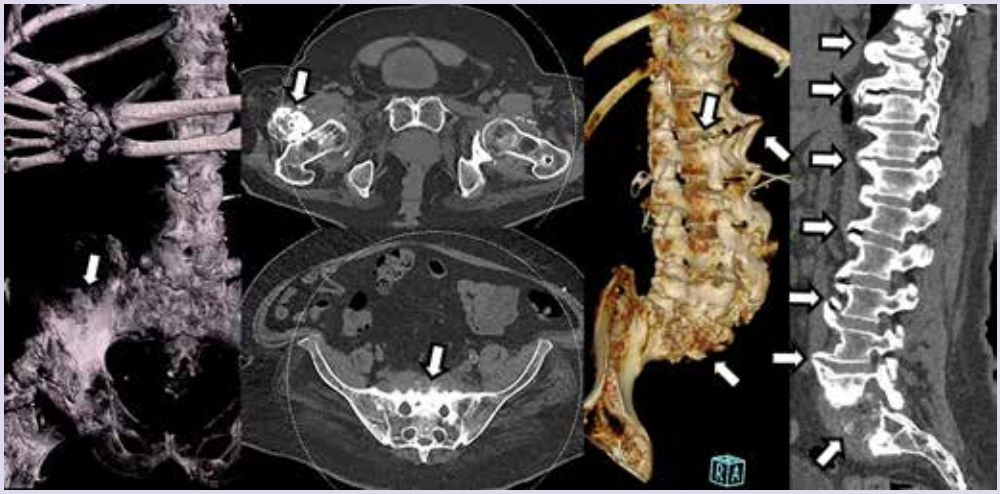
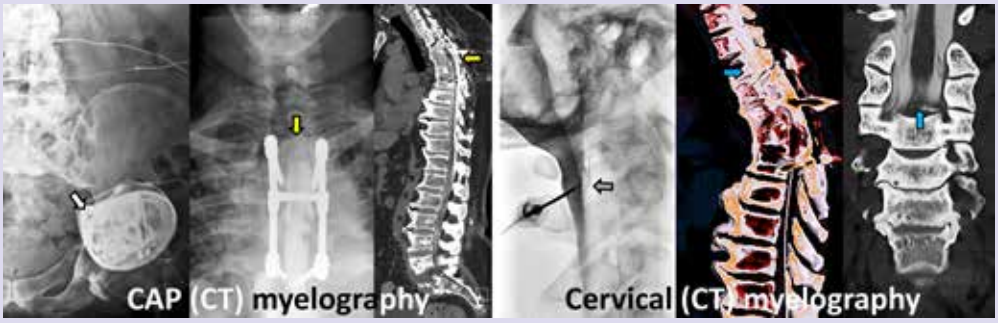
eFigure 1 The puzzle of ITB failure (Case 4)



Device, spinal catheter related? Multiple catheter(s) (parts) are present (white arrows), spinal part 8731 catheter far outside the vertebral column (yellow arrows).



Charcot spine, different neuropathic arthropathies. Sclerosis bone (periarticular and periosteal), bone destruction, massive osteophytosis, kyphotic deformities (white arrows). [1-5]



A reduced or absent rostral CSF flow? CAP injection (white arrow), contrast material stop lower level (yellow arrow). Cervical injestion (gray arrow), contrast material stop lower level (blue arrow).

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9

Intrathecal baclofen as emergency treatment alleviates severe intractable autonomic dysreflexia in cervical spinal cord injury

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ABSTRACT

Context

Episodic attacks of autonomic dysreflexia (AD) are regularly experienced by patients with a spinal cord injury (SCI) on T6 or higher levels. The episodes can result in a pounding headache, flushing, blurred vision, anxiety, a stroke, posturing, hyperthermia, retinal bleeding, seizures, myocardial ischemia, cardiac arrhythmias, and death. The observed associated bradycardia is explained as a baroreceptor reflex response to the high blood pressure. Intrathecal baclofen (ITB) has been used to treat chronic AD. This case highlights the occurrence of intractable AD after removal of the ITB delivery system because of a pump pocket infection. We describe the benefit of ITB as an emergency treatment for intractable AD.

Findings

A 53-year-old male suffered from spasticity and AD after a C5 ASI B SCI in 2002 was successfully treated with ITB for 14 years. He developed Staphylococcus aureus and Pseudomonas aeruginosa cellulitis at the orifice of his suprapubic catheter, which caused an abscess in the pump pocket. To prevent a withdrawal syndrome, the medication was reduced in three steps of 25%, and the pump was explanted. Postoperatively, he experienced severe AD and was treated with clonazepam, clonidine, and urapidil. The next day, the severely fluctuating blood pressure and pulse rate were no longer controllable with the medication. At L2-3, a temporary external intrathecal catheter for reinitiating ITB was inserted. With this treatment, the AD and the spasticity symptoms could be controlled.

Conclusion/Clinical Relevance

The case demonstrated that refractory AD could be managed with ITB in an emergency.

Keywords

spinal cord injury, spasticity, intractable autonomic dysreflexia, intrathecal baclofen, emergency, sympathetic storm.

Introduction

Episodic attacks of autonomic dysreflexia (AD) ("sympathetic storm") are regularly experienced by patients with a spinal cord injury (SCI) on T6 or higher levels (above the outflow to the splanchnic and renal vascular beds).[1-5] Noxious or innocuous visceral or somatic stimuli below the SCI lesion such as bladder and bowel irritation[1,3,6] can lead to a sudden excessive sympathetic response. Spasticity, pain, sexual activity, pregnancy, delivery, pressure sores, and iatrogenic medical procedures are also known to trigger AD.[1,3,7] Loss of descending inhibition results in higher levels of norepinephrine release, which is responsible for cold, pale skin vasoconstriction below the level of injury.[3,8] The observed associated bradycardia is explained as a baroreceptor reflex response to the high blood pressure.[2,3,6] The AD syndrome varies from silent, mild forms with diaphoresis above the lesion and piloerection to a severe, life-threatening situation.[2,7] These attacks can happen up to 40 times a day.[4] The episodes can result in a pounding headache, flushing, blurred vision, anxiety, a stroke, posturing, hyperthermia, retinal bleeding, seizures, myocardial ischemia, cardiac arrhythmias, and death.[1-3] Intrathecal baclofen (ITB) has been used to treat chronic

Figure 1. Autonomic Dysreflexia: Severe fluctuations in blood pressure (black arrow) and pulse rate (gray arrow).

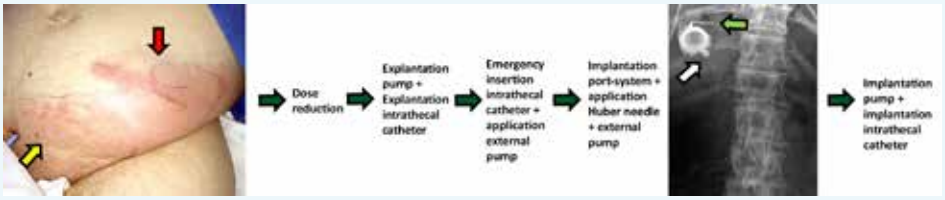

Figure 2. The treatment approach of a secondarily infected pump pocket (red arrow). The original infection was cellulitis at the orifice of a suprapubic urine catheter (yellow arrow). The implanted port system (white arrow) is connected with a hardly visible Ascenda intrathecal catheter. The port system is percutaneously punctured with a 90° Huber needle (green arrow).

AD.[9,10] We report the application of ITB in an emergency case of acute intractable sympathetic storm. After the approval of the medical ethics committee of Erasmus Medical Center (MEC-2017-326), we retrospectively studied the case. The requirement to obtain informed consent was waived.

Presentation of the case

A 53-year-old male suffered from spasticity and AD after a C5 ASI B SCI in 2002. Initially this complaint was controlled with oral baclofen. Due to progression of spasticity, ITB was administered after two years. For fourteen years, the patient was treated with ITB using an implanted infusion system (SynchroMed II, Medtronic Inc., Minneapolis, MN, USA). During that time, a neuropathic pain developed below the level of the SCI and morphine was added to the ITB. Complaints were again under control with intrathecal morphine of 1.2 mg/day and ITB of 192 mcg/day. More recently, the patient developed a cellulitis at the orifice of his suprapubic catheter. Initially, we started with flucloxacillin 4 g/day. After the bacteriological culture revealed both Staphylococcus aureus and a Pseudomonas aeruginosa, the antibiotic treatment was changed to piperacillin/tazobactam 16/2 g/day, and vancomycin 2 g/day. The local infection quickly subsided with the antibiotic treatment, but the development of erythema and swelling around the pump in the left abdominal wall indicated that the infection had spread to the device. We feared that the abscess would force the infection to spread along the catheter to the epidural and intrathecal space in a matter of days.

Explantation of the pump was thus deemed necessary. To prevent a withdrawal syndrome, we reduced the medication in three steps by 25%. Concomitantly, as a cross titration we started with oral baclofen and transdermal fentanyl (50 mcg). As intrathecal baclofen was still administered, we started with a low oral ba-

clofen dose of 40 mg, which was increased to 80 mg while concomitantly reducing the intrathecal administration. At day four we removed the entire device. We did not find any sign of an infection dorsally at the catheter insertion site, but we identified an abscess in the abdominal pump pocket. The day thereafter, the patient developed episodic a severe headache, excessive perspiration and piloerection in the upper part of the body, and severely varying blood pressures (BP), and pulse rates (PR), without pain, fever, respiratory insufficiency, and with except for a C-reactive protein of 73 mg/ml and an alkaline phosphatase of 135 U/l all laboratory values were normal and remained unchanged in the following days (Fig. 1). Thereby was his spasticity under control with oral baclofen and intravenous clonazepam.

With a diagnosis of AD, related with a withdrawal syndrome, the patient was admitted to the ICU and initially was successfully treated with a mixture of clonazepam, clonidine and urapidil. However, the next day the clinical situation was complicated by the patient's diminished consciousness, later diagnosed as a posterior reversible encephalopathy syndrome (PRES).[11] The severely fluctuating BP and PR returned, and the maximum tolerable oral and intravenous substitution was insufficient to compensate for the prior highly efficient route of administration of his baclofen.

A distinct subarachnoid hemorrhage (SAH) in the left frontal lobe was identified with MRI (Fig. 2). To alleviate the AD, we inserted at L2-3 a temporary external catheter (Perifix 19G, B. Braun, Oss, The Netherlands) 30 cm intrathecal for reinitiating ITB (Fig. 2). After a positive 50 mcg single bolus, we titrated ITB up to 240 mcg/day using a standard syringe pump. With this treatment, we could manage the AD and the spasticity symptoms. After one week, we removed the temporarily external catheter and replaced it with a definite intrathecal Ascenda catheter (Medtronic Inc., Minneapolis, MN, USA). In order to bridge the time until the pump pocket infection was cured, we temporarily connected the catheter to a subcutaneously implanted portal system (Porthales 4000, Tricumed Medizintechnik GmbH, Kiel, Germany) at the opposite site (costal 10–11 level). After a dose titration ITB up to 384 mcg/day using a CADD-Solis external pump (Smiths Medical ASD, Inc., St. Paul, MN, USA), we discharged the patient from the hospital. Ten weeks later, we removed the portal system and connected the catheter to a new pump in the lower right abdominal quadrant. The patient gradually recovered from the PRES. His spasticity and AD were brought under control with ITB of 384 mcg/day, and his pain by intrathecal morphine of 1.2 mg/day.

Discussion

To our review, emergency resumption of ITB as treatment of life-threatening withdrawal syndrome with AD that has not been reported before. The cyclic character, the excessive regional perspiration, piloerection in the absence of pain and missing symptom control by an additional administrated opioid, we assumed opioid withdrawal was not likely. To preempt or minimize a withdrawal syndrome,[12] we performed a cross titration initially with only oral baclofen, and later with the addition of clonazepam; furthermore, to prevent an opioid withdrawal, we used transdermal fentanyl. In our practice, we wean the intrathecal medication arbitrarily in steps of 25% while concomitantly starting oral and transdermal treatment. This manner of weaning is the compromise to prevent a withdrawal syndrome versus the potential for development of meningitis. Based on our experience, we assume the same clinical aggravation would have emerged after a slower weaning protocol. Thereby, it should be taken into consideration that the fear the abscess would force the infection to spread along the catheter to the epidural and intrathecal space in a matter of days is

the reason for other physicians deciding upon the immediate removal of the implanted infusion system, thus preferring to take the risk of a withdrawal syndrome instead of the development of severe meningitis. The symptomatology, in this case, differed from the regular ITB withdrawal syndrome, as his spasticity was under control with no signs without fever, respiratory insufficiency, or a multiorgan failure. Our patient was previously diagnosed with severe AD that was successfully suppressed with ITB.

The patient exhibited intractable sympathetic storms as a result of a spasticity exacerbation. Possible confounding factors could be the cessation of intrathecal morphine and the presence of an infection, which itself could lead to an autonomic disturbance. However, AD did not occur in the previous cellulitis at the orifice of the suprapubic catheter period, but developed several days later. Per protocol, we explored the common causes of an autonomic disturbance, including bowel, bladder, and skin problems. Also, a physical examination and computed tomography did not reveal additional treatable disorders to remove the triggers. Also, to our best knowledge a relation between the presence of morphine in the ITB pump and the development of AD is unknown. A primary concern is the paucity of knowledge of the syndrome AD among caregivers[8] and additionally the limited knowledge of ITB, in particular its value in preventing AD.[9,10] We observed a protracted duration of the syndrome over hours, which is consistent with prior studies.[13,14] The patient revealed an excessive fluctuating BP and PR. the patient's varying systolic BP of 90 to 155 mmHg exceeds the norm of 150 mmHg[5,7] as well as the sudden 20–40 mmHg elevation[7,15] and should therefore also be considered excessive. Moreover, the associated HR of 149/min was extreme. Because we could not control the clinical situation with the applied medication, we were forced to reinitiate ITB. With no sign of a local dorsal infection, clear CSF, and a CSF Gram examination that had not revealed microorganisms at the removal of the implanted device, we decided upon a catheter insertion, although we were at that time not informed about the bacterial culture. We regarded the insertion of a foreign body such as the temporary intrathecal catheter into a potentially infected area as a calculated risk for the introduction of meningitis. We considered the development of PRES and SAH as a direct complication of the frequently repeated hypertensive crises.

Based on this case, we propose that ITB infusion using a temporary intrathecal catheter during emergency situations could be possible in every hospital. In our experience, the higher ITB dose at the end after a catheter replacement is not uncommon. We are not aware of a clear explanation. A different intrathecal catheter tip level or other ventral/lateral/dorsal position could be an option. Also, it is not excluded that the clinical situation has worsened the spasticity and AD complication, resulting in the need for a higher dose. A limitation of this study is the retrospective design and the experience in only one patient.

Conclusion/Clinical relevance

The premise of the case is the rapid reintroduction of ITB (as opposed to iv and oral antispasmodics) in the setting of ITB withdrawal in particular when associated with AD to prevent complications (in this case, PRES, SAH). Further in-depth study is necessary to validate our observation.

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10

General discussion

Background

The knowledge of many physicians about ITB is limited as ITB is a treatment with low volume. This problem is exacerbated by the lack of concentration ITB therapy in a limited number of treatment centers and the need for involvement of many medical specialists including neurologists, rehabilitation physicians, nursing home physicians, neurosurgeons, interventional anesthesiologists, emergency physicians, radiologists, and nuclear physicians. The restricted application of ITB treatment and resulted limited expertise has led to incorrect referrals and insufficient diagnostic and treatment procedures, a lack of awareness of potentially lifethreatening situations, and a lack of around-the-clock availability of professionals with expertise of ITB. This situation is at odds with the critical nature of the assessment of the indication for ITB, the logistical requirements involved in patient selection, the surgical intervention, ITB aftercare, and ITB troubleshooting. It is therefore not surprising that incorrect assessment of drug tolerance and unjustified conclusions regarding the exacerbation of the underlying disorder are common. The abovementioned issues were the main reason for the studies in this thesis, aiming to improve 1) ITB aftercare, 2) the diagnosis of ITB related complications and 3) the treatment of ITB treatment failure.

The specific objectives of the thesis

Objective 1: To evaluate the safety and efficiency of a home-based ambulant clinic for aftercare (Chapter 2)

In the study that focused on the development and evaluation of the home-based Ambulant Care Clinic, the efficiency and safety of high-level standard aftercare with intrathecal baclofen on location were proven.

For safety management, the Dutch Technical Agreement 8009 "Safety management system for hospitals and organizations which administer hospital care was followed. For risks management of the near incidents, the "Healthcare Failure Mode and Effect Analysis (HFMEA) of the "National Center for Patient Safety (NCPS) was applied. In case of a high risk of frequency and severity of consequences, an extensive PRISMA Medical analysis (Prevention Recovery Information System for Monitoring and Analysis) to manage structural human errors in practice was made. A quality and safety certification procedure were performed annually by an independent professional inspection institute (KIWA, Rijswijk, the Netherlands). With the approach of the home-based Ambulant Care Clinic, transport to the hospital or center, which is often a burden for severely handicapped patients, was significantly reduced. This approach paves the way for further applications of ITB therapy in severely handicapped spastic patients and therefore has the potential to address ITB undertreatment.

To improve ITB troubleshooting, an expert center that engages in close cooperation with a home-based Ambulant Care Clinic was established. In addition to addressing the importance of daily care, the partnership was used to provide a solution to the problem of realizing around-the-clock availability of experienced caregivers. The center also features a double-check facility, i.e. a real-time control by two persons. This control check is crucial for protecting not only the standard "five rights"[1] (right person, right drug, right dose, right route of administration, and right time) but also for the appropriate concentration of the medication and the appropriate complex pump programming. With the support of the nurse practitioners of the home-base Ambulant Care Clinic in our center, a unique infrastructure required for around-the-clock ITB troubleshooting was realized. Currently, in the Netherlands, the home-based Ambulant Care Clinic is responsible for the aftercare of 40% of the patients. In other countries, the discussed

aftercare approach does not exist, which is tremendously problematic in severely handicapped spastic patients. Missing the aftercare structure will result in frequent visits of the patients to the neuromodulation center, which seems to be an important factor of the worldwide ITB undertreatment. (See comments of the reviewers Chapt.2) In some countries the drug device company technicians take care for the refills and reprogramming in severely handicapped patients, which does not meet the current requirements of patient care (Personal communication).

Objective 2: To describe the various causes of ITB failure (Chapter 3,6,7)

The majority of the different diagnostic procedures were performed in patients referred from other centers with the diagnosis of ITB drug delivery failure, in which the underlying cause could not be found. The patients were referred with the diagnosis: "tolerance for the treatment" or "an exacerbation of the underly-ing disorder". This conclusion could have an enormous impact on the quality of life of patients with intractable spasticity. We performed an extensive diagnostic imaging workup which could include multiple diagnostic modalities. As described in the thesis we could find the cause of the failure in a substantial number of patients, followed by successful treatment. In cases where we could not identify an abnormality, extensive attempts with dose adaptations were undertaken to obtain again a positive effect of the ITB treatment. With dose adaption we were also successful in a substantial number of cases.

Reported drug delivery device-related adverse events are[2-26]: pump failure, hypermobility of the pump, skin irritation with wound dehiscence, infection, and catheter related problems. However, most of the adverse events are caused by intrathecal catheter failure.[2-26] The main reasons for this are migration, lacerations, occlusion, and disconnection of the catheter. Although the performance of the current Ascenda catheter felt to be improved,[27] a definite conclusion about its superiority over the old catheters cannot be made yet. Besides its potential improvement, a significant problem arose after its introduction caused by a reduced opacity on plain radiography, which hinders the diagnosis of catheter-related problems.

Our study is hampered by a bias of a highly selected patient population. The majority of the patients with catheter-related problems were not referred but were already treated in the original center. As a result, we were dealing with referred patients of intractable ITB failure in a subacute or chronic situation. The identified causes after our diagnostic workup were mainly catheter problems like occlusion, catheter leakage, epidural and subdural position, dura leakages, and CSF flow obstructions. Pump-related problems were not found.

CSF flow obstruction resulting in inadequate distribution of the medication has not been described in the literature as a relevant component in ITB failure. The studies on intrathecal drug delivery are concentrated on the applied infusion device and not on the rostral distribution of the medication in the subarachnoid space. This is probably caused by previous reports in which only the segmental effects of intrathecally delivered baclofen medication was described.[28,29] Based on the results of successful treatment of the underlying causes of ITB failure, which were detected after extensive diagnostic procedures in our studies, we concluded that in ITB failure, a final diagnosis of "tolerance" or "an exacerbation of the underlying disorder" is only justified after extensive diagnostic procedures.

Objective 3: To assess the role of radiological and nuclear imaging techniques in identifying the cause of ITB failure (Chapter 3,5,6)

The advanced radiological and nuclear imag-

ing techniques performed in the studies have played a crucial role in identifying the cause of ITB failure, which was not found in the referral centers. In about half of radiological and two-thirds of nuclear medicine procedures, we could identify the cause of ITB failure.

Plain radiological imaging is currently the cornerstone for the diagnosis of catheter-related adverse events in ITB. Catheter-pump or catheter-catheter segment disconnections, dislodgement, shearing, and pump displacements are crucial issues related to the sudden termination of ITB infusion. However, with plain radiography, only the metal catheter tip, unfolded fixation anchor, and needlelike catheter–catheter segment of the currently standard Ascenda intrathecal catheter are visible; as such, pivotal information regarding the catheter course and its connections may be missed. Although earlier models of catheters that are still in use exhibit better opacity, their visibility can also be problematic.

We implemented and optimized as advanced imaging procedure pump catheter access port (CAP) myelography and CAP-CT myelography. These procedures allow the evaluation of the catheter over its full length and improved the diagnosis of disconnection, catheter leakage, dural leakage and malposition. In addition, we applied ^{111}In-DTPA scintigraphy when we could not aspire CSF via the CAP, or when the CAP-procedures did not reveal the diagnosis, or when we were uncertain about it. We also optimized the procedure and assessed the accuracy of the modification of its use in ITB failure. With ^{111}In-DTPA scintigraphy functional information about the temporal distribution of medications was helpful in detecting CSF flow obstruction as the cause of ITB failure. In some patients, we have used MRI to identify an intrathecal process.

Despite an optimal diagnostic approach, an additional problem is the restricted application of ITB treatment, which has the consequence that, for many radiologists, imaging assessments may be hindered by insufficient knowledge of the structure of the drug delivery system. Missing a standardized assessment of interpretation, a 14-step interpretation checklist for systematic assessment of plain radiography was developed based on an analysis of the procedures performed in our clinic. The same checklist could be used in case plain radiography will be replaced by low dose CT scan.

Another problem is the lack of awareness of emergency issues related to abnormal radiological findings indication potential failure in drug administration. A sudden termination of ITB ad-ministration may cause a progressive and potentially life-threatening withdrawal syndrome. The multidisciplinary discussion of patients and diagnostic exams in our center has increased the awareness of reporting radiologists.

Objective 4: To investigate the optimization of radiological and nuclear imaging techniques (Chapter 3-5)

The appropriateness of existing algorithms in troubleshooting and the involved diagnostic procedures is under debate. Of particular concern is the use of CAP myelography. Based on the results of our study, we agree with Saulino et al.[30] that CAP (CT) myelography should be included in the algorithm of ITDD failure. As a new approach, we optimized the CAP CT myelography with 1) the addition of dualenergy CT, 2) with 2D/3D reconstructions and volume ren-dered images, 3) with image reconstruction with a large field of view. With dual-energy CT beamhardening artifacts around the implanted titanium pump could be reduced. 2D/3D reconstructions and volume-rendering provide optimal visualization of the pump and catheter structures. A large field of view visualizes not only the vertebral column but also the pump and the extra-vertebral path of the catheter, which allows the detection of cathe-

ter leakage, catheter obstruction, or abnormal rostral spread of injected contrast material.

^{111}In-DTPA scintigraphy was optimized by 1) standardizing the pump flow rate, 2) the addition of SPECT-CT and 3) a stepwise and standardized interpretation of images. With this improved procedure, the cause of delivery failure could be correctly identified in more patients, which resulted in a diagnostic improvement compared to the conventional approach in ^{111}In-DTPA scintigraphy. With the standardized pump flow rate, intrathecal tracer transit time to the cerebral cisterns could be assessed. We demonstrated that the tracer transit time and the related magnitude of the tracer activity in the cerebral cisterns are pivotal for correct imaging interpretation. Delayed tracer transit time and reduced tracer in the cerebral cisterns is an indication for hindered transport in the catheter or intrathecal space caused by partial obstruction.

Based on our studies we disagree with the statement in the literature that presence of tracer activity in the intrathecal space[31] or the cerebral cisterns[32] excludes an abnormality. The studies indicated also that the addition of SPECT-CT[33] improves the localization of tracer accumulation caused by structural or functional disorders.

Objective 5: To investigate the role of low-dose single-energy computed tomography as a replacement for plain radiography (Chapter 4,5,7)

The currently used standard intrathecal catheter imaging with plain radiography is hampered by inferior catheter opacity. For this reason, there is an urgent need for improvement of the limited opacity of the applied catheters. We investigated the use of low-dose CT as a replacement of conventional plain radiography as the first line of diagnostic evaluation. CT with 2D/3D post-processing reconstructions based on maximum intensity projection, multiplanar reformation, and volume rendering techniques could provide optimal visualization of the entire catheter pathway. However, the rather high radiation exposure associated with standard high-resolution CT imaging limits its use for routine imaging. To examine the possibility of obtaining high-resolution imaging with a reduced dose, a phantom study focusing on a low-dose single-energy 2D/3D CT scan was conducted. Scans were performed with various acquisition and image reconstruction settings to evaluate the trade-offs among the catheter visibility, the pump beam-hardening artifacts, and the radiation dose. A clinical protocol using Sn100 kVp with 2D/3D single-energy CT reconstruction as a substitute for routine observational plain radiography was defined. We expect that in the future, plain radiography for postoperative documentation and for exclusion of catheter-related problems in the emergency setting will be replaced by low-dose single energy CT with 2D/3D reconstructions.

Objective 6: To evaluate the appropriateness of cerebrospinal fluid (CSF) flow restoration in case of spinal canal obstruction (Chapter 8)

ITB treatment failure in patients with spinal cord lesion can have specific causes related to CSF flow obstruction. In case of ITB failure catheter replacement will not solve the clinical problem. These patients normally will be considered to be tolerant to the treatment. In several of these patients, who were ultimately referred to our center, we were able to diagnose intrathecal CSF flow obstruction. The obstruction could be identified with a catheter access port CT myelography or scintigraphy. Occasionally lumbar CT myelography was performed. Before adhesiolysis, information about the length of the obstruction in the spinal canal is crucial. Cervical retrograde CT myelography can be performed to assess the upper limit. The catheter access port or lumbar CT myelography can be used for estimation of the lower limit.

We hypothesized that the intrathecal obstruc-

tion was probably related to chronic arachnoiditis, that chronic arachnoiditis hampers rostral flow of CSF and baclofen and that rostral CSF flow is a prerequisite for successful ITB treatment. Based on this hypothesis, CSF flow in these patients was restored with either microsurgical repair or percutaneous balloon adhesiolysis, which resulted in a solution for ITB failure. Remarkably, with the exception of one case, the ITB treatment proved successful for many years. Scarce information is present in the scientific literature. Only one patient with a subarachnoid-to-subarachnoid shunt treatment has been reported.[34] How long the performed adhesiolysis will last is unclear, and the clinical results should be followed.

Objective 7: To report about emergency ITB treatment in severe, intractable autonomic dysreflexia as result of an ITB withdrawal syndrome (Chapter 9)

In addition to the baclofen withdrawal syndrome that can be caused by the sudden termination of ITB, severe sympathetic hyperactivity in patients with a spinal cord lesion above T6 or a cerebral lesion can occur. The associated extreme fluctuations in blood pressure can give rise to stroke, posturing, hyperthermia, retinal bleeding, seizures, myocardial ischemia, cardiac arrhythmias, and death.[35-39] In one of our patients the ITB delivery device had to be explanted due to infection. Discontinuation of ITB resulted in a therapy-resistant life-threatening sympathetic storm which occurred as a result of autonomic dysreflexia. To continue ITB, it was decided to use a temporary intrathecal catheter and infusion with an external pump device as an emergency treatment. The results indicate that a life-threatening sympathetic storm can successfully be treated with ITB. It seems that ITB not only prevents severe autonomic dysreflexia, as stated in some case reports,[39] but is also of value as an emergency treatment.

Strength and limitations

- The concept of aftercare on location (Chapter 2) is an innovative and patient-friendly initiative. Despite the retrospective nature of the study included a large number of patients and was able to demonstrate its efficacy and safety.
- The proposal for a systematic analysis of plain radiography in patients treated with intrathecal drug delivery using an implantable pump device (Chapter 3) is the most extensive description of potential problems that can be detected. The study has significant education and clinical aspects for radiologists who lack knowledge about the used implanted drug delivery device and the consequences of an abrupt cession of the intrathecal drug delivery. In addition to this, systematic assessment of plain radiography has also clinical implications for treating physicians.
- Phantom studies were performed to evaluate the optimal acquisition and reconstruction parameters of a low-dose CT with a side-by-side evaluation with plain radiography (Chapter 4). This technological approach guarantees that a new imaging approach enters the clinical domain arena after adequate evaluation and optimization. The results are promising with important clinical implications as it solves the problem of poorly visible intrathecal catheter structures on routine observational plain radiography.
- The study of the catheter access port (computed tomography) in the intrathecal drug delivery study (Chapter 5) is a unique analysis with a significant educational and clinical implication of the optimized procedure.
- Reports on application of ^{111}In-DPTA SPECT-CT is limited to 11 procedures in 9 patients.[33, 40] Our study reporting on 36 examinations in 27 patients is therefore extensively increasing the number of reported cases. The multiple image acquisitions per patient allowed us to study temporal distribution of medication

and to detect CSF flow alterations. This was only possible after optimizing and standardizing the imaging procedure (Chapter 6).
- As a next step after the detection of CSF flow obstruction we hypothesized that rostral CSF flow is needed for an effective ITB treatment. This hypothesis was leading in the development and implementation of a surgical or minimal invasive restoration of rostral cerebrospinal fluid flow in patients with a proven obstruction. The preliminary results showed indeed that the restoration of the rostral CSF flow might result in an effective ITB treatment in patients with a spinal cord lesion complicated with an intrathecal obstruction (Chapter 8).

However, the studies also have several limitations:
- Although, the different studies in this thesis included the largest number of patients compared to previous studies, the sample sizes are too small to draw firm conclusions. The number of patients per year treated in the Netherlands is approximately 1000, with an incidence of new treatments of 100 per year. We have focused on problem solving in intractable ITB failure which has restricted the number of patients that could be included in our studies.
- This thesis is a retrospective analysis based on available data. This has resulted in a heterogenous data set as clinical work up and data collection was unstructured. The observational routinely collected data analysis could not be addressed with existing reporting guidelines such as Strengthening the Reporting of Observational in Epidemiology (STROBE).[41]
- As we included patients referred from other hospitals with intractable ITB failure we have studied a highly selective group of patients. This could be result in an overestimation of the diagnostic accuracy of the evaluated advanced imaging techniques.
- In all studies we were faced with the absence of a standardized reference test. In most studies the reference test was based on a composite of all available data. Ideally all patients should have undergone an intervention to find out what the real cause was of ITB failure. This was considered to be unneeded and unethical in those patients in whom the diagnostic procedure was normal. However, even not all patients with image abnormalities underwent an intervention. On the other hand, one may argue that the best prove for a good diagnosis is not the interventional confirmation, but improvement of symptoms after treatment focused on the potential cause of ITB failure

Implications for clinical practice

The results of the thesis indicate possibilities for improvements in the diagnosis and treatment of ITB failures. More precisely, the implications for clinical practice are:
- The radiologist must be informed about the systematic medication delivery path assessment, starting at the pump and ending at the catheter tip or the cerebral cisterns.
- The radiologist must be informed about the emergency of a radiological examination, and their interpretations in ITB withdrawal syndrome and (s)he must immediately inform the involved clinician about potential causes of ITB failure.
- Plain radiography can be replaced by low-dose energy CT with 2D/3D reconstructions.
- With the optimized catheter access port, dual-energy CT myelography with 2D/3D reconstructions, precise information about the delivery system can be obtained with a reduction of beam-hardening artifacts.
- With the optimized ^{111}Indium-DTPA SPECT-CT, more correct diagnoses can be made.
- The nuclear medicine physician is aware of the systematic assessment of the drug deliv-

ery path, starting at the pump to the cerebral cisterns taken into consideration the pivotal tracer transit time.
- The involved ITB-treating physician is informed about the importance of advanced diagnostic image procedures. Both catheter access port (CT) myelography and scintigraphy have their role in the diagnostic algorithm.
- Percutaneous balloon fenestration for adhe-siolysis in the spinal canal in spinal cord le-sion patients with ITB failure seems to be promising. However, the definite conclusion about its clinical value has to be evaluated.
- ITB can be used as an emergency treatment in life-threatening autonomic dysreflexia in high level spinal cord patients.

Future research

Following the completion of this thesis, several questions remain unanswered; in addition, improving the treatment presents new challenges. Suggestions for future research include the following:

Prospective studies

Randomized controlled trials (RCT's) of intrathecal baclofen bolus injections, and a study of three months continuous infusion[42] have provided significant evidence that ITB reduces intractable generalized spasticity.[26,42-46] The latter study of three months duration in patients with a spinal origin of spasticity[42] has not a blinded evaluation of the out-come because all patients have undergone a lumbar baclofen bolus injection test in advance and as reported in the study all patients have experienced a positive result of this bolus. Repeating the study and omitting the lumbar baclofen test bolus is unjustified in RCT's in which patients with a spinal origin of spasticity are included. However, RCT's on patients with spasticity of supraspinal origin are lacking and randomization between three months treatment versus placebo is possible in certain circumstances. In addition, advanced clinical insight has revealed that in particular in this specific group not all patients respond to a lumbar baclofen bolus test. It might well be that patients with a negative test lumbar bolus injection will respond to long-term continuous infusion with an intrathecal catheter tip position based on the clinical manifestation of the spastic syndrome. This means that patients with a negative lumbar test bolus injection, placebo controlled RCT with cervical or low thoracic catheter tip position for respectively lower and upper extremity spasticity could be performed.
Since RCT's for long-term applications are unethical, the justification for chronic ITB and insights into the side effects and complications thereof must be derived from prospective observational studies.
Prospective studies could be carried out in our setting of a University Medical Center (Erasmus MC) with the integrated ambulant care clinic (Care4homecare). The standardized visits on location offer unique possibilities of reducing the known complications of noncompliance and missing outcomes.
The results of long-term application and insights into the side effects, complications and costs can be derived from certain observational studies. Such research must provide greater insight into dose escalations, dose tolerance, the possible relationship between dose escalations and the development of intrathecal obstructions, the optimal catheter tip position, and the diagnostic value of dose escalation for the development of failure. The study could also include a long-term evaluation of the CSF restoration treatment in cases involving CSF flow obstructions and increased sympathetic activity in spinal cord injury and cerebral lesion patients. Finally, this study will also provide data which is needed to justify reimbursement of the treatment.

Peroperative contrast material injection followed by low-dose 2D/3D single-energy computed tomography

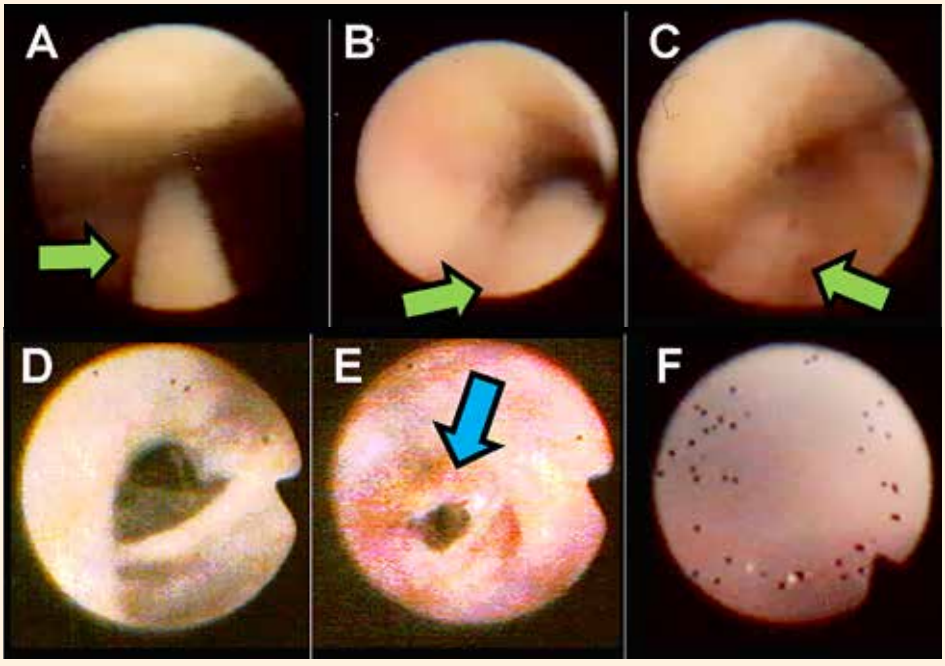
Reliable assessment of CT myelography in cases of intrathecal drug delivery failure is difficult, as normal reference images are lacking. To improve the detection of abnormalities as a cause of ITB failure postoperative CT myelography could be performed after peroperative injection of contrast material via the catheter. The obtained CT myelography could be prove the optimal positioning of the catheter and the baseline images could be used for comparison with follow-up studies in the case of drug delivery failure.

Computed tomography myelography before intrathecal baclofen treatment in spinal cord lesion patients

The rostral CSF flow obstruction observed in spinal cord lesion patients treated with ITB could be a reason to perform CT myelography prior to ITB treatment. The goal is to obtain information regarding the presence of obstructive arachnoiditis and to acquire a baseline image for comparing when treatment failure occurs. A topic for further study is whether an identified CSF flow obstruction should be treated before the start of ITB treatment or when ITB treatment failed to relieve symptoms immediately after the start of treatment or during follow-up.

The measurement of cerebrospinal fluid pressure as a diagnostic tool for obstruction

A partial or complete obstruction within either the drug delivery system or in the spinal canal with reduced CSF flow is difficult to identify. Flow measurement at the catheter tip is not possible with the SynchroMed II drug delivery system. Pressure measurement via an inserted needle in the pump CAP[47] has been recently proposed.



Normal catheter visible (A), some fibrotic reactions around the catheter (B), severe fibrosis around the catheter (C), normal intrathecal image (D), partial obstruction (E), and complete obstruction (F).

Spinaloscopy

Further research could explore the use of spinaloscopy to evaluate normal imaging findings and as a tool to support the treatment of (partial) intrathecal obstruction. The advantage would be obtaining information about obstructions in the intrathecal space and the ability to compare the results with those of radiological and nuclear scintigraphy examinations. The disadvantages are the interventional nature of the procedure and the vulnerability of the applied fiber optic scope device.

Intrathecal drug distribution

Numerous factors influence intrathecal drug distribution, including anatomical abnormalities, patient posture, infused medication, infusion baricity and rate, catheter diameter, lumbosacral CSF volume, CSF density and pressure.[48] Intrathecal infusions can therefore lead to high interpatient variability in drug distribution, even with the same dosage and under controlled settings.[49] Recently, it has been hypothesized that variations in CSF pulsatility (in terms of frequency and stroke volume) might lead to inter- and intrapatient variability in drug distribution.[48] A cine phase-contrast MRI with a computer model[50,51] a 4D phase-contrast flow analysis[52] would likely yield more insights into baclofen distribution in different patient populations. Such a study could also help to identify the ideal catheter tip position and volume of administered ITB. When 4D phase-contrast flow analysis revealed to be a suitable tool to determine CSF flow disturbances, it might be used in the initial onset and the later phase of the upper motor neuron syndrome as a result of a spinal cord lesion. If present or worsening CSF flow will be identified an RCT on the value of restoration of the flow with balloon fenestration could be considered.

Needle and template improvements

In CAP myelography, we found substantial problems with needle insertion in the CAP funnel. We found that the thin, vulnerable 24G Huber needle exhibited a tendency to bend and distort, particularly when inserted into a more deeply positioned pump or in the presence of rigid fibrotic scar tissue, which results in the procedure being challenging. We thus suggest the application of a conical 20G–24G needle. Another proposal is modifying the template of the CAP kit to include a partial open ring.

Remote control

Patients with an implanted SynchroMed II drug delivery system face potentially significant danger should they undergo an MRI examination in a hospital that does not have expertise in ITB and therefore does not have a means of restarting the pump. Although the pump generally restarts automatically after the MRI procedure, it is possible that this restart will not take place, which could potentially lead to a severe withdrawal syndrome. Remotely controlling of the pump is probably a potential solution when an MRI is performed. A further step could be minor remote dose adaptations, which would relieve disabled patients of the burden of traveling to the treatment center or eliminate the need for a home visit by the aftercare organization.

Conclusion

As a last available therapy of spasticity for the patient, the consequences of ITB failure are high, which deserves appropriate attention from all caregivers involved. The studies in this thesis demonstrate that advanced diagnostic and therapeutic procedures in ITB-failure are crucial for the restoration of the therapy. The results provide insight into the current possibilities of advanced diagnostic procedures. Applying the proposed systematic assessment of plain radiological imaging will probably reduce the number of missed diagnoses. The application of low-dose CT scan instead of plain radi-

ography could solve the problem of poorly visible intrathecal catheter structures, which seems to be an important clinical improvement. With catheter access port (CAP) CT myelography using dual-energy CT scanner with metal artifact reduction algorithm and 2D/3D reconstructions, we could demonstrate that CAP CT myelography is an essential step in the diagnostic algorithm for cases involving ITDD failure. Also, the application of ^{111}In-DTPA SPECT-CT is crucial when fluid cannot be aspirated for the CAP procedure or when CAP-CT myelography does not reveal the cause of the ITDD failure, or when information on the CSF fluid dynamics is needed for the correct diagnosis. When the studied diagnostic possibilities are applied, unjustified conclusions of "tolerance" or "exacerbation of the underlying disorder" can be reduced. A successful diagnosis followed by adequate treatment and complementary involvement of different medical specialists is an important prerequisite for a good outcome.

The preliminary results of the restoration of rostral cerebrospinal fluid flow might lead to the development of an effective ITB treatment in spinal cord lesion patients with an intrathecal obstruction.

The thesis suggests a need for improvement of communication and close cooperation of different medical specialists. Although out of the scope of the studies the niche character and the fragmentation of the available care could be a hindrance for the implementation of an interdisciplinary approach. In a non-acute situation of ITB failure, the required cooperation can probably be reached with increased knowledge of available structures. A significant concern is the appropriate approach to ITB failure in an emergency. For adequate troubleshooting, 24 hours per day, seven days per week, availability of expertise on pump analysis and programming, an infrastructure for "double-check" of highly concentrated medication, advanced radiological diagnostics, and an operating room and intensive care are required. These requirements are not easy to reach. The close collaboration between an expert center and an experienced ambulant clinic, allowing a permanent availability of the needed expertise might solve this problem.

This thesis gives answers on questions, but a substantial number of unanswered questions remain, which will continue to challenge the caregivers performing ITB.

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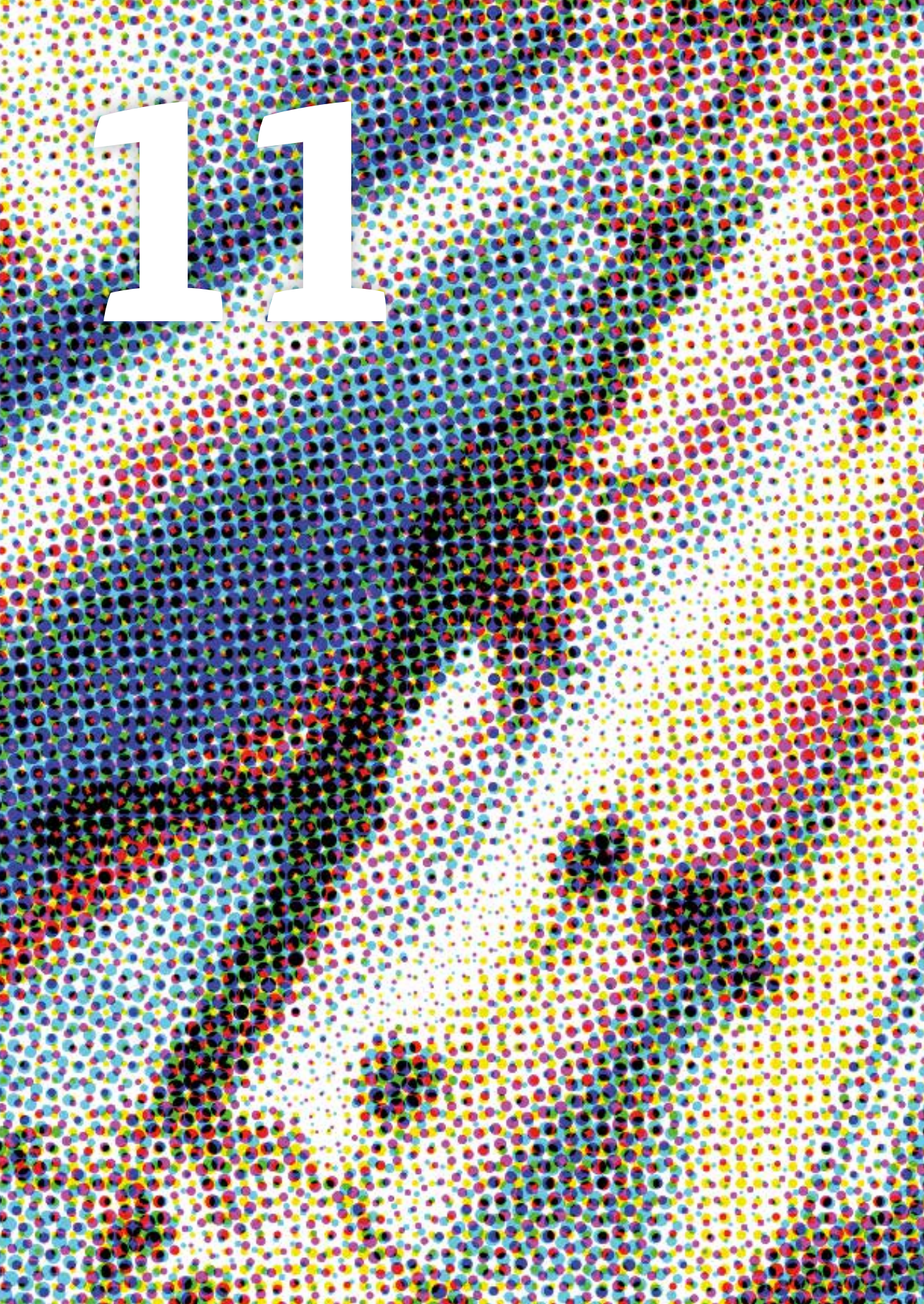
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Summary / Samenvatting

Chapter 1

Introduction

In the introduction, spasticity syndrome was briefly described. Spasticity is an important symptom of upper motor neuron syndrome. This syndrome results from damage to the descending cortical-reticulospinal motor pathways at the cortical, brainstem, or spinal cord level. Baclofen, a vigorous and selective GABA-B receptor agonist in the central nervous system, is usually used for drug therapy. However, due to the blood-brain barrier, relatively low CSF concentrations are realized after oral administration, which makes the treatment of moderate to severe spasticity insufficient. With higher oral doses, many side effects can occur. Intrathecal administration allows for significantly higher baclofen levels to be achieved at much lower doses and with fewer side-effects Intrathecal baclofen is indicated as a last-resort treatment for therapy-resistant disabling generalized spasticity of spinal or cerebral origin. The principle and the problems associated with intrathecal baclofen administration (ITB) were described. The relative rarity of ITB in the clinical setting may lead to a lack of knowledge on the part of medical practitioners and a subsequent underutilization of this treatment. In the event of complications, diagnostic procedures seem to be too few, too limited, or performed too late. Surgical reinterventions are frequently conducted with only limited diagnostics or in the absence of any such procedures. Furthermore, the effects of sudden termination that were not recognized by caregivers in all cases or was underestimated, which could prove life-threatening. These observations indicated a need for improved ITB failure treatment, which motivated this thesis.

For adequate troubleshooting of intrathecal drug delivery and to ensure around-the-clock availability of the expertise required for patient relief and pump analysis and programming, the ability to "double-check" highly concentrated medication and pump programming is required, as well as access to advanced radiological diagnostics, an operating room, and intensive care facilities. However, in particular, achieving 24-hour availability for such a "double-check" service would not be straightforward. Therefore, in order to offer around-the-clock care, we decided to cooperate with the home-based Ambulant Care Clinic.

Chapter 2

Efficiency and safety of ITB aftercare on location

Regular outpatient follow-up care is required when treating therapy-resistant spasticity with ITB. Logistically, however, this can be challenging. A solution could be to perform treatment at home. In the Netherlands, the Dutch Healthcare Authority initiated a project intended to deliver ambulatory ITB-related services via a home-based Ambulant Care Clinic. Nurse practitioners provide this aftercare with support from medical specialists. The study demonstrated the efficiency and safety of ITB care for patients with severe disabling spasticity in their home settings.

Chapter 3

Plain radiography in patients treated with intrathecal drug delivery using an implantable pump device

Adverse events related to the pump and catheter still occur. The majority of such events, such as migration, damage, disconnection, and occlusion, are related to the spinal catheter. This overview aimed to update radiologists' knowledge of how plain radiography of the implanted ITB delivery system should be interpreted. A secondary goal was to increase awareness of the need for immediate multidisciplinary troubleshooting. The interpretation of radiographic images of catheter-related adverse events was described, and a proposal for the

stepwise interpretation of standard plain radiographic images was drafted.

Chapter 4

Low-dose computed tomography with two- and three-dimensional postprocessing as an alternative to plain radiography for intrathecal catheter visualization: a phantom pilot study

The inferior opacity of intrathecal catheters (in particular, the Ascenda) is problematic. For troubleshooting purposes, plain radiography was extended with dual energy CT with 2D/3D reconstructions. Using this approach, optimal visualization of the entire catheter pathway and a reduction in the beam-hardening effects of the implanted titanium pump was achieved. However, clear catheter imaging is also required for routine plain radiography. In a phantom pilot study with a variety of different scanning protocols, high-resolution imaging with low- dose single-energy CT 2D/3D reconstructions which resulted in limited radiation exposure was found to be optimal to substitute for plain radiography. Ultimately, a CT setting of Sn100 kVp was identified as the best trade-off between visibility and reduction of artifacts.

Chapter 5

Catheter access port myelography in intrathecal drug delivery

In 53 adult patients, 70 CAP CT myelograms were performed on patients who underwent evaluation due to intrathecal drug delivery failure. In all cases, the cause could not have been identified through procedures that were previously routinely used. Data concerning needle insertion into the CAP funnel were retrieved from 65 cases of 70 cases. Of these cases, 19 were associated with mild and 6 with severe needle distortion. CAP fluid aspiration contrast medium injection was not possible (n=17). In one case contrast was injected in de the pump pocket unintentionally. In the remaining fifty-two examination CAP myelography was performed but had limited value for the diagnosis. CAP-CT myelography was performed in 50 cases and the examination revealed 19 abnormal results: dorsal dural leak, subdural catheter position, limited rostral flow of contrast material, limited and abnormal contrast distribution, obstruction of rostral flow, a leak at the pump-catheter connection, and a sheared catheter localized in the pump pocket. A limited contrast distribution in two examinations turned out to be false positive findings. CAP-CT myelography was normal in 31 procedures. Four normal CT-CAP myelographic procedures were false negative as the reference tests revealed a cause of ITDD failure. CAP-CT myelography had a sensitivity of 81% and in a specificity of 93%. With the use of CAP-CT myelography with 2D and 3D images, an improvement of imaging of the drug delivery system was achieved which indicated the need for an essential step in the troubleshooting algorithm used for intrathecal drug delivery failure.

Chapter 6

Diagnostic accuracy of optimized planar-SPECT low-dose computed-tomography ^{111}In-DTPA examinations in intrathecal drug delivery failures

Thirty-six ^{111}In-DTPA procedures were performed in 27 patients who had experienced intrathecal drug delivery failure and the cause could not be identified via other diagnostic modalities. The diagnostic protocol was optimized through standardization of the pump flow rate, the stepwise and standardized interpretation of the images and the application of SPECT-CT. Using optimized scintigraphy, 22 abnormal cases were detected (leakages, spinal catheter obstructions, and obstructions in the CSF flow). In addition, 14 cases were assessed as normal. In all 19 patients who underwent operations, we could confirm the scintigraphy diagnosis. It was found that the optimized ^{111}In-DTPA SPECT-CT scintigraphy is a powerful diagnostic tool

in ITDD failure when conventional diagnostic modalities do not reveal the cause.

Chapter 7

Complications associated with intrathecal drug delivery systems

An overview of our experience of the diagnosis and treatment of intrathecal drug delivery failures was presented. A particular focus was on the potential of abrupt withdrawal of intrathecal drug administration to be life-threatening. Furthermore, the therapeutic dilemma posed by the development of meningitis or withdrawal syndrome as result of an infection of the drug delivery system was discussed. Attention was also paid to potentially treacherous non-pathogenic bacterial meningitis with minor, or even absent, clinical symptomatology. An additional topic that was discussed was that dura leakage could result in CSF accumulation in the pump pocket.

Chapter 8

Restoration of cerebrospinal fluid flow to solve treatment failure caused by obstruction in long-term intrathecal baclofen administration

Six spinal cord lesion patients with an ITB failure caused by a CSF flow obstruction were described. The diagnostic workup treatment, and potential causes were described. When the cause of failure could not be identified by investigating a patient's history, a physical spasticity examination, the pump readout, confirming the absence of medication fluid in the pump, or plain radiography or CAP (CT) myelography was performed. To obtain information concerning the obstruction length, additional cervical CT myelography was initiated. In three cases, a laminectomy with microscopic surgical adhesiolysis was carried out. In two of these cases, CSF flow restoration was not achieved. The laminectomy was not enlarged, but an intradural bypass was placed. Recently, a less invasive technique of percutaneous fenestration of the obstruction with balloon dilatation was applied in three cases, resulting in CSF flow restoration with spasticity control. Preliminary results show that in an intrathecal obstruction using restoration of CSF flow appears to be an effective.

Chapter 9

Case report: Intrathecal baclofen as emergency treatment alleviates severe intractable autonomic dysreflexia in cervical spinal cord injury

The episodic syndrome of severe overactive sympathetic discharge ("sympathetic storm") is well-known in patients with a chronic spinal cord injury above the outflow to the splanchnic and renal vascular beds (T6 level). Noxious or innocuous visceral or somatic stimuli below the lesion, such as bladder or bowel irritation, can lead to a sudden excessive sympathetic response due to the loss of descending inhibition; this can occur up to 40 times a day. The effects of this syndrome can vary from silent, mild forms with flushing, diaphoresis above the lesion, and piloerection to a pounding headache, blurred vision, anxiety, stroke, posturing, hyperthermia, retinal bleeding, seizures, myocardial ischemia, cardiac arrhythmias, and even death. In chronic cases, ITB has been used to prevent the symptomatology. In the reported case, the therapy-resistant life-threatening autonomic dysreflexia was successfully managed with emergency ITB treatment.

Chapter 10

General discussion

In the general discussion presented in this chapter the results of the studies were reviewed and opportunities for future research identified.

Hoofdstuk 1

Introductie

In de introductie wordt kort het syndroom spasticiteit beschreven. Spasticiteit is een belangrijk symptoom van het bovenste motorneuronsyndroom als gevolg van schade aan de dalende corticale-reticulospinale motorische banen op corticaal, hersenstam- of ruggenmergniveau met o.a. aanzienlijk variërende spasticiteit. Voor de medicamenteuze behandeling wordt meestal baclofen gebruikt — een krachtige en selectieve GABA-B-receptoragonist in het centrale zenuwstelsel. Echter door de bloed-hersenbarrière ontstaan na orale toediening relatief lage liquorconcentraties, met vaak onvoldoende effect en bij hogere doseringen veel bijwerkingen. Veel hogere baclofenspiegels bij een veel lagere dosering met minder bijwerkingen worden bereikt bij de intrathecale toediening. ITB wordt toegepast, bij onvoldoende regulering van gegeneraliseerde, matige tot ernstige spasticiteit met orale toediening. Het niche aspect van ITB kan leiden tot gebrek aan kennis en onvoldoende behandeling. Bij complicaties wordt diagnostiek vaak te weinig, te beperkt of te laat uitgevoerd en worden chirurgische re-interventies gedaan met beperkte, of zelfs zonder, diagnostiek. Bovendien wordt een plotselinge ITB-beëindiging niet in alle gevallen herkend of onderschat — een situatie die levensbedreigend kan zijn. Deze observaties zijn de aanleiding voor onderzoek naar een verbetering van de ITB-behandeling, wat heeft geleid tot dit proefschrift.

Voor adequate probleemoplossing, is 24 uur per dag expertise voor de patiëntenzorg, het uitvoeren en het dubbel kunnen controleren van de pompanalyse, programmering en medicatie, de mogelijkheid van geavanceerde radiologische diagnostiek, beschikbaarheid van een operatiekamer en intensieve zorg vereist. Met name de permanente mogelijkheid van dubbele controle door gekwalificeerde professionals, is niet eenvoudig voor de ITB-behandeling te realiseren. Daarom werd besloten om samen te werken met de thuiskliniek voor ambulante zorg. De structuur van de samenwerking werd beschreven.

Hoofdstuk 2

Efficiëntie en veiligheid van ITB-nazorg op locatie

Voor de behandeling van therapieresistente spasticiteit met ITB is regelmatige poliklinische nazorg nodig. Logistiek gezien kan dit problematisch zijn. Een oplossing kan zijn de behandeling thuis uit te voeren. Met financiering van de Nederlandse Zorgautoriteit, is daartoe een innovatieproject uitgevoerd om op locatie ITB-nazorg te leveren met een ambulante kliniek. Deze nazorg is uitgevoerd door verpleegkundig specialisten met ondersteuning van een medisch specialist. Met de studie is de efficiëntie en veiligheid van ITB-nazorg in de thuisomgeving aangetoond bij patiënten met ernstige invaliderende spasticiteit.

Hoofdstuk 3

Blanco radiologisch onderzoek bij patiënten die worden behandeld met intrathecale toediening van geneesmiddelen met behulp van een implanteerbaar toedieningssysteem

Complicaties bij de intrathecale medicatie met een geïmplanteerde pomp en spinale katheter komen regelmatig voor. De meeste, zoals migratie, beschadiging, disconnectie en occlusie, houden verband met de katheter. Van de analysegegevens van alle gemaakte Röntgenfoto's werd een overzicht gemaakt, bedoeld om om de een kennisupdate te geven aan radiologen hoe blanco radiologisch onderzoek van het geïmplanteerde ITB-toedieningssysteem dient te worden geïnterpreteerd. Daarnaast werd geattendeerd op de noodzaak van een mogelijke onmiddellijke multidisciplinaire probleemoplossing. Van de analyse werd een protocol vervaardigd voor de stapsgewijze beoordeling van de Röntgenfoto's.

Hoofdstuk 4

Lage dosis CT met 2D/3D bewerking als alternatief voor routine blanco röntgendiagnostiek voor visualisatie van intrathecale katheters: een fantoom-pilot-studie

De geringe opaciteit van intrathecale katheters, in het bijzonder de Ascenda, is problematisch. Bij complicaties is daarom de blanco röntgendiagnostiek vervangen door een "dual-energy" CT met 2D/3D-reconstructies. Met deze aanpak konden we een optimale visualisatie van het gehele kathetertraject bereiken en beeldvervorming, veroorzaakt door het metaal van de geïmplanteerde pomp, verminderen. Echter, voor routinecontrole van het toedieningssysteem is ook goede beeldvorming nodig. Met een fantoom-pilot-studie met verschillende scanprotocollen, konden we hoge-resolutie beeldvorming met een lage stralingsdosis "single-energy" CT met 2D/3D-reconstructies als vervanging voor blanco röntgendiagnostiek bereiken. Uiteindelijk werd voor een Sn100 kVp CT-instelling gekozen als beste keuze voor de zichtbaarheid en de reductie van artefacten.

Hoofdstuk 5

Catheter access port (CAP)-CT myelografie bij intrathecale medicatietoediening

Bij 53 volwassen patiënten met een falen van intrathecale medicatie toediening werd 70 keer CAP-CT myelografie verricht. In alle gevallen, kon de oorzaak niet worden vastgesteld met de gebruikelijke procedures. Zeventien keer kon geen vloeistof worden opgezogen uit de CAP. Eén keer werd abusievelijk het contrastmiddel in de pomppocket gespoten. In de resterende 52 gevallen werd CAP-myelografie verricht, wat bleek van beperkte waarde te zijn voor het vaststellen van de diagnose. CAP-CT myelografie werd 50 keer uitgevoerd met 19 afwijkingen als resultaat: dorsaal liquor lek, subdurale katheter positie. Verminderde rostrale verspreiding van het contrastmiddel, verminderde rostrale, abnormale verspreiding van het contrastmiddel, obstructie van de rostrale verspreiding, lekkage van de pomp-katheter connectie, gescheurde katheter gelokaliseerd in de pomppocket. Twee keer bleek de verminderde verspreiding van het contrastmiddel vals positief te zijn. CAP-CT myelografie was normaal in 31 gevallen. Vier als een normale CAP-CT myelografie beschouwd, werden op basis van de referentie test als vals negatief beoordeeld. CAP-CT myelografie had een sensitiviteit van 81% en een specificiteit van 93%. Vastgesteld werd dat de toepassing van de CT-myelografie met 2D/3D beeldbewerking een essentiële stap is in het algoritme voor het vaststellen van de oorzaak van het falen van de ITB therapie. Additioneel werd van de 65 beschikbare gegevens het inbrengen van de naald CAP geanalyseerd. Negentien keer werd bij het inbrengen de naald verbogen, met 6 keer een ernstige vervorming. Een voorstel werd gedaan voor het ontwerp van een conische naald en de bijbehorende mal.

Hoofdstuk 6

Analyse van een geoptimaliseerd ^{111}In-DTPA-onderzoek (planair en SPECT) bij intrathecale medicatietoediening

Zesendertig keer in 27 patiënten werd een ^{111}In-DTPA-scintigrafie uitgevoerd bij patiënten met een falen van de intrathecale medicatie-toediening, waarbij de oorzaak niet kon worden gevonden met andere diagnostische modaliteiten. Het protocol voor het nucleaire werd geoptimaliseerd door standaardisatie van de pompsnelheid en de stapsgewijze interpretatie van de verkregen beelden met daarnaast de toepassing van SPECT-CT. Met de geoptimaliseerde scintigrafie werden 22 afwijkingen gevonden, (lekkages, spinale katheterobstructies, obstructies in de liquorruimte). Daarnaast werden 14 als normaal beoordeeld. Bij alle 19 geopereerde patiënten kon de scintigrafische diagnose worden bevestigd. Gebleken is dat de geoptimaliseerde ^{111}In-DTPA-scintigrafie een

krachtig diagnostisch hulpmiddel is bij het falen van intrathecale medicatietoediening wanneer met conventionele onderzoeken de diagnose niet kan worden gesteld.

Hoofdstuk 7

Complicaties geassocieerd met intrathecale medicatie toedieningssystemen

Op invitatie werd een overzicht van onze ervaring met de diagnose en behandeling van intrathecale medicatietoediening gepresenteerd. Bijzondere aandacht werd besteed aan potentieel levensbedreigend abrupte beëindiging van de intrathecale medicatie toediening. Verder werd ingegaan op het therapeutisch dilemma, bij het ontstaan van een meningitis of een onttrekkingssyndroom bij een geïnfecteerd toedieningssysteem. Aandacht werd ook besteed aan de verraderlijke niet-pathogene bacteriële meningitis met geringe, of zelfs afwezige, klinische symptomatologie. Ook werd besproken dat een dura-lekkage kan resulteren in liquorophoping in de pomppocket.

Hoofdstuk 8

Herstel van de liquorcirculatie bij het falen van de behandeling veroorzaakt door een obstructie bij langdurige intrathecale toediening van baclofen

Zes dwarslaesie patiënten met een falen van de ITB-therapie werden behandeld. De diagnostiek, behandelingen potentiele oorzaken werden beschreven. Wanneer de oorzaak van het falen niet kon worden gevonden uit de anamnese, het lichamelijk onderzoek, de pompuitlezing, controle van de juiste hoeveelheid aanwezige van medicatievloeistof in de pomp of blanco Röntgenfoto's, werd CAP (CT) myelografie uitgevoerd. Om informatie te verkrijgen over de lengte van de obstructie, werd een cervicale CT-myelografie verricht. In drie gevallen werd als behandeling een laminectomie met microscopische chirurgische adhesiolyse uitgevoerd. Twee keer werd geen herstel van de liquorcirculatie bereikt. Besloten werd de laminectomie niet verder uit te breiden, maar een intradurale bypass geplaatst. Recent werd 3 maal een minder invasieve techniek van percutane fenestratie van de obstructie met ballondilatatie toegepast, resulterend in liquorstroom herstel met als resultaat weer controle over de spasticiteit. De voorlopige resultaten tonen aan dat herstel van liquorstroom bij een intrathecale obstructie een effectieve lijkt te zijn.

Hoofdstuk 9

Case report: Spoedbehandeling met intrathecaal toegediend baclofen als behandeling van een ernstige therapieresistente autonome dysreflexie bij een cervicale dwaerslaesie

Het paroxysmaal optredend syndroom van ernstige sympathische overactiviteit ("sympathische storm") is bekend bij patiënten met een dwarslaesie boven de uitstroom naar de splanchnische- en niervaten (T6-niveau). Schadelijke of onschadelijke viscerale of somatische stimuli onder de laesie, zoals blaas- en darmirritatie, kunnen dagelijks veelvuldig, tot 40 keer per dag, leiden tot een plotselinge buitensporige sympathische reactie op basis van een afgenomen remming. Het syndroom varieert van niet herkende, milde vormen met transpiratie boven de laesie, blozen en pilo-erectie tot een beukende hoofdpijn, wazig zien, angst, beroerte, houdingsstoornis, hyperthermie, netvliesbloeding, epileptische aanvallen, myocardiale ischemie, hartritmestoornissen en overlijden. In chronische gevallen is ITB gebruikt om de symptomatologie te voorkomen. In de beschreven casus van een geïnfecteerd toedieningssysteem waarbij de ITB-behandeling moest worden beëindigd, werd met een ITB-spoedbehandeling de therapieresistente, levensbedreigende autonome dysreflexie met succes behandeld.

Hoofdstuk 10

Algemene discussie

In de algemene discussie werden de resultaten van de studies beschreven en werden voorstellen gedaan voor toekomstig onderzoek.

Dankwoord

Eindelijk na veel wachten en niet verder kunnen, is dit proefschrift klaar; de kers op de taart na meer dan dertig jaar bezig te zijn geweest met de intrathecale toediening van baclofen (ITB). In de loop der jaren is van verschillende zijden getracht mij te overtuigen te promoveren op ITB. Nu aan het einde van mijn carrière heb ik de rust en tijd gevonden voor verdieping en nader onderzoek, wat heeft geresulteerd in dit proefschrift.

Ik heb de ITB leren kennen als een geweldige therapie. Na een beperkte toepassing van het Promedos implanteerbaar pompsysteem van Siemens ben ik overgegaan op het Synchromed toedieningssysteem van Medtronic. De oorsprong daarvan ligt bij het bezoek van Pieter de Jonge, toenmalig medewerker van Medtronic. Het implanteerbare, programmeerbare pompsysteem was toen nieuw en vanwege mijn ervaring met pompsystemen en de intrathecale toediening van opioïden bij pijn bij kanker kwam Pieter zich oriënteren omtrent toepassingsmogelijkheden van het Synchromed toedieningssysteem. In 1984 had Prof.Penn in de Lancet het succes van ITB bij therapieresistente spasticiteit gepubliceerd. Ik was ervan overtuigd dat dat de indicatie was voor de toepassing van het pompsysteem. Groot probleem was de financiering. Dankzij de financiële steun van het Sophia Ziekenhuis te Zwolle, de "paraplu"-constructie en een budget voor het maken van de videotape "Bending the Unbendable" door Jo Merkun, toenmalig directeur van Medtronic Nederland, konden we aan de slag. Na jaren van moeizame strijd, met "case bij case" onderhandelen met zorgverzekeraars heeft uiteindelijk wijlen Prof.Dr.E.Borst, Minister van VWS, na een persoonlijke benadering, gezorgd voor een vergoedingssysteem.

Aanvankelijk was de behandeling met ITB gericht op de functionele verbetering ("cure") van therapieresistente spasticiteit. In de loop der tijd werd duidelijk dat de therapie ook van groot waarde is voor verbetering van de zorg en kwaliteit van leven ("care") bij zeer ernstige spastische patiënten. Eén van de problemen om bij deze categorie patiënten de behandeling te realiseren waren de belastende ambulance- of rolstoeltransporten. Om hiervoor een oplossing te vinden, heb ik samen met Simone Goslinga de ambulante kliniek Care4homecare opgericht, waarbij gebruikmakend van videoconferencing, patiënten zoveel mogelijk op locatie konden worden behandeld. Vervolgens heb ik Prof.Dr.F.J.P.M.Huygen benaderd met het voorstel om samen met Markus Wijffels, revalidatiearts van Rijndam Volwassenrevalidatie een ketenzorg ITB te ontwikkelen en deze zorg regionaal in Rotterdam Erasmus Medisch Centrum te concentreren. Hierbij werd steun verkregen van de Raad van Bestuur met als voorwaarde dat in 2018 de behandeling aantoonbaar academisch zou moeten zijn. Dit is dan ook mede de spin-off geweest voor dit proefschrift. Zonder hulp van velen zou dit proefschrift niet gerealiseerd. Ik tracht iedereen te bedanken, maar mogelijk zijn toch een aantal niet genoemd. Hiervoor mijn excuses.

Allereerst wil ik mijn promotor Prof.Dr.F.J.P.M. Huygen, anesthesioloog/pijnspecialist bedanken. Beste Frank, bedankt voor je vertrouwen in mij om de ITB in het EMC te integreren en je rol als mijn promotor. Ik waardeer je inzet, de kritische beoordeling van het manuscript en de plezierige samenwerking. Zonder jouw inzet was de ITB in het EMC nooit van de grond gekomen.

Ook mijn mede-promotor Prof.Dr.A.van der Lugt, neuroradioloog wil ik bedanken. Beste Aad, ik herinner mij ons eerste gesprek nog als de dag van gisteren. Ik heb toen aangegeven dat ik geen verstand heb van neuroradiologie, maar dat radiologen dat niet hebben

van het geïmplanteerde toedieningssysteem en van de soms levensbedreigende gevolgen van een acuut stagneren van de intrathecale medicatietoediening, maar dat als we samen zouden werken de "troubleshooting" bij ITB aanzienlijk zouden kunnen worden verbeterd; en dat het gelukt is, is wel duidelijk. Ik ben je zeer dankbaar voor onze geweldige discussies en de tijd die je eraan hebt besteed, ook toen nog niet duidelijk was dat jij mede-promotor zou zijn. Jij hebt mij gerelateerde delen van de neuroradiologie bij gebracht en mij, tot in detail, geleerd de bevindingen te beschrijven.

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Prof.Dr.J.B.R.J Brouwers, ziekenhuisapotheker. Beste Koos, samen hebben we in het verre verleden activiteiten omtrent intrathecale medicatie toediening opgezet; samen gepubliceerd en gepresenteerd op meerdere symposia. Was altijd een genoegen. Dank voor je bereidheid als externe deskundige in de Corona zitting te willen nemen.

Dr.S.Frankema, anesthesioloog/pijnspecialist. Beste Sander, dank voor je tijd bij de promotie besprekingen en je kritische benadering bij de behandelingen en het manuscript.

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Dr.D.M.E.van Assema, nucleair geneeskundige. Beste Danielle, Fijn dat je bereid was de begeleiding van het scintigrafisch onderzoek over te nemen. Ik ben onder de indruk hoe minutieus je te werk gaat en de puntjes op de "i" weet te zetten. Dank voor je tijd en inzet als medeauteur en om de nucleaire diagnostiek bij ITB falen te verbeteren.

Dr.A.van Es, Drs.P.J.van Doormaal, Drs.W.Dinkelaar. Beste Ad, Pieter-Jan, Wouter, het was een geweldige ervaring om samen met jullie de

interventie van ballonfenestratie bij liquorobstructies bij dwarslaesie patiënten te ontwikkelen, uit te voeren, te mogen presenteren op het Europese Neuroradiologiecongres en uiteindelijk te publiceren. Hiervoor mijn dank.

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PhD portfolio

Name PhD student: Elmar Delhaas
Erasmus MC: Center for Pain Medicine
Radiology and Nuclear Medicine
PhD period: between 1-10-2013 and 1-1-2019

General courses	**Year**	**Workload (ECTS)**
Basiscursus klinisch onderzoekers (BROK)	2017	1.5
Research Integrity	2017	0.3
Medical Libary Endnote	2016	0.2
Heimiddag Centrum voor Pijngeneeskunde	2014	0.2
High Professional Training Courses Center for Pain Treatment (17x)	2014-18	3.4

Attendance (and presentations) national and international conferences/meetings (Thesis period)		
Annual Meeting European Society of Neuroradiology, Rotterdam	2018	1.0
ITB Meeting, Center for Pain Treatment, EMC Rotterdam	2018	0.2
Refereeravond opioïdgebruik, EMC, Rotterdam (voorzitter)	2018	0.2
Users Group ITB, St.Michielsgestel (2days)	2018	0.4
Troubleshooting in ITB, Wetenschapsdag Anesthesiologie ErasmusMC, Rotterdam	2018	1.0
50 jaar Academische Anesthesiologie Rotterdam	2016	0.2
6th International Evidence Based Interventional Pain Medicine Symposium (WIP), Maastricht	2015	0.2
ITB Troubleshooting, ITB Expert Meeting, St.Michielgestel (2days)	2015	1.0
Neuromodulation of the dorsal root ganglion, EMC Center for Pain Treatment, Rotterdam	2015	0.2
DOT's, reimbursement and PROM aspects Meeting Dutch Association for Neuromodulation, Utrecht	2015	1.0
Palliative Care on location OLVG Amsterdam	2015	1.0
No place like home, Mosadex Experience, Utrecht	2015	1.0
Samenwerking tussen drie zorgaanbieders: De opbouw van het expertcentrum in het Erasmus MC voor Intrathecale drug delivery (ITB/ITDD), Rotterdam	2014	1.0
Achmea Quality Award, Zeist	2014	1.0
De anesthesioloog als pijnarts, VVAP/NVA, Brugge, Belgium	2013	0.2

Poster presentation

M.L.Dijkshoorn, **E.M.Delhaas**, T.P. de Man, F.J.P.M.Huygen, B.S.Harhangi, A. van der Lugt, Comprehensive evaluation and optimization of CT imaging strategies in intrathecal drug delivery (ITDD) failures, RSNA, Chicago, USA.	2018	1.0
Elmar Delhaas, Marcel Dijkshoorn, Daniëlle van Assema, Frank Huygen, Biswadjiet Harhangi, Aad van der Lugt, Algorithm for diagnostic imaging and interventional radiology in intrathecal drug delivery (ITDD) failure, RSNA, Chicago, USA.	2018	1.0
Simone M.E.Goslinga-van der Gaag, **Elmar M.Delhaas**, S.Frankema, Frank,J.P.M.Huygen, Unjust reluctance for starting intrathecal baclofen treatment in severe spasticity. The All-in-one-ITB-concept as a contribution to overcome initial hesitation. INS 13th World Congress, Endinburgh, Scotland.	2017	0.5
A.Fröberg, **E.Delhaas**, F.Huygen, B.Harhangi, A.van der Lugt, F.Verzijlbergen, ^{111}Indium-DTPA- Scintigraphy including SPECT-CT can be extreme helpful in solving intrathecal drug delivery failures. An analysis of 15 cases, EANM, Barcelona, Spain.	2016	0.5
L.T.Burgers, S.M.E.Goslinga-van der Gaag, **E.M.Delhaas**, W.K.Redekop, Cost analysis of two aftercare strategies in chronic intrathecal baclofen therapy in patients with intractable spasticity, ISPOR 17th Annual European Congress Amsterdam.	2014	0.5

Invited lectures, meetings (Thesis period)

Diagnosis and balloon fenestration in subarachnoid obstruction in spinal cord injury patients treated with intrathecal baclofen, Annual meeting ESNR, Rotterdam	2018	0.2
Breakthrough Cancer Pain Therapies, KOL Perspective (2x), Gerson Lehrman Group, New York, USA	2017	0.4
Opioid Use Disorder Treatment Trends II, KOL Perspective, Gerson Lehrman Group, New York, USA	2017	0.2
ITB in intractable spasticity, Neurology Albert Schweitzer Hospital, Dordrecht	2016	1.0
ITB in intractable spasticity, Symposium Sophia Rehabilitation Center, The Hague	2016	1.0
ITB, Low-volume,complexe zorgconcentratie, Health Care Assurance Company Achmea, Leusden	2016	1.0
ITB treatment in severe spasticity, Nursing homecare physicians, Humanitas, Rotterdam	2015	0.5
ITB treatment in severe spasticity, Nursing homecare physicians Laurens, Antonius, Rotterdam	2015	0.5
Spinal cord stimulation for chronic pain (2x), KOL Perspective, Gerson Lehrman Group.	2015	0.4
Troubleshooting in ITB, Anesthesiology Medicine Erasmus MC, Rotterdam	2015	1.0
Postoperative Pain Therapies, KOL Perspective, Gerson Lehrman Group., New York, USA	2015	0.2
Interventional Pain Devices, KOL Perspective, Gerson Lehrman Group, New York, USA	2015	0.2
New care delivery model: Care4homecare, Targeted drug delivery expert forum: Advancing spasticity and pain management, (faculty) (2days), Lisboa, Portugal	2015	1,5
ITB treatment in severe spasticity, Careyn, Brielle	2014	0.5

ITB, No place like home, E-Health zorg op afstand, OLVG, Amsterdam	2014	1.0
No place like home, EBMT congress, (3days) Milan, Italy	2014	1.0
ITB treatment in severe spasticity, Symposium Multiple Sclerosis, Gouda	2014	0.5
Spasticity: Logistics and reimbursement, Symposium 25 year's neuromodulation, Groningen	2014	1.0
Problem of ITB aftercare, Medtronic, Geneva, Switzerland	2014	1.0
Principles of intrathecal baclofen (ITB) for severe spasticity, 4th Biannual Multidisciplinary Pain Congress, Eindhoven (4days)	2014	1.0
Under- and overdosing in ITB, 4th Biannual Multidisciplinary Pain Congress, Eindhoven (4days)	2014	1.0
ITB treatment, Rehabilitation course, Rehabilitation Center Rijndam, Rotterdam (2x)	2013	1.5
Current status of ITB in The Netherlands. Proposals for improvement, Meeting Dutch Association for Neuromodulation, Utrecht	2013	1.0
ITB treatment in severe spasticity, Nursing homecare physicians Thebe, Bergen op Zoom	2013	1.0

Teaching activities

Intrathecal baclofen delivery alleviates severe paroxysmal sympathetic hyperactivity, Intensive Care Erasmus MC, Rotterdam	2018	1.0
^{111}Indium-DTPA-scintigraphy in ITDD troubleshooting, Nuclear Medicine Erasmus MC Rotterdam (3x)	2018	2.0
Imaging in intrathecal drug delivery (Carrousel education) (4x), Rotterdam	2018	2.0
Infections in intrathecal drug delivery, Erasmus MC, Rotterdam	2018	1.0
Training ITB troubleshooting, OR-assistants, Erasmus MC, Rotterdam	2018	1.0
Radiological aspects of intrathecal drug delivery, Neuroradiology Erasmus MC, Rotterdam	2016	1.0
Scintigraphy studies in intrathecal drug delivery, Nuclear Medicine Erasmus MC, Rotterdam	2016	1.0
Troubleshooting in ITB, Anesthesiology Medicine Erasmus MC, Rotterdam	2015	1.0
Basic training ITB OR-assistants, Erasmus MC, Rotterdam	2015	1.0
ITB education and hands-on training (neurosurgeons Irak) (3 days, course leader), Rotterdam	2014	2.0
Physicians training troubleshooting ITB, Medtronic Israel, TelAviv, Israel	2014	1.0
Pittfalls in radiology examinations ITDD, Neuroradiology Erasmus MC, Rotterdam	2014	1.0
ITB treatment, Neurosurgeons EMC, Rotterdam	2014	1.0
ITB in Erasmus MC; Anesthesiologie/pijngeneeskunde hoofdbehandelaar, Rotterdam	2013	1.0
Nuclear use of baclofen-^{111}Indium-DTPA in ITB troubleshooting, Rotterdam	2013	1.0

Supervising

Master Thesis Simone Goslinga	2014-19	2.0
Protocol Infection Intrathecal Drug Delivery System Krishna Bharwani	2018	1.0

Participation in projects		
Innovatieproject CZ-Care4homecare Ambulante Zorg voor Neuromodulatie (El-290) in het kader van regeling CA-415. Beleidsregel innovatie ten behoeve van nieuwe zorg-prestaties (NZa), 's-Hertogenbosch	2013-2014	1.0
Development and implementation ITB Expert Center EMC/Revalidatiecentrum Rijndam/ Care4homecare, Rotterdam	2012-2014	1.0
Development Guideline Spasticity, Member working Group, representative Dutch Society of Anesthesiology, Federatie Medisch Specialisten, Utrecht	2014-2016	3.0
Development DBC ITB, NZA/DBC-Onderhoud/Care Assurance Companies, Utrecht	2015	1.5
Fase III Trial Arterial Hepatic Infusion (HIA), Erasmus MC, Rotterdam	2016	1.5
Economic Value ITB aftercare on location, Utrecht	2016	0.5
Masterplan Implementation ITB RadboudUMC, Nijmegen	2015	1.5
Reviewing scientific articles		
Archives of PM&R	2018	1.0
J Neuromodulation (2x)	2017	2.0
Archives of PM&R	2017	1.0
J Spinal Cord Medicine	2014	1.0
Other		
Report on Value of ITB on request Federal Drug Administration	2015	1.0
Business report Universitair Multidisciplinair Expert Centrum ITB UMCG	2014	1.0
Total		**75.6**

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Delhaas EM, van Assema DME, Fröberg AC, Zwezerijnen B, Harhangi BS, Frankema SPG, Huygen FJPM, van der Lugt A, Isotopic scintigraphy in intrathecal drug delivery failure. A single institution case series, submitted.

Delhaas EM, Harhangi BS, Frankema SPG, Huygen FJPM, van der Lugt A, Catheter access port (computer tomography) myelography in intrathecal drug delivery troubleshooting. A single institution case series, accepted for publication in Neuromodulation. DOI: 10.1111/ner.13153.

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Curriculum vitae

Elmar Delhaas werd geboren op 30 mei 1946. Na het behalen van het HBS-B diploma aan de 2e Christelijke HBS te Groningen studeerde hij geneeskunde aan de Rijksuniversiteit te Groningen. Gedurende zijn studie heeft hij onderzoekservaring opgedaan als student-assistent bij de Experimentele Neurochirurgie en als doctoraal-assistent bij de Endocrinologie. Na zijn 6 jaar werkzaam te zijn geweest als arts bij de Koninklijke Marine, gestart met de opleiding anesthesiologie in het Antonius Ziekenhuis Utrecht (opleider: Drs.G.A.Schurink). Na beëindiging, enige waarnemingen en uiteindelijk 12 jaar gewerkt als anesthesioloog in het Sophia Ziekenhuis te Zwolle, nadien 10 jaar in het Zuiderziekenhuis te Rotterdam. Na de vervroegde pensionering in 2006 waarnemingen in Amphia Ziekenhuis te Breda en Franciscus Ziekenhuis te Roosendaal. In Oktober 2013 is hij begonnen met de invoering van de intrathecale baclofentoediening (ITB) in het ErasmusMC Centrum voor Pijngeneeskunde (Prof. Dr. F.J.P.M.Huygen) te Rotterdam. In de loop der jaren aan meerdere onderzoeksprojecten (pijn bij maligniteiten en de intrathecale toediening van farmaca) deelgenomen. Uiteindelijk met het accent op ITB. In het Leids Universitair Medisch Centrum heeft hij in samenwerking met de afdeling neurologie (Prof.dr.J.J.van Hilten) de ITB bij dystonie ontwikkeld. In 2010 werd de ambulante kliniek Care4homecare door hem opgericht om de ITB zo veel mogelijk op locatie te kunnen verrichten. In de meer dan 30 ervaring met ITB bleek er een duidelijke behoefte aan onderzoek omtrent "troubleshooting" bij ITB wat tot dit proefschrift heeft geleid.