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

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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.

Keyword: Balloon dilatation, CSF flow, ITB, Neurosurgery, Obstruction, 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, 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 111Indium-diethylene-triamine-penta-acetic acid scintigraphy (111In-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. 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 (Cases 3, 4). When in doubt of an obstruction, we additionally performed 111In-DTPA (Cases 1, 2, 3). We mixed the medication in the pump reservoir with 20 MBq of 111In-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. 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
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 and B), which was confirmed by 111In-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.

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 1374 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–T10 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.

**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/lower-thoracic transition, a narrowed thoracic region, and no tracer activity in the cisterns, suggesting an obstruction (Fig. 4B). 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 and C), and, in a second session, cervical CT myelography (Fig. 5D and E). 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.
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).

Figure 3  CAP CT myelography (A) with 5 consecutive sagittal reconstructions revealed narrowed contrast material column (red arrow), suspicious for contrast material stagnation. $^{111}$In-DTPA SPECT CT at 48 h (B) showed obstruction at the level of the spinal cord lesion (red arrow). $^{111}$In-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).
5 × 120 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 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. 6B) revealed contrast material stagnation at the SCI level. With the same percutaneous fenestration procedure (Fig. 6D–J) 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 disappeared 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 spasmylytic 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 2216 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 1109 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 1109 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

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).
hinderance 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 inspiration 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 posttraumatic 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 cultures17 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 111In-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. 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 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). A syndrome that can even be life-threatening. 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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