Intrathecal baclofen treatment in children with neurological disorders

Laura A. Bonouvrié

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The work presented in this thesis was performed at the department of Rehabilitation Medicine, VU University Medical Center, Amsterdam, the Netherlands and the department of Child Neurology, Maastricht University Medical Center, Maastricht, the Netherlands.

The trials in this thesis were funded by the Phelps Stichting voor Spastici (projectnumber 2011037 and projectnumber 99.047), HandicapNL (previously Revalidatiefonds) (projectnumber R2011032/), Kinderrevalidatie Fonds Adriaanstichting (projectnumber 11.02.17-2011/0035) and the Johanna KinderFonds (projectnumber 2011/0035-357).

Printing of this thesis was supported by non commercial grants from Phelps Stichting voor Spastici, Dystonie vereniging, OIM Orthopedie (Assen, the Netherlands), Kamer Orthopedie, and Ipsen Farmaceuticals.

ISBN: 978-94-0281448-4

Design cover and chapter pages by Rik Vrijman, Reklamebureau.it
Layout and design by Eduard Boxem, persoonlijkproefschrift.nl.
Printed by Ipskamp Printing, proefschriften.net

VRIJE UNIVERSITEIT

Intrathecal baclofen treatment in children with neurological disorders

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op woensdag 30 oktober 2019 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Laura Alexandra Bonouvrié

geboren te Utrecht

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I love it when a plan comes together

-Col. Hannibal Smith-

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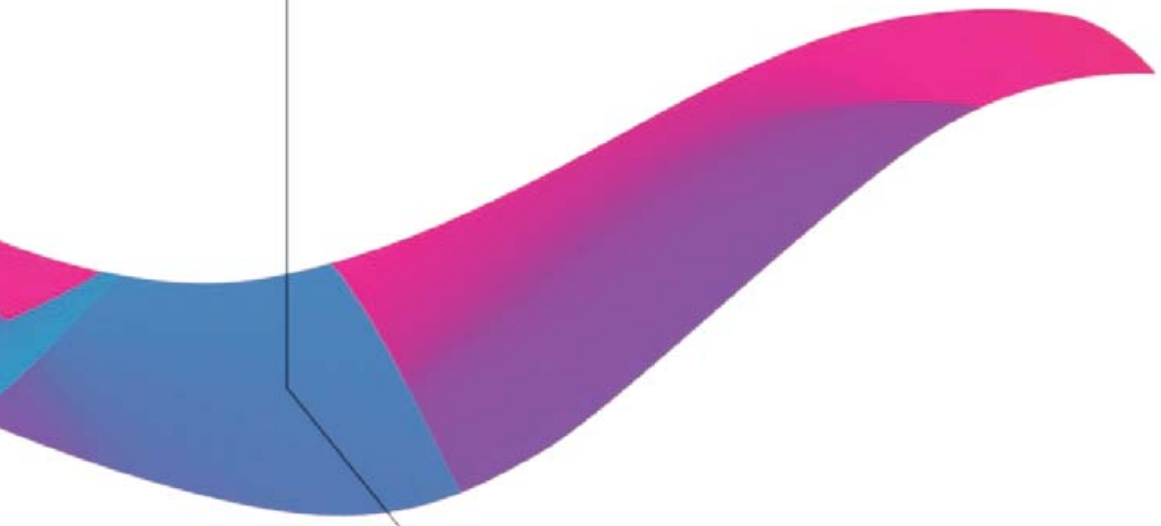
CHAPTER 1

General introduction



INTRODUCTION

Movement disorders in childhood are mostly caused by dysfunction of the developing brain due to brain lesions or brain abnormalities. These so called cerebral movement disorders can lead to positive signs (signs of abnormal muscle activity) such as spasticity or dyskinesia, together with negative signs such as muscle weakness, decreased selective motor control and impaired coordination.[1-3] Secondary musculoskeletal problems can arise during growth including muscle contractures, bony deformities, scoliosis and hip displacement.[3] Consequently, the impairments on the level of body functions and structures can lead to problems in activities and participation such as (but not limited to) mobility, self-care, communication and learning. Activities and participation are furthermore influenced by environmental factors such as the availability of assistance for personal care and aids for mobility. To comprehend the extent of problems due cerebral movement disorders, the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) can be used as a framework (Figure 1 and 2).[4] The spectrum of the severity of cerebral movement disorders is broad. This thesis will focus on severely affected children, which are children with cerebral palsy (CP) classified with the Gross Motor Functioning Classification System (GMFCS) in levels IV and V or children with progressive neurological disorders (PND) who are equally affected (Figure 3).

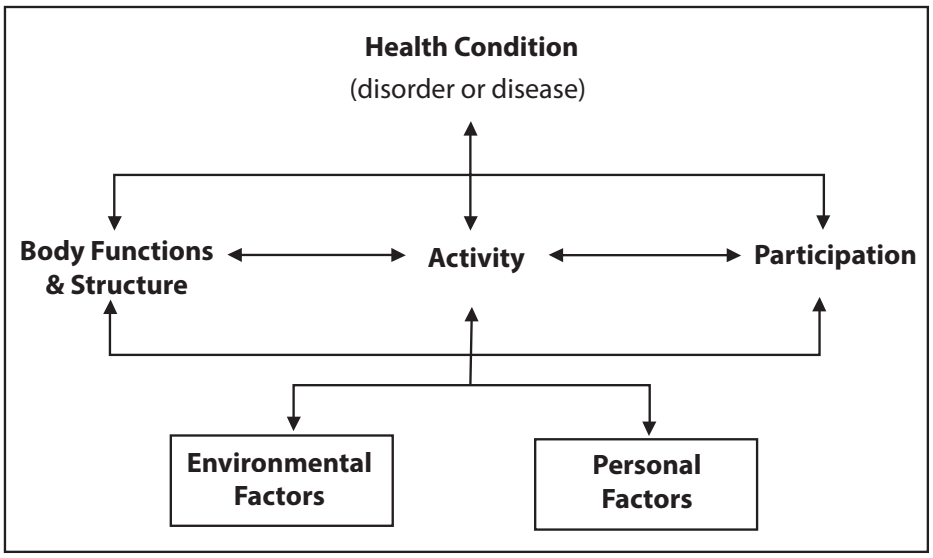


Figure 1. **The International Classification of Functioning, Disability and Health for Children and Youth model (ICF-CY).**[4]

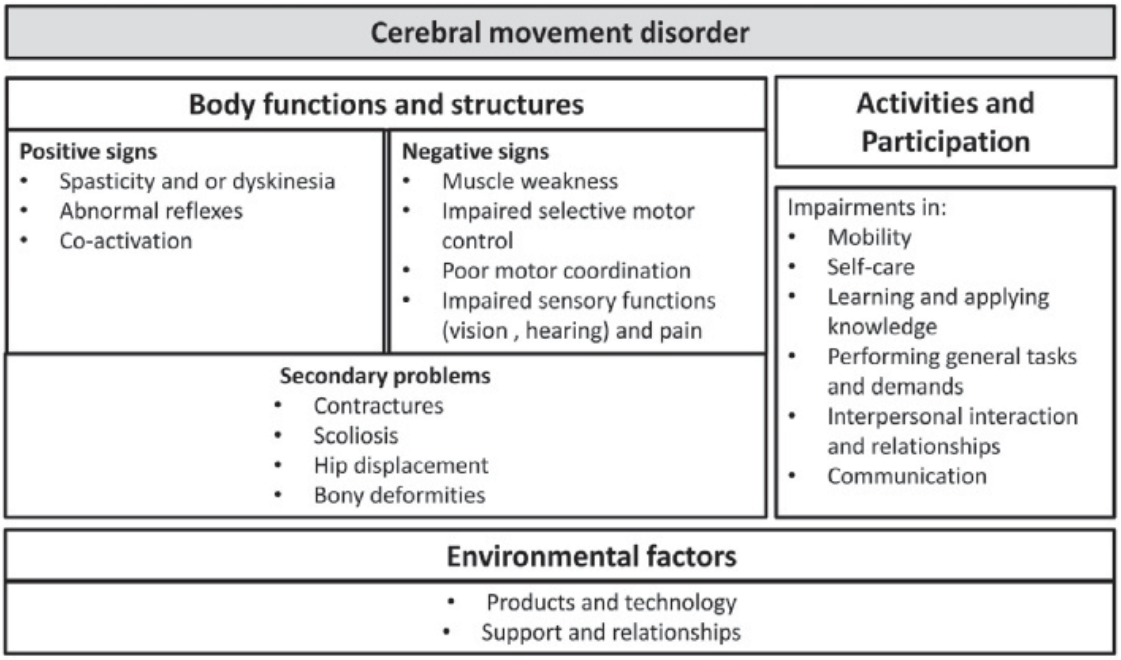


Figure 2. **The International Classification of Functioning, Disability and Health for Children and Youth model for cerebral movement disorders**

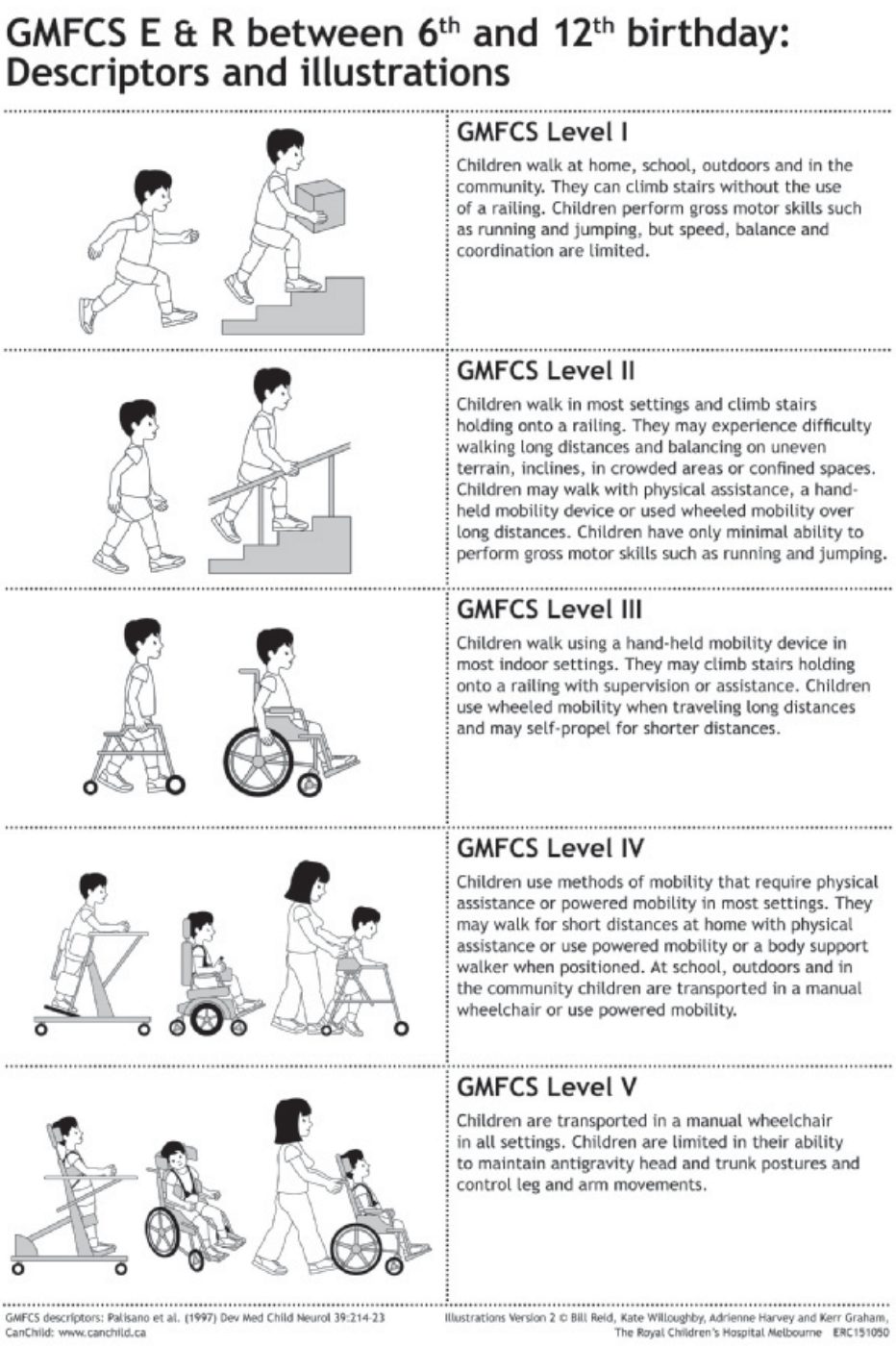


Figure 3. Gross Motor Functioning Classification System (GMFCS)[5]. Image on the courtesy of K. Graham, The Royal Children's Hospital, Melbourne, Victoria, Australia.

CEREBRAL PALSY

The most common cause of cerebral movement disorders and physical disability in childhood is cerebral palsy (CP). The prevalence of CP in Western countries is 2.11 per 1000 livebirths and has been fairly stable for many years.[6] A European cohort study showed a prevalence of 1.96 per 1000 livebirths in 2010.[7] CP comprises a group of developmental disorders of movement and posture, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[8] The motor impairments are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and by secondary musculoskeletal problems.[8-10]

Neuroimaging in CP reveals several types of underlying brain lesions (Figure 4). The pattern of lesions is strongly related to the stages of brain development in which they occurred: prenatal, perinatal or neonatal.[11] Furthermore, the pattern of lesions corresponds with clinical findings.[12]

Brain maldevelopment origins from the first and second trimester.[13] Disorders of proliferation, migration or organization can occur at this stage. Underlying causes can be genetic, vascular and infectious. Depending on the localisation and extent of the maldevelopment clinical symptoms range from easily controllable epilepsy without further abnormalities to uncontrollable epilepsy accompanied by spasticity and, severely impaired motor and cognitive development.[14]

In the early to mid-third trimester periventricular white matter lesions are the dominant finding.[13] This type of damage occurs approximately before 34 weeks of gestation and is the main pattern in preterm born children.[12,14,15] However, 25% of children with these lesions are born at term.[12,13] In this last group of children the origin of the lesions is presumably prenatal due to chronic placental insufficiency with prolonged periods of moderate intensity insufficient oxygenation.[11,14] Ischemia and inflammation, which can be due to perfusion failure, infection or both can cause periventricular leukomalacia (PVL).[15] A less common cause of white matter lesions is periventricular haemorrhagic infarction (PHI). PHI is a complication of intraventricular haemorrhage which occurs in the first days after birth, especially in very preterm children due to susceptibility for haemorrhage of the germinal layer.[16] White matter lesions result mostly in spasticity.[12,17] The more extensive the brain lesions, the more severe the clinical findings will be, not only for the movement disorder but also for additional disturbances such as cognitive impairment and cerebral visual impairment.[12,14,16]

Events in the late third trimester mostly cause cortical/subcortical and basal ganglia gray matter lesions.[13,14] Lesion of the basal ganglia and in some cases additional damage to the central cortex is a common pattern in asphyxiated infants born at term who present with low Apgar scores after birth.[11,14,17,18] Possible mechanisms of the selective vulnerability are the high glucose metabolism during the neonatal period and the pattern of myelination starting in the affected central cortical region.[14] Children with basal ganglia lesions present with the dyskinetic form of CP.[11,12,18] Imaging studies show involvement of the lentiform nuclei (putamen and globus pallidus) in all children with dyskinetic CP. There appear to be two patterns: lesions in the putamen only or in both the putamen and globus pallidus.[19] Cognitive deficits are less profound in children with basal ganglia compared to children with white matter lesions, but when additional (i.e. severe) central, (sub)cortical and/or hippocampal involvement is present, spasticity can be the dominant movement disorder with additionally cognitive impairment.[18,20] Lesions to the globus pallidus can also occur due to postnatal hyperbilirubinemia-induced kernicterus. In these children hearing impairment is often accompanying the movement disorder.[21,22] Kernicterus can both occur in preterm and term born infants.[23,24] The bilirubin threshold for development of basal ganglia lesions is lower in very preterm infants (25 to 29 week of gestation) making them more susceptible to the occurrence of kernicterus.[22,24] In high income countries this condition has become less common due to preventive strategies.[23]

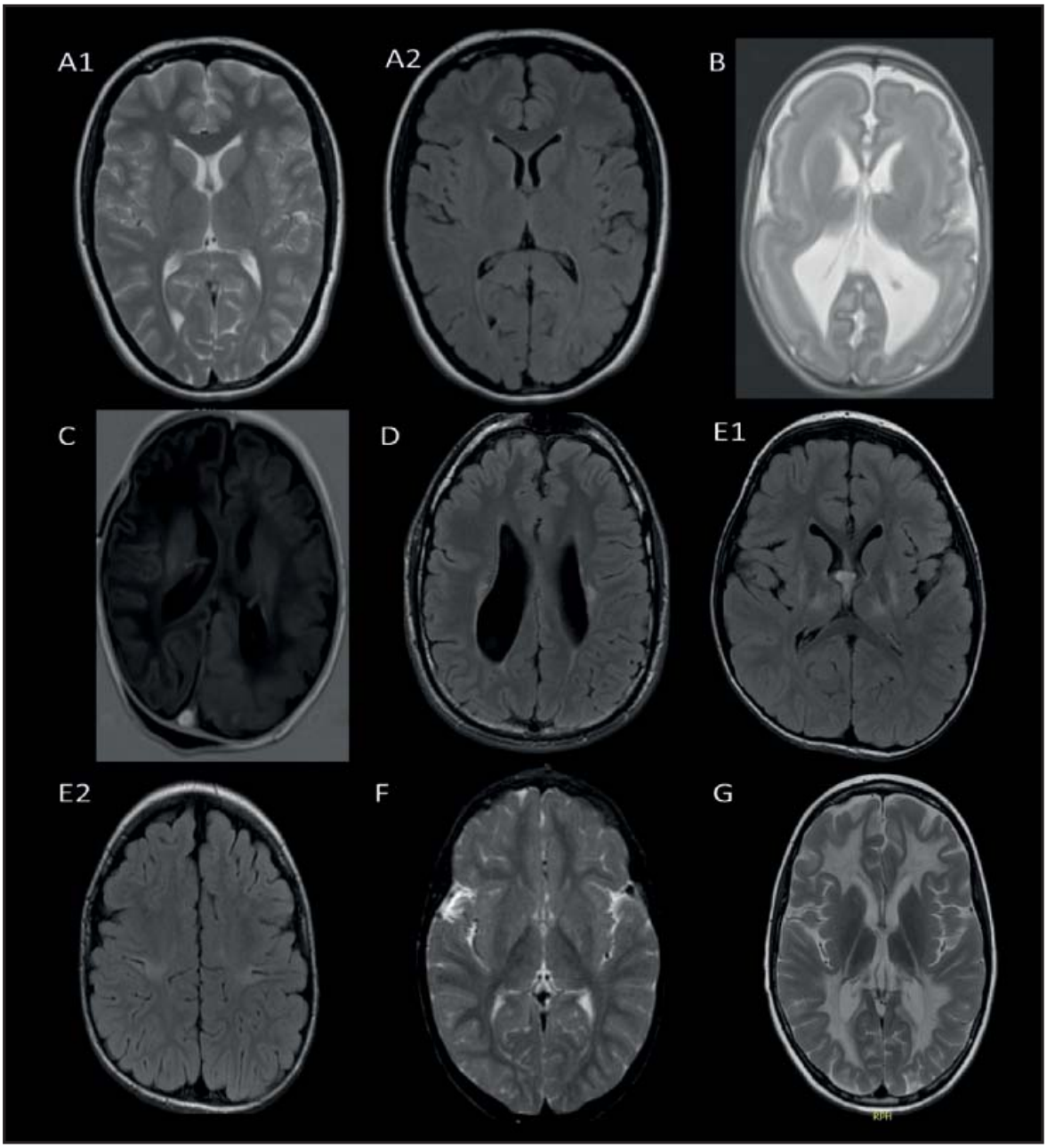


Figure 4. Brain lesions in cerebral palsy. A) Normal brain (1) T2 weighted MRI image); (2) FLAIR MRI image; B) Brain maldevelopment: neuronal migration disorder with complete periventricular band heterotopia (double cortex syndrome) and dilated posterior horn of ventricles (T2 weighted MRI imaged). Clinically bilateral spastic CP, GMFCS II, epilepsy and moderate cognitive impairment; C) Brain maldevelopment: hemimegalencepahly with polymicrogyria of the left hemisphere (FLAIR MRI image). Clinically neonatal status epilepticus; D) Periventricular leukomalacia with loss of white matter and enlargement of ventricles (FLAIR MRI image). Clinically bilateral spastic CP, GMFCS IV. E) Acute perinatal asphyxia with (1) lesions in the ventromedial thalamus and posterior lentiform nucleus and (2) lesions in the motor cortex (rolandic cortex) (both FLAIR MRI images). Clinically bilateral dyskinetic CP, GMFCS V; F) Kernicterus: bilateral globus pallidus lesions (T2 weighted MRI image). Clinically bilateral dyskinetic cerebral palsy, GMFCS II; G) Metachromatic leukodystrophy: symmetric bilateral white matter abnormalities and corticospinal tract abnormalities (T2 weighted MRI image). Clinically severe bilateral spasticity, legs more than arms, comparable to GMFCS V.

Classification of cerebral palsy

The severity of the impairment of functional mobility in CP is classified using the GMFCS (Figure 3).[5] Similar 5 point scales are used to describe the level of manual function (Manual Ability Classification System, MACS), and the level of communication function (Communication Function Classification System, CFCS).[25] [26] This thesis will focus on CP patients with GMFCS level IV and V.

CP is furthermore categorised by the dominant movement disorder: spastic, dyskinetic or ataxic.[10] Spasticity is the dominant movement disorder in 72 to 91% of CP patients,[9,11] and dyskinesia in approximately 15%.[11]

Spasticity

Spasticity is defined as a velocity-dependent, increased resistance to externally applied passive muscle stretch which is forthcoming during physical examination.[3,27] Spasticity is the result of an imbalance of the excitatory and inhibitory responses to a sensory input signal. Lesions of the central nervous system result in loss of descending inhibitory commands and abnormal impulses, subsequently resulting in overactive and spastic muscles.[2] The intensity of spasticity can vary depending on posture, activity, emotional state, pain and other triggers.[27]

Dyskinesia

Dyskinesia is characterized by involuntary, uncontrolled, recurring, occasionally stereotyped movements with fluctuating muscle tone.[28] Dyskinesia can be further separated in dystonia and choreo-athetosis.[28,29] Dystonia is a movement disorder with involuntary movements, distorted voluntary movements and abnormal postures due to sustained or intermittent muscle contractions such as slow rotation, extension or flexion of body parts.[28,29] The abnormal postures can give the impression of hypokinesia while they are actually caused by sustained muscle contractions. Tone is fluctuating but easily increased (hypertonia).[28] Choreo-athetosis is characterised by (faster) hyperkinetic movements and tone fluctuation (mainly hypotonia).[28] Dystonia and choreoathetosis can be simultaneously present with dystonia often being the more dominant feature. They can both manifest during rest and both increase during activities.[30] Studies shows that dystonia is, in contrast to choreo-athetosis, significantly related to activities of daily life, participation in society and quality of life.[31]

Clinicians find dyskinesia difficult to recognize and the distinction between dystonia and choreo-athetosis troublesome.[32] Measurement scales are therefore not used often.[32] Two measurement scales for dystonia are specifically designed for CP, the

Barry-Albright Dystonia Scale (BADS) and the Dyskinesia Impairment Scale (DIS).[33-35] The Burke-Fahn-Marsden Dystonia Rating scale was designed to assess primary dystonia but is frequently used in CP as well.[35] Scales are presented at the end of this thesis (Appendix I. Dyskinesia Measurement Scales). All three scales assess dyskinesia on the ICF-CY level of body functions and structures. For all scales, studies looking at the validity, reliability, responsiveness and clinical utility in children with CP are limited in number and/or quality. There are no test-retest studies. For clinical utility the BADS seems the easiest and quickest scale to use. The DIS is the most extensive and time consuming scale making it less suitable for clinical practice but it could be of added value in research. The DIS is also the only scale addressing choreo-athetosis and the only scale comparing rest versus activity.[35]

Dyskinetic CP is the most disabling form of CP with 59-80% of patients being GMFCS level IV or V.[36,37] This is substantially higher compared to children with bilateral spastic CP in whom GMFCS IV and V account for under 20% of cases.[37] Comprehensive studies on dyskinetic CP are rare and outcomes are mostly on the level of body functions and structures (e.g. dystonia). Reported goals for treatment of patients with dystonia are on all domains of the ICF-CY: improve pain and comfort, prevent worsening of deformities (level of body functions and structures), improve positioning and transfers (level of activities and participation), and improve ease of personal care for both patients and caregivers (including dressing and hygienic related care) (level of activities and participation and level of environmental factors).[38,39]

PROGRESSIVE NEUROLOGICAL DISEASE OF CHILDHOOD

Spasticity and dyskinesia in children can also be caused by progressive neurodegenerative or neurometabolic diseases (PND).[40-42] Neurodegenerative diseases are disorders with progressive loss of neurological function due to structural abnormalities of the central nervous system.[42] Neurometabolic diseases refer to a group of disorders that are characterized by a lack or dysfunction of an enzyme or vitamin necessary for a specific chemical reaction in the body.[43] Most of the neurodegenerative and neurometabolic disorders are (very) rare. A brief selection of the (relatively) most common disorders seen in clinical practice and described in literature, causing spasticity or dystonia, is summarized in table 1.[40-43]

Progression of PND can be rapid or slow and other symptoms such as epilepsy, cognitive deterioration and muscle weakness can appear during disease progression. Treatment is often symptomatic and aimed at increasing comfort and decreasing pain, especially when the disease is rapidly progressive. For spasticity and dystonia the treatment is

largely similar to that of cerebral palsy. For some diagnoses promising options are available when early treatment is possible such as enzyme replacement, bone marrow transplantation or substrate inhibition. Early recognition of the disease and early start of these specific treatments may benefit outcome.[44]

Table 1. A selection of progressive neurodegenerative and neurometabolic diseases of childhood causing spasticity and/or dystonia[40-43]

Diagnosis	Pathogenic features	Spasticity/ Dystonia
Leucodystrophy - Metachromatic leucodystrophy - Adrenoleucodystrophy - Vanishing white matter - Pelizeus-Merzbacher disease	White matter abnormalities due to demyeliniation caused by deficient activity of different lysosomal enzymes	Both
Rett's syndrome	Cerebral atrophy and hyperammonaemia	Both
Neuronal ceroid-lipofuscinosis	Failure of fatty oxidation	Both
Niemann-Pick-type C (dystonic lipidosis)	Defective cholesterol esterification, neuronal storage	Dystonia
Niemann Pick type A	Sphingomyelinase activity deficient, neuronal and visceral storage of sphingomyeline	Spasticity
Mucopolysaccharidosis	Deficient activity of specific lysosomal enzymes causing accumulation of acidic polysaccharides in various organs including the brain	Both
Lesh Nyhan Syndrome	Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) deficiency	Both
Spinocerebaillar degeneration - Friedreich's ataxia - Spinocerebellar ataxia	Degeneration in both central and peripheral nervous system	Both
Hereditairy spastic paresis	Genetic cause, several known and unknown genes	Spasticity
Leigh-syndrome	Subacute necrotizing encephalomyopathy Autosomal recessive	Both

TREATMENT OPTIONS

Since this thesis focusses on severely affected children with generalized spasticity or dyskinesia (GMFCS level IV or V for CP and equally affected for non-CP disorders), treatment options discussed below apply to this group of children and involve pharmacological and advanced (neurosurgical) treatment options. Focal treatment options are therefore not discussed.

Spasticity

Oral pharmacological treatment with baclofen, tizanidine, dantrolene or diazepam has been described in literature. There is insufficient data to make clear recommendations for oral pharmacological treatment since study numbers are low and the described populations small.[45] Baclofen is the agent most commonly prescribed in clinical practice, however, there is insufficient evidence for the use for either decreasing spasticity or improving motor function in patients with spastic cerebral palsy.[45,46] The working mechanism of baclofen and intrathecal use are described later in this chapter.

A surgical option for the treatment of severe spasticity of the lower limbs is selective dorsal rhizotomy (SDR). SDR is mostly used in children with GMFCS I and II and aims to preserve or even improve mobility during growth.[47] In children with GMFCS IV and V daily comfort and care (dressing and washing) can improve after SDR.[48]

Dyskinesia

Since dystonia is the dominant feature in dyskinetic CP, treatment is mostly aimed to decrease dystonia and not choreo-athetosis.[30] For generalized dystonia, the use of trihexyphenidyl, baclofen, benzodiazepines and other agents has been described in literature. The level of evidence is low and effects in studies are mostly disappointing and inconsistent.[49-53]

Intrathecal baclofen treatment (ITB) is an option in patients with severe dyskinesia in whom oral pharmacological treatment is insufficient or causes side effects such as sedation, prohibiting further increase to a therapeutic dosage. Another surgical treatment option for severe dystonia is deep brain stimulation (DBS). Good results are shown in pediatric patients with primary dystonia but the reported effects are variable in patients with dyskinetic cerebral palsy.[50,54]

BACLOFEN

Baclofen is a gamma-aminobutyric-acid (GABA) B receptor agonist and binds on receptors on the pre- and post-synaptic neuron.[55,56] The presynaptic action is likely to be the most dominant in decreasing spasticity.[56] By binding to the pre-synaptic receptors, baclofen inhibits the release of the excitatory neurotransmitter glutamate via downregulation of the calcium channels (Figure 5). Calcium uptake required for the release of the excitatory neurotransmitters is inhibited. Hereby neuronal signal transmission onto spinal motor neurons is prevented.[55,56]

The site of action of baclofen in treatment of spasticity is thought to be the superficial layers of the dorsal spinal cord.[57] This is different for treatment of dystonia where baclofen is thought to act on the intracranial level[55,58]. Clinical findings support this hypothesis: in contrast to spasticity, a single intrathecal lumbar bolus of baclofen does not decrease dystonia. It actually takes several days after continuous intrathecal infusion to see improvement of dystonia, time needed for the baclofen to spread to the intracranial level.[59]

Dystonia in CP is the result of lesions in the basal ganglia causing disturbance of the indirect basal ganglia pathway. Lesions of the putamen and globus pallidus cause decreased inhibition of the thalamus. Subsequently the thalamus stimulates the supplementary motor and premotor cortex causing excessive movements (e.g. dystonia). Intrathecal baclofen can hypothetically act upon different intracranial levels. One idea is that by administrating baclofen, the external globus pallidus is exogenously suppressed, resulting in normalization of the indirect basal ganglia pathway with inhibition of the thalamus and thereby inhibition of stimulation of the supplementary motor and premotor cortex, decreasing dystonia.[55] Another working mechanism could be that GABA is an inhibitory neurotransmitter in the human cerebral cortex,[57,60] and that baclofen directly inhibits post-synaptic signal transmission from the cortex. A third option is that baclofen inhibits the thalamus. An overview of different working mechanisms is presented in figure 5.

Due to its low lipid solubility, orally administered baclofen does not pass the blood brain barrier well.[57] Plasma concentration levels ranging from 50 to 445 (ng/ml) render cerebrospinal fluid (CSF) concentration levels between <12 and 64 ng/ml. A higher plasma concentration does not correspond to a higher CSF concentration.[61] This means that in many cases, high oral dosages are needed to acquire sufficient CSF concentrations. In severe cases the therapeutic effect remains insufficient while additional adverse effects, such as sedation, occur.[57,61]

Intrathecal baclofen treatment

The blood brain barrier can be bypassed by delivering baclofen intrathecally using an implanted micro-infusion pump (Figure 6). Higher levels of CSF concentration with simultaneous very low plasma concentrations can be easily achieved without the limitative adverse effects seen with oral administration.[57,62] Sedation for instance occurs in less than 5% of patients.[57]

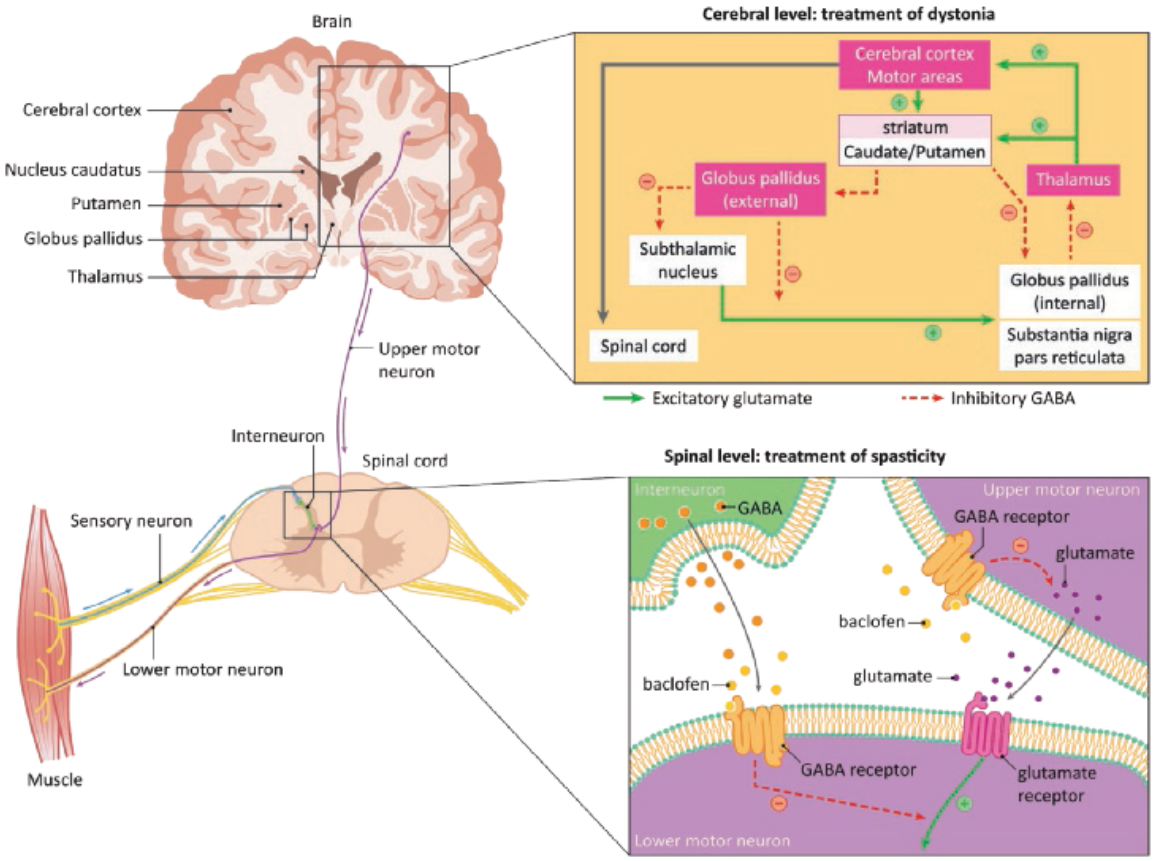


Figure 5. Baclofen working mechanism. On the spinal cord level baclofen binds to the presynaptic $GABA_B$ receptors and hereby inhibits the release of the neurotransmitter glutamate. As a consequence, neuronal transmission onto the lower motor neurons is inhibited. It also binds to the postsynaptic $GABA_B$ receptors inhibiting the signal transmission in the lower motor neuron. This is the working mechanism in the treatment of spasticity (lower right image). On the cerebral level baclofen inhibits the excessive stimulation of the cortex by inhibiting the globus pallidus, thalamus or supplementary motor and premotor cortex (upper right image). This is the presumed working mechanism of intrathecal baclofen in the treatment of dystonia.

To provide the baclofen intrathecally, a micro-infusion pump (Medtronic Synchromed II) is implanted subcutaneously, mostly in the left lower abdomen (Figure 6). A catheter connects the pump with the intrathecal space providing the baclofen at the site of action: the spinal cord for spastic patients and at the intracranial level for dyskinetic patients.[58] Since there is a significant reduction of concentration of drugs in the CSF cranially along the spinal canal from the place of insertion, the tip of the catheter is placed at the low (effects on legs) or mid (effects on arms and legs) thoracic level in spastic patients and at the cervical level for dyskinetic patients.[58,63-65] Intraventricular baclofen administration has also been described in patients with dyskinetic CP.[66-68] Once the pump is implanted, the dosage can be adjusted to the patients' needs using an external pump programmer. The effective therapeutic dosage varies enormously between patients and is not predictable: a low dosage for one patient can cause

symptoms of overdose in another. The pump has to be refilled approximately every 2 to 6 months by puncture through the skin and a small membrane located in the center of the pump. After approximately 7 years, the battery expires and the pump has to be replaced.

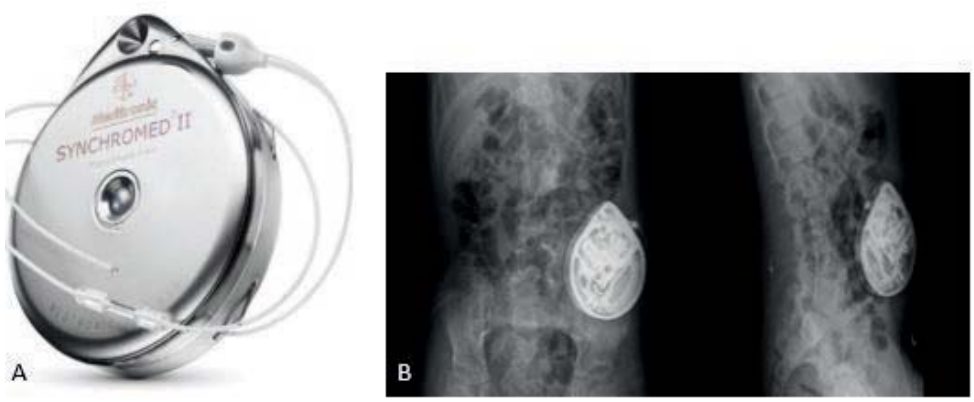


Figure 6. The intrathecal baclofen pump
A. The baclofen pump (Medtronic, Synchromed II) and catheter. Source: www.medtronic.com
B. X-ray of an implanted pump in the abdomen of a 10 year old boy with cerebral palsy, frontal and lateral view.

The most common complications of ITB are infection (14-28%), CSF leak (33%, with 8% requiring surgery) and catheter related problems (including catheter migration, occlusion and disconnection) (21-23%).[58,69,70] Signs of underdosing or acute withdrawal can be symptoms of catheter related problems but the cause can also be iatrogenic. Overdose is mostly iatrogenic due to wrong pump settings or inadequate pump filling.[58,69,70]

In 2010 a consensus was reached on the selection criteria for ITB for patients with spasticity (Table 2).[71] There are no specific selection criteria formulated for the treatment of dystonia and in clinical practice selection criteria analogous to those for spastic CP can be used.

Table 2. Selection criteria for ITB

- Intractable spasticity *or dystonia*
o With preferably known etiology
o Not optimally managed by other treatment options
o Which impedes activities of daily life or quality of life
- Clear and realistic treatment goals
- Ability and motivation to attend follow-up and monitoring
- Sufficient body size to allow pump implantation and filling

The italic written criteria are criteria not specifically described in the consensus but are criteria that are used additionally in our clinical practice.

The efficacy of intrathecal baclofen treatment

Spastic cerebral palsy

Spasticity is the most common outcome measure on the level of body functions and structures. A few placebo controlled double blind randomized trials looking at the effect of ITB test treatment with multiple single bolus injections, show a significant decrease of spasticity after ITB injections.[72-74] Several other studies with various designs (prospective and retrospective, small cohort or case series studies, some with and some without a control group awaiting ITB treatment) report a significant decrease in spasticity after continuous ITB treatment via an implanted pump (follow up ranging from six months to nine years).[38,73-80]

Pain and discomfort are problems which are often reported in children with severe spastic CP. The same studies as described above report improvement of pain and comfort during ITB test treatment.[72,74] Similar results are found with long term continuous ITB treatment.[78-80] Quality of life is assessed in several of the described studies. Various questionnaires are used and all studies report improvement of quality of life.[38,75,79,80]

Outcomes on the level of activities and participation are often not systematically measured. Furthermore, outcome measures are heterogeneous, making comparison between studies difficult. Individually formulated problems of daily life measured on a visual analogue scale (VAS) are described to significantly improve after ITB bolus test treatment compared to placebo, as did VAS scores for ease of care.[72] Prospective cohort studies show that improvements maintain after 6 months, 12 months, and even after 6 to 9 years of continuous ITB treatment.[78-80] In individual cases, improvements were noted on transfers, operating the electric wheelchair and arm function.[72] In a telephone

survey, parents indicated that seventy-two percent of pre-set goals were completely achieved during ITB treatment.[38]

Active functioning and social participation are found not to improve in children with GMFCS IV and V during ITB treatment.[76] On global scales of functioning, such as the Gross Motor Function Measure (GMFM) and the Pediatric Evaluation of Disability Inventory (PEDI), no changes are reported with ITB.[38,76,78] For severely affected GMFCS IV and V patients, no significant changes on standardized questionnaires are expected since they do not adequately meet the functional level of these children.

Taking care of a child with severe disability puts a burden on the caregivers (level of environmental factors) and a prospective cohort study shows that with long term ITB treatment, caregivers report to experience fewer emotional concerns and fewer limitation in time.[80] One other study reported no change in the impact of disability for children and parents.[76] Caregiver satisfaction is high, and most of them would choose for ITB treatment again.[38,75,80]

Dyskinetic cerebral palsy

For the effect of ITB in children with dyskinetic CP few studies are available. Studies contain only prospective and retrospective case series, resulting in a low level of evidence for the effect of ITB in these patients.[58,81,82]

On the level of body functions and structures dystonia (BADS) is the most common outcome measure. BADS scores are reported to decrease in all studies.[58,81,82] A significantly higher decrease in BADS scores was seen with a higher placed catheter tip (T4 and higher) compared to a lower placed tip (T6 and lower).[58] Other reported outcomes on the level of body functions and structures are reduction in pain, better mood, improved sleep, and a stable range of motion. [58,81,82] Quality of life improved in 86% of the questioned patients.[58,81,82]

On the level of activities and participation several case series report the outcomes of structured interviews or questionnaires.[58,81,82] Improvement is reported for feeding and swallowing, sitting and posture control, upper limb use, communication/speech. In the majority of patients no change in autonomy of carrying out daily activities was seen.[82] Furthermore, there was no change in gross motor function.[81]

On the level of environmental factors (e.g. caregiving by others), ease of care is reported to improve in most patients.[58,81,82]

Treatment goals are fully reached in 76% and partly in the remainder of patients.[81] Almost 80% of patients were satisfied with ITB treatment and 74% of patients would choose for ITB treatment again.[82]

Progressive neurological disease in childhood

ITB has been used in clinical practice for the treatment of spasticity or dystonia in patients with PND. Treatment goals are mostly to improve comfort and ease of care. In literature, reports on the effect of ITB in children with progressive neurologic disease are very rare and the few existing papers describe mostly single cases. Spasticity, spasms and pain seem to decrease and activities of daily life are reported to improve.[83-88] It is however unclear if the effects of ITB maintain during disease progression.

CONCLUSION

Treatment of disabling movement disorders such as spasticity or dyskinesia in children is challenging. Oral pharmacological treatment options are often insufficient and/or cause side effects. Intrathecal baclofen treatment might be an option for these patients. There is some evidence, provided by single bolus randomized trials, for the effectiveness of ITB for treatment of spasticity in children with spastic cerebral palsy on the level of body functions and structures (spasticity). There is a low level of evidence of the effectiveness of continuous ITB, especially on the level of activities/participation. For dystonia in children with dyskinetic CP, there is no substantial evidence for the effect of ITB treatment on any ICF-CY level. For the treatment of spasticity and/or dystonia, not due to CP but due to PND, it is unclear what the effect is and what the evidence for the effect is, especially on the longer term when disease progresses.

AIM OF THE STUDY

1. The primary aim of this thesis is to investigate the effect of ITB in the treatment of dyskinetic CP. The focus lies mostly on the level of activities and participation and the level of environmental factors (attainment of individual treatment goals) and secondary on the level of body functions and structures (dystonia, choreo-athetosis, spasticity, pain, comfort).

2. The secondary aim is to describe the effect and the current level of evidence of ITB treatment in PND of childhood on all ICF-CY levels.

OUTLINE OF THIS THESIS

Chapter 2 provides a narrative review on the presentation and management of dyskinetic CP. **Chapter 3** describes the results of a pilot study comparing ITB and placebo bolus dosing in patients with dyskinetic CP. Individual problem of daily life were individually formulated and scored on a VAS. Dystonia was measured using the BADS. **Chapter 4** contains the study protocol of the IDYS trial (Intrathecal baclofen treatment in Dystonic cerebral palsy). This study is a multi-center, placebo-controlled, double-blind randomized trial. The primary aim was to determine the effects of ITB in dyskinetic CP mostly on the level of activities and participation, and environmental factors, but also on the level of body functions and structures (goal attainment scaling of individual treatment goals). Secondary outcomes are on the level of body functions and structures (dystonia, spasticity, pain, comfort). **Chapter 5** shows the results of the IDYS trial. **Chapter 6** provides a systematic review of literature on the reported effects of ITB in PND of childhood. **Chapter 7** shows the results of a questionnaire about satisfaction of ITB, conducted in patients with PND and their caregivers. Satisfaction was scored using a visual analogue scale (VAS). In **Chapter 8** the similarities and differences in the effect of ITB between spastic CP, dyskinetic CP and PND are described. A questionnaire addressing the level of activities and participation was used. The effects were scored using a 5 point Likert Scale (much better, somewhat better, no change, somewhat worse, much worse). **Chapter 9** discusses the overall findings of this thesis. The aims of the thesis as described above are reviewed in this chapter and suggestions for further studies are done.

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CHAPTER 2

Clinical presentation and management of dyskinetic cerebral palsy

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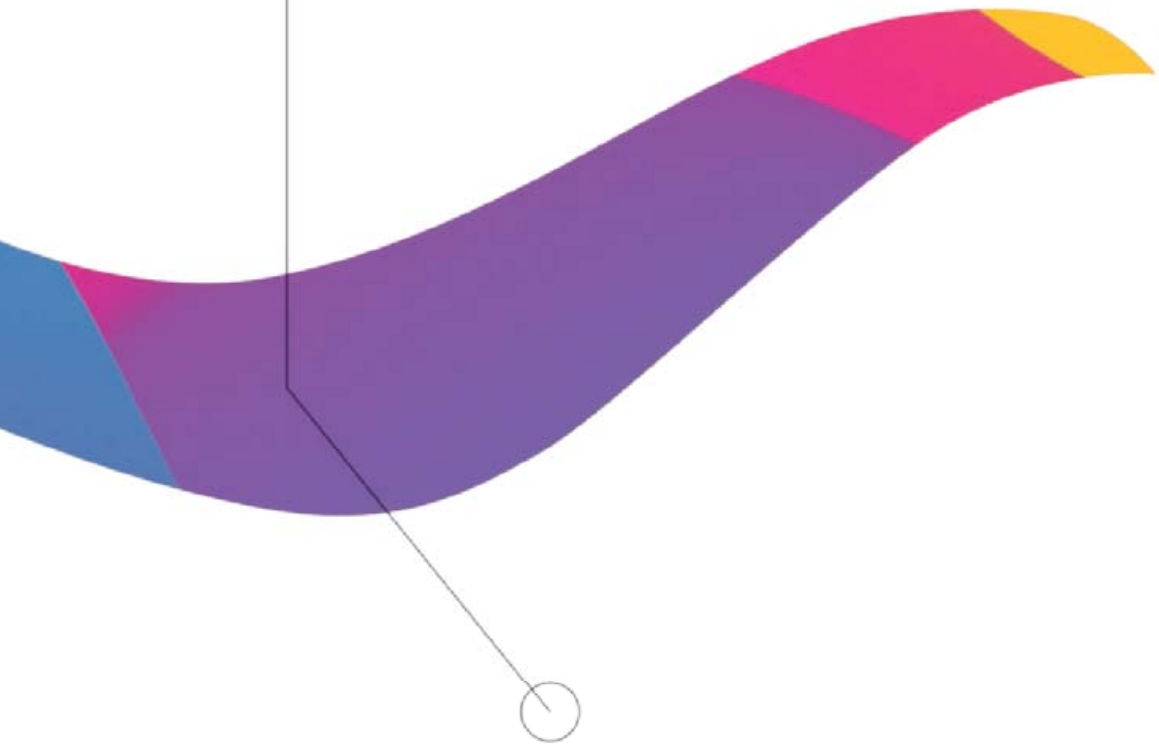
Lancet Neurology 2017; 16:741-749



ABSTRACT

Cerebral palsy is the most frequent cause of severe physical disability in childhood. Dyskinetic cerebral palsy (DCP) is the second most common type of cerebral palsy after spastic forms. DCP is typically caused by non-progressive lesions to the basal ganglia or thalamus, or both, and is characterised by abnormal postures or movements associated with impaired tone regulation or movement coordination. In DCP, two major movement disorders, dystonia and choreoathetosis, are present together most of the time. Dystonia is often more pronounced and severe than choreoathetosis, with a major effect on daily activity, quality of life, and societal participation. The pathophysiology of both movement disorders is largely unknown. Some emerging hypotheses are an imbalance between indirect and direct basal ganglia pathways, disturbed sensory processing, and impaired plasticity in the basal ganglia. Rehabilitation strategies are typically multidisciplinary. Use of oral drugs to provide symptomatic relief of the movement disorders is limited by adverse effects and the scarcity of evidence that the drugs are effective. Neuromodulation interventions, such as intrathecal baclofen and deep brain stimulation, are promising options.

INTRODUCTION

Cerebral palsy comprises a group of developmental disorders of movement and posture, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor impairments are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems.[1]

Cerebral palsy is the most common cause of severe physical disability in early childhood, with a prevalence of 1.7–3.1 per 1000 livebirths in high-income countries, and higher prevalence in low-income countries.[2,3] Cerebral palsy is clinically categorised into spastic, dyskinetic, and ataxic cerebral palsy on the basis of the predominant motor disorder.[1] Dyskinetic cerebral palsy (DCP) is characterised by abnormal postures or movements associated with impaired muscle tone regulation, movement control, and coordination comprising two major movement disorder patterns: dystonia and choreoathetosis.[4] DCP is sometimes referred to as dystonic, athetoid, extrapyramidal, choreoathetotic, or choreoathetoid cerebral palsy. DCP accounts for up to 15% of cerebral palsy cases, making it the second most common type after spastic cerebral palsy.[2,5]

DCP can have many causes, including perinatal hypoxia–ischaemia in infants born near to term, neonatal hyperbilirubinaemia, brain maldevelopment, intracranial haemorrhage, stroke, or cerebral infection.[5] Hyperbilirubinaemia-induced kernicterus (ie, deposition of bilirubin in the basal ganglia) can occur during the preterm and term period. This condition has become less common in high-income countries because of preventive strategies, but is still a notable issue in low-income countries. In addition to primary prevention of hyperbilirubinaemia, postnatal monitoring remains essential, and promising prevention approaches have been developed in resource-constrained settings.[6] Causes outside the neonatal period, such as cardiorespiratory arrest or near drowning in the first year, are rarer.

We critically reviewed the literature to provide an update on the diagnosis and management of DCP, and identify research priorities. This Review will focus on the clinical presentation, the management, and emerging therapeutic approaches of this motor disorder.

CLINICAL PRESENTATION

Motor impairments are often more severe in people with DCP than in patients with the other types of cerebral palsy.[7] Non-motor comorbidities are also common; more than half of patients with DCP have a combination of severe intellectual impairment, anarthria, and epilepsy.[4,5,7] Visual and hearing impairments are also common.[5] Despite normal birthweight in most cases, more than half of patients became underweight at follow-up in a population-based study from western Sweden, presumably as a result of high energy expenditure due to involuntary movements combined with poor feeding, dysphagia, gastro-oesophageal reflux, and suboptimal nutritional intake.[7,8] Sleep and respiratory function are often disturbed. Drooling, dental problems, constipation, faecal and urinary incontinence, pain, and musculoskeletal deformities[9] (including scoliosis) are common, and degenerative cervical changes causing myelopathy and motor deterioration have been described in adults.[10] Mental health problems, including depression, are increasingly recognised. The risk for early death in these patients is higher than in other types of cerebral palsy,[11] and in the general population, most commonly through respiratory failure due to aspiration and pneumonia.

Dystonia and choreoathetosis

Dystonia and choreoathetosis are present in most DCP cases (figure 1; videos 1–4),[4,12] but they can be identified as distinct movement disorders.[1,13,14] Both movement disorders occur independently, but dystonia predominates in most patients with DCP.[4] In childhood, dystonia refers to abnormal postures, involuntary twisting, and repetitive movements due to sustained or intermittent muscle contractions.[11–13] Choreoathetosis in cerebral palsy is characterised by hyperkinesia and muscle tone fluctuation. Although choreoathetosis can be separated into chorea (ie, rapid, involuntary, jerky, and often fragmented movements) and athetosis (ie, slower, constantly changing, writhing, or contorting movements), this distinction does not appear to be clinically useful in people with DCP.[13,14]

Dystonia and choreoathetosis are complex and difficult to measure. However, reliable measurement is crucial for the characterisation of clinical patterns and evaluation of the effects of targeted management. Clinical measures can be used for discriminative, predictive, or evaluative purposes. The Hypertonia Assessment Tool[15,16] distinguishes dystonia from other hypertonic movement disorders, such as spasticity and rigidity. However, the current evidence base is insufficient to precisely differentiate between different types of cerebral palsy or between motor disorders, such as dystonia and choreoathetosis, in so-called pure DCP and spasticity. Dystonia can be exacerbated by non-specific stimuli, including emotion, cognitive tasks, stress, pain, and the

intention to move, and is always relieved by sleep; by contrast, spasticity is a velocity-dependent increase in muscle tone.[17] To date, no established clinical measure can discriminate between hyperkinetic movement disorders. Therefore, good familiarity with the operational consensus definitions is crucial for the reliable recognition of choreoathetosis and other hyperkinetic movement disorders. Several video-based measurement scales can be used to evaluate the severity of dystonia in DCP, such as the Burke-Fahn-Marsden Dystonia Rating Scale (BFMS),[18] the Barry-Albright Dystonia Rating Scale,[19] and the Dyskinesia Impairment Scale.[20] The BFMS and Barry- Albright Dystonia Rating Scale show good reliability in DCP but have limited sensitivity.[21] These limitations and the absence of choreoathetosis measurements are resolved in the Dyskinesia Impairment Scale (DIS), which was specifically developed for the assessment of people with DCP.[20,22] The DIS consists of dystonia (DIS-D) and choreoathetosis (DIS-CA) subscales that determine the presence of and rate the severity (amplitude and duration) of either movement disorder in various regions of the body during activity and rest. The BFMS and DIS are used as outcome measures in intervention studies, such as those investigating deep brain stimulation (DBS)[23] or intrathecal baclofen.[24]

Dystonia is often more noticeable and severe than choreoathetosis.[4] Both are generalised over all body regions (arms, legs, trunk, neck, mouth, and eyes), with higher severity in the upper limbs than in the lower limbs, and both substantially increase with activity. Dystonia has a major effect on the daily activity, quality of life, and societal participation of individuals with DCP.[8,25] Dystonia particularly affects posture, mobility, hand and oral-motor function, and—to a lesser extent—non-verbal communication.[4] By contrast, no functional associations with choreoathetosis have been found, which suggests that the sustained muscle contractions typical of dystonia restrict functional abilities to a much greater extent than the hyperkinetic hallmarks of choreoathetosis.[4] Occasionally, status dystonicus can occur, which is characterised by prolonged or increasingly frequent generalised dystonia and requires early detection and urgent management.[26]

Around 70% of patients with DCP have lesions in the basal ganglia or thalamus, or both on MRI (figures 2, 3); other brain lesions can also occur and few patients have apparently normal scans.[4,7,28–30] The basal ganglia and thalamic lesions can be associated with the higher vulnerability of these regions because of high metabolic demand during the late third trimester of pregnancy[27] or the perinatal period. In neonates with kernicterus, often associated with high-frequency deafness, the globus pallidus is usually involved,[31] but brain lesions are not always seen in the years following development of kernicterus. More severe presentations in DCP include cortical-subcortical involvement with

increased dystonia and spasticity.[27,32] A pattern of increasing clinical severity has been described based on an MRI classification system.[33] MRI does not necessarily detect the full extent of the affected brain region, therefore research with more advanced imaging techniques is recommended; however, imaging is difficult to perform in these patients because of the involuntary movements and postures.

At present, it is unclear how brain abnormalities produce dystonia and choreoathetosis. Emerging hypotheses based on inherited or primary (mainly focal) dystonia studies highlight three pathophysiological aspects, namely loss of inhibition, sensory dysfunction, and impaired plasticity in basal ganglia circuits.[34] Briefly, two basal ganglia pathways exist: a direct, excitatory pathway (from the striatum, through the globu-s pallidus internus, and to the thalamus) and an indirect, inhibitory pathway (from the striatum, through the globus pallidus externus, the subthalamic nucleus, and the globus pallidus internus to the thalamus). The direct pathway controls voluntary movements, whereas the indirect pathway inhibits unwanted movements. Imbalance between the direct and indirect pathways, for example because of overactivity in the direct pathway or underactivity in the indirect pathway, causes excessive movement and a loss of inhibition.[35]

Abnormal sensorimotor integration is a key feature in the pathogenesis of many movement disorders,[36] and the basal ganglia might function as a gate for sensory input. Abnormal plasticity during motor learning might lead to abnormal sensorimotor integration, resulting in consolidation of abnormal motor engrams.[34] According to this hypothesis, therapeutic management might have little immediate effect on dystonia because so-called bad motor memories are difficult to erase.34 This hypothesis suggests that living longer with dystonia makes clinical management more difficult.37 However, based on the different underlying causes of the condition, whether this hypothesis also applies to dystonia in DCP is questionable.

A study in patients with DCP found no significant association between the severity of dystonia and brain lesions in the basal ganglia and thalamus.[4] Some findings suggest that different brain regions that are involved in motor control can cause or contribute to dystonia, including the cerebellum, brainstem, cerebral cortex, and other motor and sensory thalamo-cortical pathways.[38,39] Therefore, dystonia might be most accurately described as a neuronal network disorder, with different phenotypes possibly reflecting different pathophysiological states triggered by various insults or abnormalities.[40] This network model provides testable hypotheses that are directly relevant to new treatment strategies that extend beyond the basal ganglia.[41] From this perspective,

we hypothesise that the pathophysiology of dystonia caused by an inherited disorder (ie, primary dystonia) differs from that of secondary dystonia in DCP, as supported by different responses to treatment and by differences in motor cortex plasticity and cerebellar function in the modulation of dystonic features.[40,41] Therefore, further research is needed to unravel the pathophysiology of dystonia, specifically in DCP, because the focus of pathophysiological studies over the past two decades has been almost exclusively placed on inherited (primary) dystonia.

Choreoathetosis has been underexplored in clinical studies, except in selected conditions (ie, not DCP). Recent findings have shown a stronger association of selective thalamus and basal ganglia lesions for choreoathetosis than for dystonia,[4] suggesting that further research on choreoathetosis in DCP is warranted.

Combined approaches can further advance understanding of dystonia and choreoathetosis in people with DCP. High-resolution MRI and voxel-based morphometry might improve understanding of structural injury, and clarify the implication of selected deep grey matter nuclei and other brain lesions, including the motor cortex and the cerebellum, and their correlation with appropriately described motor phenotypes. The current description of DCP might not be relevant to a pathophysiological explanation of the motor manifestations; therefore, it may be necessary to define several motor phenotypes. Diffusion tensor imaging provides information about connectivity and might help to predict the likelihood of responsiveness to DBS.[42] Electrophysiological assessment, including transcranial magnetic stimulation,[43] central motor conduction time[44] and somatosensory evoked potentials,[45,46] might also contribute towards diagnosis and management of DCP.

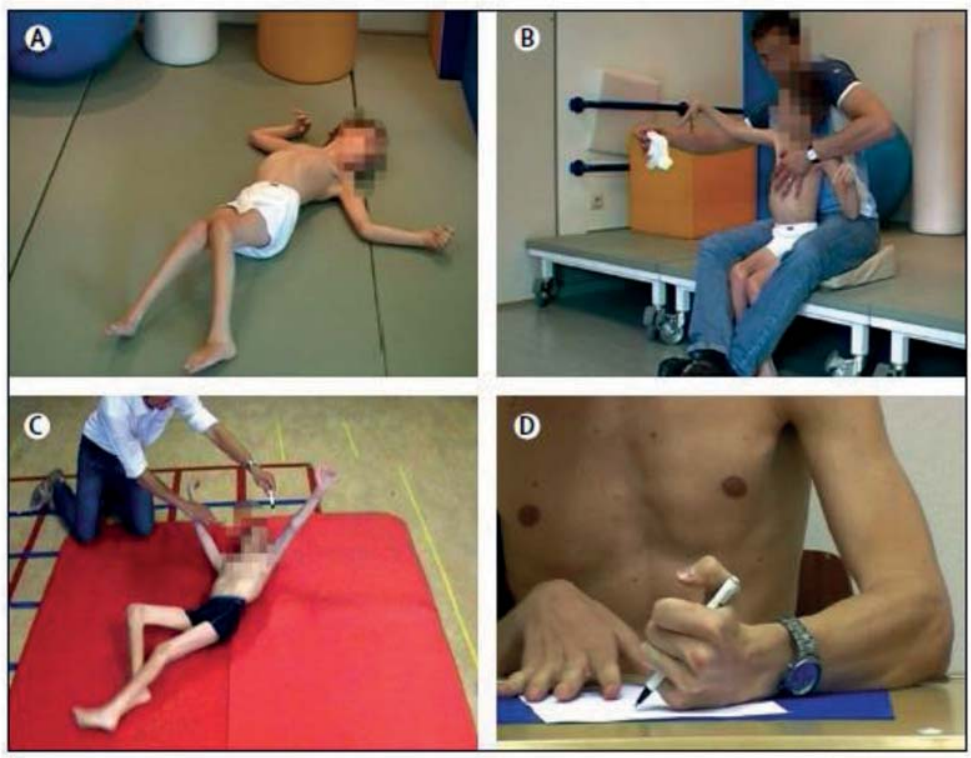


Figure 1. Abnormal posture and movement in dyskinetic cerebral palsy. (A) Primitive asymmetric tonic neck reflex typically present in patients with dyskinetic cerebral palsy. (B) Lack of coordination when in an upright position and grasping objects. (C) Large, uncontrolled involuntary choreo-athetosis movements during activities. (D) Dystonic postures and movement due to sustained or intermittent muscle contractures.

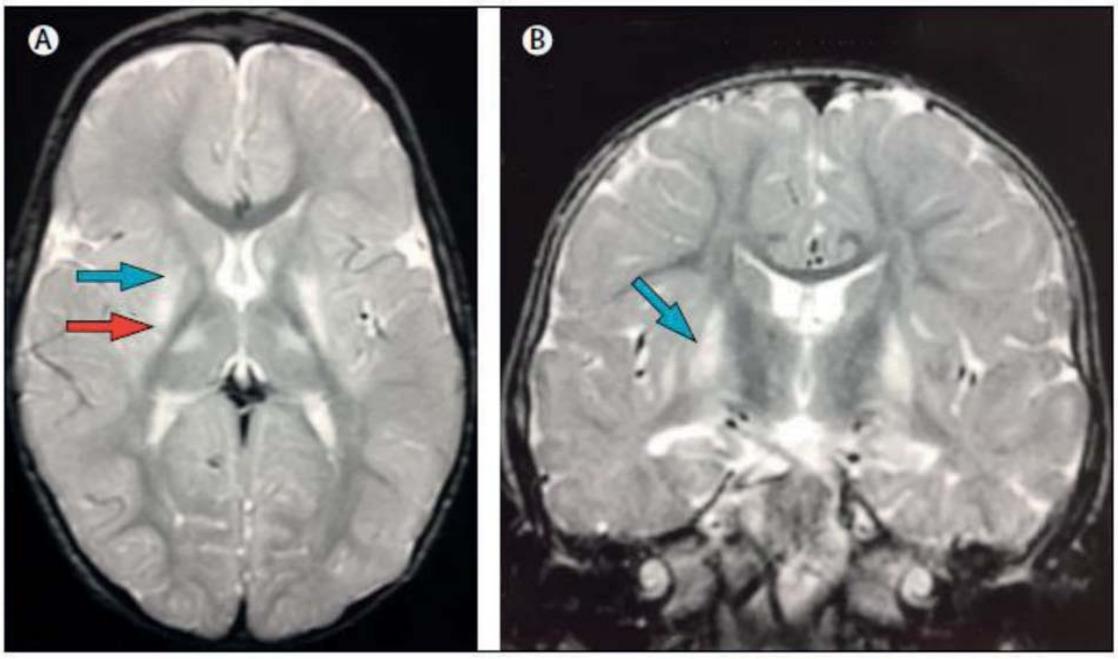


Figure 2. Basal ganglia and thalamic lesions after hypoxic-ischaemic encephalopathy
T2-weighted MRI images of the transverse plane (A) and coronal plane (B) show bilateral focal hyperintensity in posterior putamen (blue arrow), mediolateral thalamus (red arrow), and central region. Images are courtesy of Kate Himmelmann (Department of Pediatrics, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden).

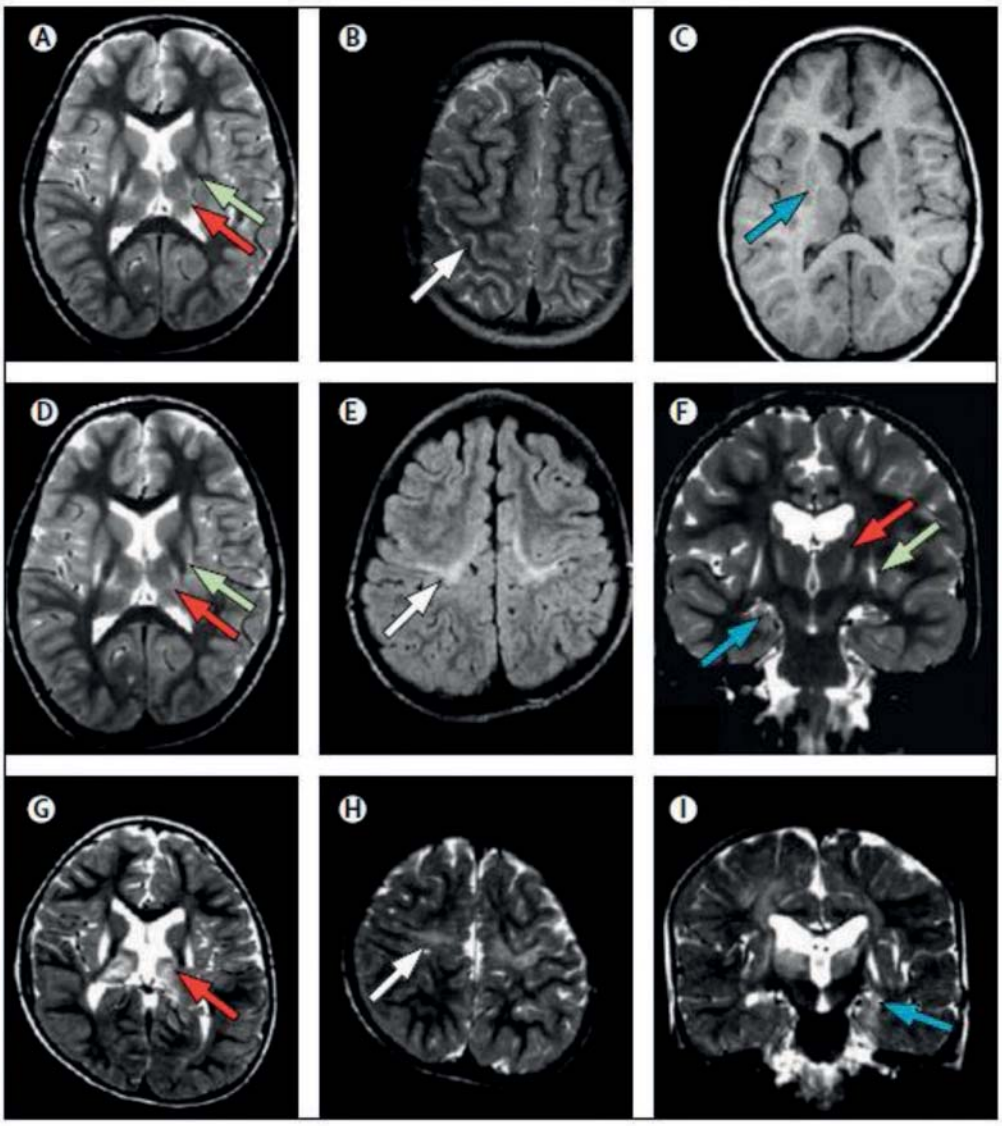


Figure 3. Mild, moderate, and severe MRI patterns of basal ganglia and thalamus lesions
(A–C) Mild pattern of basal ganglia and thalamus lesions (T2-weighted, red and green arrows; T1-weighted, blue arrow); central region not involved (T2-weighted, white arrow). Clinical outcome: dyskinetic cerebral palsy. (D–F) Moderate pattern: Basal ganglia and thalamus lesions (T2-weighted, red and green arrows); central cortical and subcortical lesions (FLAIR, white arrow); and hippocampus not involved (T2-weighted, blue arrow). Clinical outcome: dyskinetic cerebral palsy with spastic traits, or spastic cerebral palsy with dyskinetic trait, depending on the involvement of the motor cortex. (G–I) Severe pattern of basal ganglia and thalamus lesions (T2-weighted, red arrow); central cortical and subcortical lesion (T2-weighted, white arrow); and hippocampus lesions (T2-weighted, blue arrow). Clinical outcome: severe bilateral spastic cerebral palsy. Images are courtesy of Krägeloh-Mann and colleagues.[27]

MANAGEMENT

Management of dystonia and choreoathetosis should be timed and targeted to maximise the potential for cerebral plasticity in people with DCP.[47] As suggested by the WHO International Classification of Functioning, Disability and Health, management should aim to improve daily activity and quality of life by improving movement and posture and relieving any associated disability, pain, and discomfort.[25]

Non-motor comorbidities, such as epilepsy or depression, require specific treatment. To ensure optimal nutrition, gastrostomy tube feeding can be considered on the basis of a comprehensive assessment by a multidisciplinary team.[48,49] Management should also focus on prevention of contractures and orthopaedic complications.[49]

Little evidence supports the use of pharmacological treatment of dystonia and choreoathetosis in people with DCP.[50] Many patients with DCP take multiple oral drugs with low efficacy and unwanted side-effects.[51] Nevertheless, in some patients, oral drugs can be useful. Before considering medical treatment of dystonia, it is important to determine whether the patient also shows spasticity, as this requires a specific approach. Particularly in patients without MRI abnormalities, the possibility of dopamine-responsive dystonia as a mimic DCP should be considered. However, levodopa shows limited efficacy in patients with DCP.[52] Less research has been done concerning treatment for choreoathetosis. Dopamine-depleting agents can influence the hyperkinetic component of dyskinesia.[51] Other studies have reported a positive effect of levetiracetam in children with choreoathetosis.[53,54]

The table provides an overview of medications used to manage dystonia and choreoathetosis in people with DCP. Oral baclofen, a GABA-B agonist used for spasticity management, is the most commonly used oral drug for DCP despite its low efficacy.[51] The efficacy of trihexyphenidyl, an anticholinergic drug, on dystonia is also low[61,62] and its use in people with DCP is often restricted by the risk of adverse effects. Adverse effects can include worsening of choreoathetosis, possibly owing to so-called unmasking when severe dystonia is reduced (ie, dystonia prevented the full expression of choreoathetosis).[4]

Intrathecal baclofen treatment was introduced as an alternative to oral administration with fewer side-effects, and much lower dosage. Many studies of intrathecal baclofen treatment have reported significant decreases in dystonia[63–65] and subjective improvements in mobility,[66,67] speech and communication, swallowing,[59] head control,[68] sleep,[66] pain and mood,64 comfort,[66,68–71] and ease of care.[66] Patient satisfaction and

attained goals are generally high.[71] Although intrathecal baclofen decreases dystonia in most patients, the treatment usually leads to no changes in functional independence for daily activities[64] Therefore, treatment goals mainly focus on improving pain and preventing deformities.[64,69,71,72] Such therapy could be particularly appropriate in patients with both dystonia and spasticity.[72] Whereas the benefits to improve dystonia are well known, the effect of intrathecal baclofen on choreoathetosis has not been investigated.

In people with DCP, the intrathecal baclofen catheter tip is often placed high at the cervical spinal level, because major sites of action of baclofen are likely to be intracranial.[65] The response cannot be fully predicted and the dosage must be individualised.[73] If the effect of a continuous dose is not sufficient or has a gradually reduced effect, intermittent bolus dosing can be used.[73] Complications after intrathecal baclofen implantation are common. Infection risk is high (33–44%),[71,74] particularly in the first month after surgery,[73,75] and infection treatment always requires pump removal. CSF leaks occur in 0–21% of cases,[64,71] with an increased risk during patient transfers and mobilisation. Extended bed rest usually resolves the leak and accompanying light-headedness, but surgery is sometimes needed.[65] Catheter-related problems, such as migration, disconnection, and blockage, often manifest with signs of baclofen withdrawal, for example an increase in spasticity or dystonia, or both, generalised itching and agitation, and hypertension.[73] These issues occur in 5–33% of patients with catheter-related problems.[63,64,71] When patients are awaiting surgery, oral baclofen can be given to decrease the severity of withdrawal symptoms.

On the basis of dramatic positive outcomes in patients with inherited (primary) dystonia,[76,77] DBS has been increasingly used in people with DCP over the past decade.[23,37,78–81] Studies of DBS in people with DCP often describe the reduction of dystonia rather than its effects on functionality, quality of life, or choreoathetosis.[25,82–84] The responsiveness of dystonia to DBS treatment is variable[85] and usually less beneficial than in patients with inherited (primary) dystonia.[86] Long-term data are rare, but a case series follow-up study in Italy that included 15 patients reported that improvements in BFMS values were sustained for up to 2 years after implant.[79]

The relatively modest and often delayed effects of DBS in people with DCP might be due to abnormal plasticity and an altered neuronal cortex-basal ganglia network.[34,87] Whereas in inherited (primary) movement disorders, dystonia becomes symptomatic after a period of normal development, in people with DCP, dystonia presents in early life

before functional motor patterns have developed and, when they do, those movements and postures are often abnormal.[37,88]

Currently, the globus pallidus internus is the target of choice for electrode implantation in people with DCP.56 DBS programming is personalised based on subjective evaluations of clinical benefit; an objective approach to parameter selection would require better understanding of the underlying pathophysiology. DBS is generally safe, and a reversible method of treatment. Complications such as intracerebral haemorrhage or ischaemic infarction are rare, but infection and hardware problems of the implanted pulse generator can occur.[89] More severe adverse events of DBS have been reported in children than in adults;[23] however, large cohort studies have reported low infection rates of less than 5% in children younger than 7 years.[90]

Responsiveness of choreoathetosis to DBS has not been documented, and little is known about the effect of DBS on daily activity, societal participation, or quality of life. Various collaborative efforts are underway to systematically collect data on individuals with DBS, including age of implantation, history of eventual musculoskeletal changes, activity levels, and inclusion in an international registry.[23,91]

Botulinum toxin is often used to decrease dystonia in people with DCP.[92] Botulinum toxin causes selective (focal) muscular denervation that is temporary and reversible. Its therapeutic value has been much more extensively assessed in inherited (primary) dystonia than in people with DCP. Botulinum toxin is also used in individuals with hip dislocation or disabling limb dystonia. A few small studies have indicated that botulinum toxin has an effect on dystonia and pain in people with DCP.[93,94] Many issues remain unresolved because of variation in injection methods and a shortage of knowledge of the determinants of local spread and distant effects.[55] To date, no specific indication is available for choreoathetosis.

As musculoskeletal deformities seen in patients with DCP and those with other childhood dystonias[9] are often associated with pain, patients might undergo orthopaedic surgery.[49] However, before orthopaedic surgery is done, it is recommended that attempts are made to control dystonia and choreoathetosis with oral drugs, intrathecal baclofen, or DBS. Furthermore, based on our clinical experience, the results of soft tissue orthopaedic surgery in patients with DCP are not as predictable as in patients with spastic cerebral palsy, and adverse outcomes can easily occur. By contrast, orthopaedic procedures can be carried out more safely in patients with DCP than in those with spastic CP.

The medical management options discussed are not appropriate as standalone treatment. Combinations with rehabilitation approaches carried out by physiotherapists, occupational therapists, and speech and language therapists are key components of the management of dystonia and choreoathetosis. Evidence for rehabilitative strategies is mostly based on studies in spastic cerebral palsy and remains scarce in DCP.[95,96] Current practice is therefore mainly based on clinical expertise. This expertise is usually offered by dedicated multidisciplinary rehabilitation teams designing individualised management programmes that begin as early as possible in the life of the patient. Use of a family-centred approach and the concepts developed in WHO's International Classification of Functioning, Disability, and Health can ensure the development of skills and good quality of life.[97–99]

Most patients have substantial motor disability, therefore optimal seating and positioning should be ensured to increase stability and the coordination of movements for mobility (including electronic wheelchair use) and hand function. Combined with medical management, rehabilitative research should focus on goal-directed strategies that consider general guidelines to handle postural asymmetry and individual needs.[49] Verbal communication is almost always affected in people with DCP,[100,101] therefore augmentative and alternative communication intervention is often needed. Without appropriate communication intervention, the intellectual level of the individual with DCP could be underestimated.[7] In addition, given the potential for brain plasticity, cognitive training and motor learning research is warranted in DCP management.

Table Medications used to manage dystonia and choreo-athetosis in patients with dyskinetic cerebral palsy

	Mechanism of action	*Dystonia*	*Chorea*	*Side effects*
Dopamine agonists (levodopa)55	Enhances the activity of dopamine	Used	..	Nausea, orthostatic hypotension, and constipation
Anticholinergic (trihexiphenidyl, benzatropine) 51,55	Blocks acetylcholine muscarinic receptor	Used	..	Drowsiness, confusion, memory difficulty, blurred vision, hallucinations, urinary retention, and worsening chorea
Benzodiazepine receptor agonists (diazepam, clonazepam)55,56	Enhances GABA-A inhibition	Used	Used	Sedation, confusion, depression, ataxia, and dependence
GABA-B receptor agonist (baclofen)51,55–57	Enhances the activity of GABA-B receptor	Used	..	Worsening chorea, incontinence, sedation, dizziness, dry mouth, and increased blood glucose
Dopamine and serotonin antagonist (clozapine)56	Binds to serotonin and dopamine receptors and prevents release	Used	..	Decreased white blood cell count, sedation, hypotension, myocarditis, cardiomyopathy, drooling, arrhythmia, seizures, and diabetes mellitus
Pre-synaptic α2 receptor agonist (clonidine)58	Enhances the activity of pre-synaptic α2 receptor	Used	..	Orthostatic hypotension, bradycardia, sedation, fatigue, and headache
Dopamine antagonists (pimozide, haloperidol)55	Antagonist of the D2, D3, and D4 dopamine receptors, and the 5-HT_7 receptor	..	Used	Hypotension, sedation, QT interval prolongation, and ventricular arrhythmias (including torsades de pointes); overdose causes severe extrapyramidal symptoms
Monoamine blockers (tetrabenazine)51,55,56	Inhibits vesicular monoamine transporter 2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine storage	Used	Used	Drowsiness, parkinsonism, depression, insomnia, anxiety, and akathisia

Table 1. Continued

	Mechanism of action	*Dystonia*	*Chorea*	*Side effects*
Monoamine depleters (reserpine)51	Blocks the vesicular monoamine transporter	..	Used	Nasal congestion, nausea, vomiting, weight gain, gastric intolerance, gastric ulceration, stomach cramps and diarrhoea, hypotension, bradycardia, and worsening of asthma
Voltage-gated sodium and calcium channel blocker (carbamazepine)55	Blocks voltage-sensitive sodium channels	Used	..	Decreased white blood cell count and platelets; increased risk of suicide
Calcium channel blocker (levetiracetam)53,54	Binds to a synaptic vesicle glycoprotein and inhibits presynaptic calcium channels, reducing neurotransmitter release and acting as a neuromodulator	..	Used	Somnolence, decreased energy, headache, dizziness, and (mild) ataxia
Muscle tone reducer (dantrolene)59	Reduces skeletal muscle tone at the muscle fibre level	Used	..	Speech and visual disturbances; depression and confusion; hallucinations; headache; insomnia and exacerbation or precipitation of seizures, and increased nervousness
Voltage-gated calcium channel blocker (gabapentin)60	Antagonises binding of thrombospondin to voltage-gated calcium channel a2d-1 receptors and inhibits synthesis of glutaminergic excitatory synapses	Used	..	Dizziness, drowsiness, sedation, fever, fatigue, viral infection, ataxia

CONCLUSIONS AND FUTURE DIRECTIONS

Many epidemiological studies[2,102] are currently underway; these studies are mostly population-based or registry-based and focus on the identification of risk factors that will eventually lead to the implementation of preventive strategies. Hypothermia for term and near-term neonates with hypoxia–ischaemia,[103] and magnesium sulphate and other agents as neuroprotective approaches for fetuses are promising approaches under investigation.[104] Population-based follow-up programmes and studies will add to the evidence base regarding long-term secondary complications and results of management.

Current management options are mainly based on clinical presentation. To evaluate the efficacy of therapy and to adjust and delineate management, well designed studies and systematic use of meaningful outcome measures are needed. Future research should include additional objective and quantitative tools to assess dystonia and choreoathetosis. Moreover, owing to the relatively small population of patients with DCP, multicentre studies are crucial for the development of evidence-based guidelines for the management of dystonia and choreoathetosis. Specific evaluation of rehabilitation strategies, including physical, occupational, and speech and language therapy, is urgently required.[101] Robotics and other emerging technologies have the potential to increase independent mobility. Better understanding of motor learning processes is needed to implement these new technologies.

To date, medical interventions in DCP (eg, intrathecal baclofen, DBS, and botulinum toxin) have mainly targeted dystonia but not choreoathetosis, which requires more research attention. Further research into the effect of interventions on daily activities, societal participation, quality of life, pain, nutrition, and sleep is also required. The clinical interrelationship between dystonia and choreoathetosis after different interventions is also worth further research.

The neurophysiological basis of dystonia and choreoathetosis should be explored. To date, there are no animal models for DCP.[105] Increased insight into the neurophysiological circuits in patients with DCP can be obtained during intraoperative pallidal recordings of local field potentials and microelectrode recordings. Neuronal firing frequencies have been shown to correlate with dystonia phenotype and the timing of the insult, which could be partially predictive of DBS outcome.[43] Other non-invasive neurophysiological models in children and adults with DCP and their neuroimaging findings are needed to explore cerebral plasticity.[106,107]

In conclusion, although DCP is the second most common type of cerebral palsy, the condition is under-reported[7] and management remains empirical and largely unsatisfactory. Therefore, a better scientific foundation to therapeutic approaches is urgently required. Early detection, improved neuroimaging, and improved neurophysiological characterisation of dystonia and choreoathetosis in DCP are needed. Increased understanding of the affected brain structures could contribute to better targeted therapeutic management.

CONTRIBUTORS

All authors contributed significantly to the work, have read the manuscript, attest to the validity of the data and its interpretation, and agree to its submission. EM provided the videos and figure 1 images and KH provided the images in figures 2 and 3.

DECLARATION OF INTERESTS

J-PL has received a Guy's and St Thomas Charity New Services and Innovation Grant (G060708), grants from The Dystonia Society UK (01/2011, 07/2013) and Action Medical Research (GN2097), is a consultant for Medtronic Ltd, and has received unrestricted educational grants from Medtronic Ltd for delivering courses and attending conferences. RJV has received unrestricted educational grants from Medtronic Ltd for delivering courses and from Ipsen International GmbH for his advisory board role. All other authors declare no competing interests.

ACKNOWLEDGEMENTS

We would like to thank Marc Vermandere (Dominiek Savio Instituut, Gits, Belgium) for his support in compiling the videos.

Search strategy and selection criteria

We identified references for this Review by searching PubMed for reports published between Jan 1, 2006 and March 31, 2017, and references from relevant articles. Search terms used were "dyskinetic cerebral palsy" and "dystonic cerebral palsy", "hypoxic-ischemic encephalopathy" and "dystonia", and "choreoathetosis" and "pathophysiology" in combination with "management" or "therapy", or "treatment". We only considered peer-reviewed reports in English

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CHAPTER 3

Effects of intrathecal baclofen on daily care in children with secondary generalized dystonia: a pilot study

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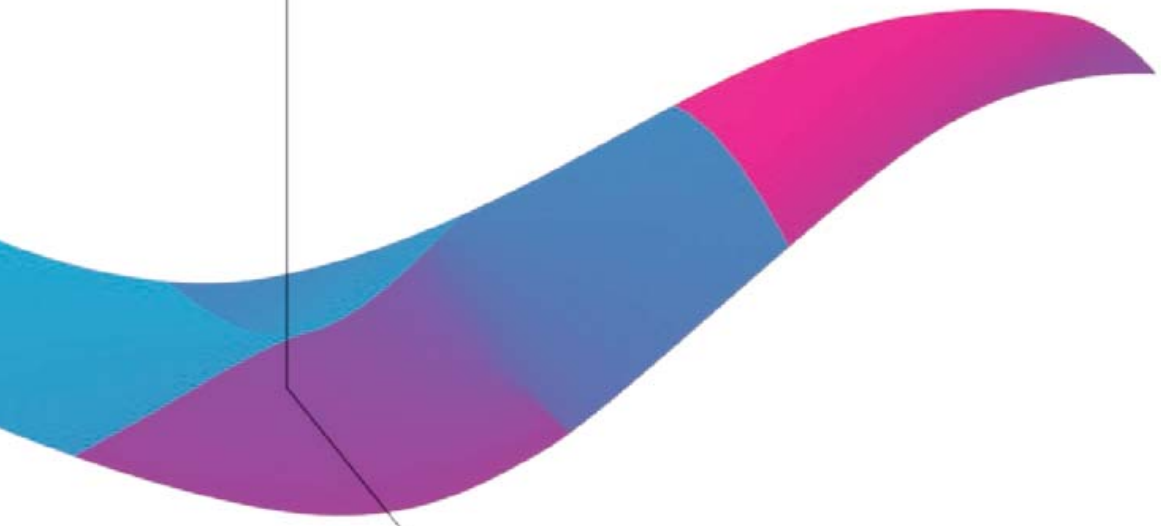
Eur J Paediatr Neurol 2011; 15(6): 539-543



ABSTRACT

Aim Treatment options for dystonic cerebral palsy (CP) are limited. Our aims were to determine whether intrathecal baclofen (ITB) improves daily care, decreases dystonia and decreases pain in patients with dystonic CP.

Methods Patients received randomized blinded treatment with ITB or placebo. Scores on problems of daily care were recorded and dystonia, pain and comfort were assessed.

Results Four patients (three males, average age 12 years 6 months) were included (all Gross Motor Function Classification System level V). During the trial period problem scores and dystonia scores decreased in all four patients.

Conclusion In this pilot study we report positive functional effects of ITB trial treatment in four patients with dystonic CP. A randomized trial with a larger cohort is needed to verify these results.

Keywords Secondary dystonia, Dyskinesia, Cerebral palsy, Intrathecal baclofen, Care giving

INTRODUCTION

Six to fifteen percent of patients with cerebral palsy (CP) have dyskinetic motor disorders[1,2] of which 70% have dystonic features.[3]

Dystonia is dominated by abnormal postures and easily elicitable fluctuating hypertonia. Characteristics are involuntary movements, distorted voluntary movements and abnormal postures due to sustained muscle contractions.[4,5] Dystonia in CP is referred to as secondary dystonia and is often associated with spasticity. It causes progressive disability, discomfort and deformity,[6] which amongst others leads to impeding of daily care.

Oral medication (e.g. baclofen or trihexyphenidyl) shows limited effect.[7-9] Intrathecal baclofen (ITB) treatment was first used for treatment of dystonia in 1991.[10] The working mechanism of ITB in dystonia remains unclear but it is thought that ITB inhibits the excitation of the pre-motor and supplementary motor cortex.[6,11-14]

Our aims were to perform a pilot study to determine if intrathecal baclofen (ITB) improves daily care and decreases dystonia and pain in patients with dystonic CP.

METHODS AND MATERIALS

The design of the study was a single center double blind randomized case controlled trial. All patients started with a trial period, in which they received ITB treatment. Hereafter they were randomized in two groups, an intervention and a control group.

Participants

Between 2001 and 2005 patients were recruited from the outpatient clinics of the departments of child neurology and pediatric rehabilitation medicine of the VU University Medical Center in Amsterdam, the Netherlands. Patients selected for ITB trial treatment, aged between 4 and 18 years old, with severe generalized dystonia, Gross Motor Function Classification System (GMFCS) level V, resulting in problems concerning daily care, were included if they and their parents were motivated and able to complete the whole study protocol.

Informed consent was signed by all parents. This study was approved by the Medical Ethical Committee of the VU University Medical Center in Amsterdam, The Netherlands.

Intervention

The trial treatment period consisted of a baseline observational period and a dose finding period. After the baseline period, an intrathecal catheter was placed under general anesthesia with the catheter tip at individually specified heights (Table 1). The intrathecal catheter was connected to either an external catheter or an external micro-infusion pump as decided by the treating physician.

Administration of ITB was either continuously via the external micro-infusion pump or in a daily bolus dosage in case of the external catheter. The dosage was increased with approximately 25 mg per day until an optimal dosage was found. The maximal dosage was 200 mg per day. If dosage related side-effects occurred, dosage was decreased until side effects disappeared. If unacceptable complications occurred treatment was aborted.

The optimal dosage was maintained for at least three days. After this period, the patients were randomized in two groups for blinded treatment and received either ITB or intrathecal placebo treatment for four days. Hereafter, the intrathecal catheter was removed. After the trial treatment, the patients, caregivers and doctors decided, for or against implantation of a definite programmable pump (Medtronic®) for continuous ITB treatment.

Outcome measures

Three main problems in daily care were identified by caregivers in a preparatory interview. The perceived severity of these problems was scored on a Visual Analogue Scale (VAS), with “0” representing “no problems” and “10” representing “impossible to do”. Parents filled out these VAS scores daily during the hospital stay. A positive effect was defined as ‘a decrease of two or more points in at least one of three problems’. ‘An increase of more than two points’ was defined to be a negative effect.

For the clinical assessment of generalized dystonia the Barry-Albright Dystonia (BAD) scale, which grades dystonia on a 0 to 4 scale in eight body regions (eyes, face, neck, trunk, upper- and lower limbs), was used.[11,15] The score ranges between 0 and 32 with a score of 0 representing no dystonia and a score of 32 representing maximal dystonic activity.

Assessments of dystonia were carried out daily at the same time of the day by one of two physicians (RJV, JGB). A reduction of 25% or more, in comparison with the baseline score, is considered clinically significant.[11,15]

Pain was assessed with a VAS, with “0” representing “no pain” and “10” representing “very severe pain”. Parents completed the VAS for pain daily, at the same time of the day, without knowledge of the baclofen dose.

Comfort was assessed using a VAS (score 0 to 10), with a higher score representing more comfort. Parents completed this score daily. Furthermore, the patients were asked to point out how they felt during the day (happiness score). They could choose from pictures, ranging from a very sad looking face (score 1) to very happy looking face (score 5).

A positive effect on pain and comfort was defined as an improvement of at least two points for pain and comfort and at least one point for child’s happiness scores.

GMFCS and Pediatric Evaluation of Disability Inventory (PEDI) were only tested prior to starting the screening treatment.

Statistical analysis

Due to the explorative setup of this study and the small number of patients we limited ourselves to descriptive results and did not perform further statistical analysis.

RESULTS

Four patients (three male, one female) with an average age of 12 years 6 months (range 8 years 9 months to 17 years 10 months) were included in this pilot study. An overview of their characteristics can be found in Table 1. All patients were wheelchair bound and fully dependent in daily life for self-care and mobility (GMFCS level V and PEDI score for assistance in self-care and mobility 0). Table 1 shows their characteristics and individual effects of ITB treatment.

Table 1. **Patients characteristics and effects of ITB treatment**

Case	*Sex*	*Age (y)*	*Catheter*[a]	*Complications*	*Interventions*	*Reported problems*	*Effect*	*BAD*	*Pain*	*Comfort*	*Happiness*
1	F	14	Th8	Nausea	Dosage decrease	1. Wheelchair transfer 2. Sitting in wheelchair 3. Communication[b]	++ ++ ++	++	++	++	++
2	M	17	Th7	Nausea, CSF leakage	Dosage decrease, bed rest	1. Dressing 2. Hyperextension in lift 3. Dressing[c]	+[d] +[d] +[d]	++	=	++	++
3	M	9	Th10	Catheter block, Meningitis	Catheter removal, antibiotics	1. Sleeping 2. Dressing 3. Speaking	++ ++ ++	++	++	=	++
4	M	8	C6	CSF leakage	Bed rest, Catheter removal	1. Hygienic care 2. Sitting in wheelchair 3. Speaking	++ ++ +[d]	++[d]	-	-	-

Abbreviations: CSF, cerebrospinal fluid; C, cervical; ITB, intrathecal baclofen; F, female; M, male; mo, monts; Th, thoracic; yr, years. [a] Catheter tip position on X-ray; [b] with wizard; [c] Socks and shoes; [d] No baseline values, change compared to blinded placebo treatment; +, 1 point improvement, ++ ≥2 points improvement, = no change; -, 1 point worsening; --, ≥2 points worsening.

Effect on daily care

Problems of daily care reported were problems with: Dressing (n=2), speaking (n=2), hyperextension of head and trunk when sitting (n=2), hyperextension of head and trunk in lift (n=1), communication problems with speech computer due to decreased head control (n=1), transfer from bed to chair (n=1), putting socks and shoes on (n=1), sleeping (n=1) and washing (n=1). During ITB trial treatment, all problem scores decreased (average of 4.7 points). During blinded treatment, an increase in problem scores was seen during both the blinded placebo and ITB treatment (respectively 1.4 and 0.5 points) but scores remained well below baseline scores (respectively with 3.3 and 4.2 points).

Effect on dystonia

During ITB trial treatment mean BAD scores decreased by 72% (19.6-5.4). During blinded treatment, an increase in BAD scores was found during both the blinded placebo and ITB treatment (respectively to 63% and 54% of baseline scores).

Effect on pain and comfort

Pain scores decreased significantly in two children, stayed low in one child and increased in another child. The last child experienced complications, explaining the increase in pain scores. Average pain scores decreased during ITB treatment with 1.1 points, but with 3.0 points if excluding the patient with complication induced pain. During blinded placebo treatment pain scores increased with 0.5 points. During blinded ITB treatment, pain scores were 2.6 points lower as at baseline.

Comfort was assessed in two manners. Parents indicated comfort to increase during ITB treatment by an average of 1.1 points. Comfort decreased in the child who also experienced an increase in pain. During blinded placebo and ITB treatment, average comfort increased by 0.5 points further. Child happiness scores increased by 2.3 points during ITB treatment.

One child, for whom parents indicated no change in comfort, indicated a large positive change (4 points). One other child, who was in pain, indicated a decrease in happiness scores. During blinded placebo treatment happiness scores decreased slightly but were still above baseline. During blinded ITB treatment scores maintained similar as during non-blinded treatment.

Complications

Several complications occurred during trial treatment: Cerebrospinal fluid (CSF) leakage occurred in two patients, which resulted in headache, nausea and premature abortion

of the blinded trial phase in one patient and in an extended hospital admission in the other patient. One child received ITB via an external catheter with bolus injections, the other via a continuous micro-infusion pump. Furthermore, in one patient two previous trial treatments using an external catheter were complicated with catheter blockage and meningitis.

DISCUSSION

In this pilot study we found clear effects of ITB treatment in patients with dystonic CP. Previously, improvement in ease of positioning in wheelchairs[12,14,16] and ease of care including hygiene, dressing and feeding have been reported with ITB treatment in patients with dystonic CP.[12,16] Furthermore speech has been reported to improve[6].

Few authors looked at the attainment of individualized goals[17,18]. After six months of ITB treatment, goals were attained in 70%, measured by Goal Attainment Scaling. Also scores for satisfaction and performance domains increased, as measured with the Canadian Occupational Performance Measure.[18] Similar to Hoving et al., we used a VAS to measure the effect on individualized problems of daily care during the trial treatment phase.[18] Problems with sitting, dressing, transfer, speech, head control and hygienic care were reported by caregivers. During ITB trial treatment problem scores decreased. Hoving et al. found the same effect in seventeen children with CP of which five had the spastic-dyskinetic type of CP.[17]

We expected an increase in problem scores during placebo treatment but remarkably the scores did not change significantly after three days of placebo treatment. They were comparable to scores during blinded ITB treatment. Furthermore, even though dystonia (BAD) scores increased during placebo treatment, they stayed below baseline values after three days of blinded placebo treatment in one patient.

One case report supports our findings.[19] In this case report, a 29 year old man with a history of traumatic brain injury ten years before, received a single ITB bolus. The authors found a prolonged anti-spastic effect measured by surface electromyography. A neural upregulation mechanism is suggested as the reason for this prolonged effect.[19] We agree with the authors that the prolonged effect of ITB cannot be caused by remaining baclofen in the cerebrospinal fluid (CSF) since baclofen in the CSF has a half-life of 1 -5 h[19] and three days is well past the expected washout period. The idea of upregulation of GABA surface receptors due to long term underexposure of spinal cord GABA-receptors causing an increased sensitivity to a bolus ITB is therefore plausible but has never been proven. Recently Lee et al[20] used the radiotracer ^{18}F-fluoroflumazenil, a

central benzodiazepine receptor antagonist to calculated the $GABA_A$ receptor binding potential. They found an increased receptor binding potential in patients with bilateral spastic cerebral palsy in the motor cortex area representing the lower extremities. They hypothesized that upregulation of $GABA_A$ receptors might be caused by a neuronal plasticity process compensating for reduced GABAergic input due to white and/or gray matter loss.

In this study GMFCS and PEDI were only tested prior to starting the screening treatment. We did not expect improvement in dependency on others for personal care and mobilization. This assumption is based on the results of previous studies, which did not show change in the degree of autonomy in carrying out everyday activities during ITB treatment.[6,14,16,18]

Consistent with other studies we found significant decrease of dystonia. Even though some patients experienced serious illness due to complications of trial treatment, we are confident we observed an anti-dystonic effect in these patients. This is confirmed by the long term effect of ITB in these patients. With continuous ITB treatment the effect on dystonia may remain to be present for many months to years of follow-up.[6,11,12,14,16,18,21] Previous studies reported improvement in comfort and mood, during continuous ITB treatment,[12,14,16] which resulted in an improved quality of life in around 85% of patients.[6,13] Besides comfort rated by caregivers, we feel it is important to furthermore include the child's happiness scores as a measure of comfort since the patient and caregivers can disagree. This phenomenon occurred in one of our patients.

As can be expected, changes in pain and comfort scores are mostly related. Happiness scores and pain improved during ITB treatment in two patients but in one other patient, the side effect of CSF leakage, causing headache and nausea, caused an increase of pain and a decrease in comfort.

A main concern of ITB treatment are the complications that may occur during ITB treatment. Infections, CSF leaks and catheter problems are the most common complications during trial treatment and continuous treatment.[13,22,23] In our study, treatment had to be stopped prior to ending the study in three events in two patients due to complications of CSF leakage, catheter dysfunction or meningitis. One other patient had an extended admission to the pediatric ward due to CSF leakage. Most cases occurred during treatment via an external catheter. Nausea occurred in two patients as a side effect of ITB and decreased when lowering the dosage. Despite side-effects and complications during this study, a programmable pump was implanted in all patients.

This study has several limitations. Most important, the number of patients in this pilot study is low and the collected data are not complete, mostly because two patients ended the study prematurely. However, we think that the results (including complications) can be very useful to design a larger prospective study.

CONCLUSION

In this pilot study we showed that intrathecal baclofen treatment decreases dystonia and alleviates daily care in patients with dystonic CP. However, the trial period with an external spinal catheter is hampered by serious complications, and in our opinion, the use of external spinal catheters should be avoided if possible. Due to the small number of patients and incomplete data, further research focused on the problems in daily care with a larger study population and prolonged ITB treatment is needed to further specify the effect of ITB in this population.

ACKNOWLEDGEMENTS

We would like to thank the Phelps stichting voor spastici (Project number: 99.047) for the financial support.

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CHAPTER 4

Intrathecal baclofen treatment in dystonic cerebral palsy: a randomized clinical trial: the IDYS trial

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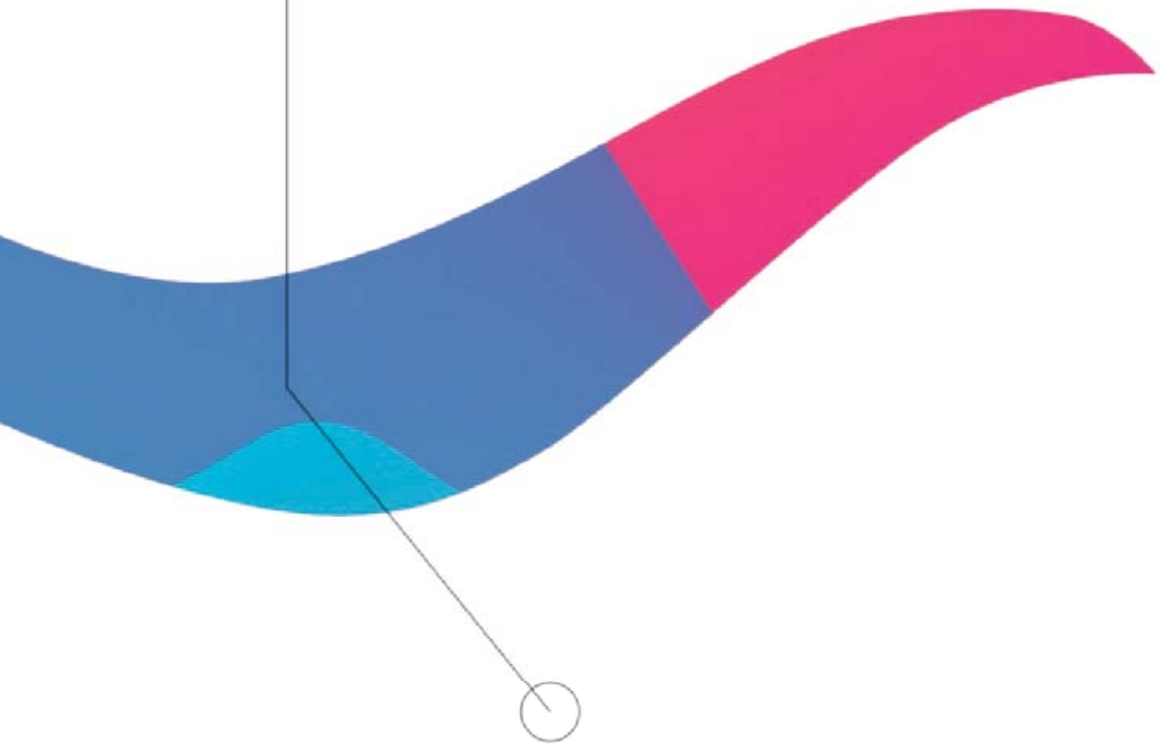
BMC Pediatrics 2013; 13: 175-182



ABSTRACT

Background Dystonic cerebral palsy is primarily caused by damage to the basal ganglia and central cortex. The daily care of these patients can be difficult due to dystonic movements. Intrathecal baclofen treatment is a potential treatment option for dystonia and has become common practice. Despite this widespread adoption, high quality evidence on the effects of intrathecal baclofen treatment on daily activities is lacking and prospective data are needed to judge the usefulness and indications for dystonic cerebral palsy. The primary aim of this study is to provide level one clinical evidence for the effects of intrathecal baclofen treatment on the level of activities and participation in dystonic cerebral palsy patients. Furthermore, we hope to identify clinical characteristics that will predict a beneficial effect of intrathecal baclofen in an individual patient.

Methods/design A double blind placebo-controlled multi-center randomized clinical trial will be performed in 30 children with dystonic cerebral palsy. Patients aged between 4 and 25 years old with a confirmed diagnosis of dystonic cerebral palsy, Gross Motor Functioning Classification System level IV or V, with lesions in the cerebral white matter, basal ganglia or central cortex and who are eligible for intrathecal baclofen treatment will be included. Group A will receive three months of continuous intrathecal baclofen treatment and group B will receive three months of placebo treatment, both via an implanted pump. After this three month period, all patients will receive intrathecal baclofen treatment, with a follow-up after nine months. The primary outcome measurement will be the effect on activities of and participation in daily life measured by Goal Attainment Scaling. Secondary outcome measurements on the level of body functions include dystonia, spasticity, pain, comfort and sleep-related breathing disorders. Side effects will be monitored and we will study whether patient characteristics influence outcome.

Discussion The results of this study will provide data for evidence-based use of intrathecal baclofen in dystonic cerebral palsy.

Trial registration Nederlands Trial Register, NTR3642

Keywords Cerebral palsy, Dystonia, Dyskinesia, Goal attainment scaling, Intrathecal baclofen, Randomized controlled trial

BACKGROUND

Dystonic cerebral palsy

Cerebral palsy (CP) is a group of disorders caused by non-progressive disturbances that occurred in the developing fetal or early infant brain. The classification of cerebral palsy includes the classical neurological terms for central motor disorders: spasticity, dyskinesia and ataxia.[1,2] Dyskinesia can be further differentiated into dystonia and choreoathetosis.[2] Dystonia is described as an abnormal pattern of posture and/or movement that is involuntary, uncontrolled, recurring and occasionally stereotyped. These movements can interfere with daily care and may be painful and uncomfortable. The dyskinetic form of cerebral palsy, including the dystonic form, is in most patients caused by lesions in the basal ganglia. Additional lesions of the central cortex are found in some cases. This type of brain damage is a common pattern in asphyxiated infants born at term.[3]

Treatment

The results of pharmacological treatment of severe dystonic CP have been rather disappointing. Positive effects on dystonia with levodopa, anticholinergic drugs or muscle relaxants including benzodiazepines and baclofen, have been reported by some authors.[4,5] In addition, Albright and co-workers described an antidystonic effect of intrathecal baclofen (ITB) treatment. Despite the fact that studies on the effects of ITB on dystonic cerebral palsy are limited in number and the level of evidence is low, ITB is now common practice in the treatment of severe dystonic CP.

Not all patients are eligible for ITB treatment. The following criteria apply: 1. The etiology is preferably known; 2. Management of aggravating factors, such as pain and discomfort, should be optimal; 3. Other treatment options should have been explored. Oral pharmacological treatment with levodopa, anticholinergic drugs or muscle relaxants including benzodiazepines and baclofen must have been attempted and must have resulted in high oral dosages with either unacceptable side effects or insufficient efficacy; 4. The movement disorder should be so severe that it interferes with activities of daily life or quality of life; 5. Treatment goals should be clear and applicable and, to avoid disappointment, it is important that patients and parents understand these goals; 6. Patients and parents should be motivated and able to adhere to the requirements of treatment, such as the frequent pump fillings and checkups in the outpatient clinic; 7. Patients should have sufficient body size to allow pump implantation.[6]

Objectives

The primary objective of the present study is to show whether ITB treatment improves activities of and participation in daily life (for example dressing, transfer, sitting in a wheelchair, hygienic care, speech) in dystonic CP patients. Certain patient characteristics, such as the location and severity of MRI lesions and Gross Motor Functioning Classification Score (GMFCS) level, might influence the effects of ITB treatment in patients with dystonic CP. Therefore, we will study whether individual patient characteristics (GMFCS, gender, age, MRI findings and co-medication) influence outcome and could be used in determining the indication for ITB in future patients. A secondary objective is to provide evidence for the effect of ITB on the level of body functions. The relevant clinical questions to be addressed are: 1. Does ITB decrease dystonia? 2. Does ITB decrease spasticity in dystonic patients? 3. Does ITB decrease pain? 4. Does ITB increase comfort? 5. Does ITB influence screening results of sleep-related breathing disorders? 6. What are the side effects of ITB?

METHODS/DESIGN

Study design

The design of the study is a double blind placebo controlled multi-center randomized clinical trial. It will be conducted in the VU University Medical Center (VUMC) in Amsterdam and the Maastricht University Medical Center (MUMC) in Maastricht (both in the Netherlands). The Medical Ethical Committee of the VU University Medical Center approved the study. In both centers local practicability was granted subsequently. Subjects will be included over a period of two and a half years and they will participate in the study for one year. Figure 1 shows the flow scheme for subjects and timing of measurements throughout the study.

Participants

Thirty subjects will be recruited from the outpatient clinics of the pediatric neurology and pediatric rehabilitation departments of the VUMC and the MUMC. Table 1 shows the inclusion and exclusion criteria. We selected ages between 4 and 25 years old because older patients often show secondary complications, such as contractures, that could introduce greater variation into both the effects of treatment and treatment goals. Furthermore, to achieve a homogeneous patient group, only GMFCS IV and V (non-walkers) will be included. All patients and/or their caregivers will sign an informed consent form before participating in the study.

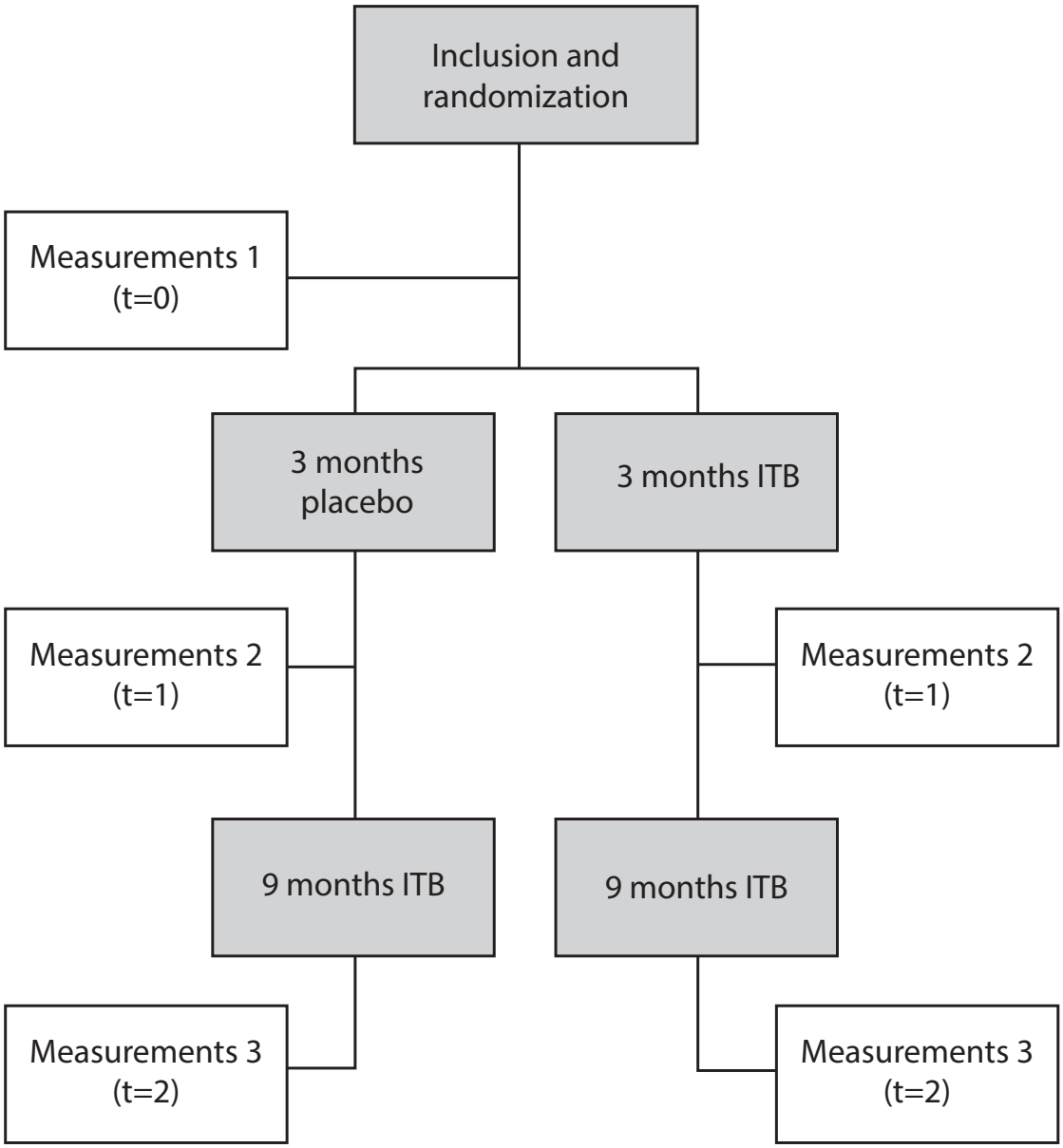


Figure 1. **Flow chart subjects**

Table 1. **Summary of inclusion and exclusion criteria**

Inclusion criteria	*Exclusion criteria*
• Dystonic cerebral palsy • GMFCS IV or V • Eligible for ITB treatment using criteria for common practice • Lesions on MRI (cerebral white matter, basal ganglia, central cortex) • Aged 4 to 25 years old • Able and willing to complete study protocol • Consensus about inclusion	• Contra-indications for general anesthesia • Contra-indications for baclofen • Oral pharmacological treatment is sufficient • Inadequate knowledge of Dutch language • Ventriculoperitoneal drain • Other disorders interfering with treatment

Sample size calculation

We will use goal attainment scaling (GAS) as our primary outcome measure. The within group change for the placebo group is anticipated to be 0, with a standard deviation (SD) of 8.5. For the intrathecal baclofen group, the within group change is anticipated to be 12.5, with a SD of 10. To achieve a power of 90% when testing for a difference in means using a two-tailed independent samples t-test and a significance level of 5%, a total of 13 subjects per group will be needed.

In a previous study in the VU University Medical Center, 4 infections occurred in 34 pump implantations[7]. Ward and coworkers reported pump removal in 5.9% of the cases with infections following implantation.[8] Extrapolating these numbers, inclusion of 30 patients is expected to lead to 3.5 infections and 1.2 pump removals. To prevent the study from becoming underpowered, due to unexpected protocol violations or subject dropout due to complications other than those related to intrathecal baclofen treatment, we will include 15 subjects per group.

Intervention

Included subjects will be randomized in two groups. Group 1 will receive placebo treatment via an implanted micro-infusion pump for three months. Group 2 will receive ITB treatment via an implanted micro-infusion pump for three months. In our opinion, it is unethical to continue placebo treatment for more than three months. If interim analysis shows that subjects in one of the groups have significant disadvantages compared to the other group, the study will be prematurely terminated. On the other hand, we know from experience that dosages for some patients are still being modified three months after starting treatment. As a consequence, the effect of treatment in these patients may not yet be optimal, which may then result in no detectable effect of ITB treatment at that point. We will try to reduce this possible effect through frequent dose modification. Patients will be seen once or twice weekly to increase their dosage, until either a stable dosage or a maximal dosage of 800 µg/day is achieved.

Subjects will be assessed at three months and the effect of treatment in the two groups compared. Since determining the most beneficial pump setting can take more than three months and because the initial effect may recede in some cases, all subjects will receive subsequent ITB treatment for nine months. Following this 9 month period, clinical evaluation will be performed in order to determine long-term effects (see Figure 1. Flow Chart of Subjects).

Dosage

Patients with dystonia seem to require larger ITB doses than the doses used to treat spasticity.[9] Albright and colleagues noticed a change in dystonia only after 4 days of continuous infusion.[10] The effective dose of ITB was in the range of 350 to 750 µg/day.[9-11] Since a screening period will not be included, we do not know how subjects will respond and which dose will be sufficiently effective. Therefore, the starting dosage will be 50 µg/24 h.

Dosage can be increased by 10-20% daily. When subjects are discharged from the hospital following pump implantation, they will be seen once a week or once every two weeks for dosage modification. After three weeks of increasing dosage, with disappearance of the effect of the increase, daily boluses will be administered to a maximum of four times a day, with a minimal interval of four hours. For the blinded part of the study, a maximum dosage of 800 µg/day will be administered. This is a reasonable estimation of the maximal dosage after three months. Since treatment during the study is blinded, the physician in charge of regular follow-up after pump implantation, including pump filling and dosage adjustments, will be unaware of the subject's allocated group. To provide optimal treatment, pump settings will be individually altered to the extent that the physician would consider necessary, based on the findings of physical examination and parental and patient interview, as were the patient not participating in the study. As a consequence, the pump settings of subjects in the placebo group will be altered as if the patient was receiving ITB treatment.

Lack of response to ITB can be caused by pump or catheter dysfunction. Placebo treatment may also cause lack of effect and for this reason no action will be taken during the first three months of the study in cases where pump or catheter dysfunction would normally be suspected. An exception will be made when the condition of the patient requires otherwise, such as in the case of signs of withdrawal. One week after pump implantation, all patients will undergo X-ray of the spine to determine the position of the catheter tip. The catheter should be placed approximately at the fourth cervical level, and at least above the level of Th1.

Outcome measures

Outcome measurements are defined on the levels of the International Classification of Functioning, Disability and Health (ICF) model of the World Health Organization (WHO). We distinguish the level of activities and participation and the level of body functions. Body functions are the physiological and psychological functions of body

systems. Activities are defined as the execution of a task or action by an individual. Participation is involvement in a life situation.[12]

Primary outcome measure

The primary outcome measurement will be on the level of activities and participation. Goal attainment scaling (GAS) will be used to measure the effect of ITB treatment. Using GAS, achievement of individual set goals can be quantified. This method was introduced for assessing outcomes in mental health settings and has been used in many other areas.[13,14] Each subject has their own outcome measure, but statistical analysis is possible because they are scored in a standardized way. This procedure is time-consuming and requires about 45 minutes per child.[15,16] However, after the scale is constructed, it should be possible to score a patient within 10 minutes.[17]

The procedure includes the following aspects:

1) Identification of goals

   Three main problems of daily care and function will be determined by caregivers. Goals will be set for these problems with the help of the team to ensure that goals are achievable. Goals should be specific, measurable, attainable, realistic and timely (SMART).[13,14] The target activity, specific support and time period should be specified and performance should be quantified using distance, frequency or time taken to accomplish a task.[14]

2) Weighing of goals:

   Some goals will be more important for subjects than others.[13] Goals can be assigned a weighing score by caregivers and a difficulty score by the team.[14] We chose not to assign weighing scores since the weighted and unweighted scores are closely correlated.[18] A value of 1 is applied to 'weight' in the formula described below.

3) Definition of expected outcomes:

   Several approaches are described in literature, varying from 5 to 7 point scales.[14,15] We will use a 6 point scale ranging from −3 to +2, since we wish to include both the possibility of partially achieving the set goal and to avoid a bottoming effect. Baseline scores will be allocated as −2. If the subject achieves the expected level, this is scored as 0. If a subject does not achieve the expected level but shows improvement, this is scored as −1. If they achieve more than the expected outcome, this is scored as +1 for somewhat more and +2 for much more. We chose to

add a score of −3 in case of deterioration. Each goal level will be defined by the investigator so as to be as objective and observable as possible.[13]

4) Scoring goal attainment:
For each assessment, one assessor will make a standardized video recording during trials for each of the three functional ability goals. The recording procedure will be identical for all measurements. Another assessor, blinded for group allocation, will rate the subject's performance from the video recordings. Although the GAS only simulates the subject's own functional setting, parents were convinced that the outcome of scaling was representative of their own setting.[19]

Goal attainment scores will be recorded at baseline, after three months of blinded treatment and after nine months of ITB treatment. Goal attainment change scores will be determined by subtracting the baseline score from the outcome score. Subjects who achieve a GAS T-score >50 achieved their goals.[8] Clinical relevance will be defined as an improvement of at least two points in at least one of the three goals.[19]

A single aggregated score (T-score) can be produced by a standardized mathematical formula: Overall GAS = 50+ $10\Sigma(w_i x_i) / \sqrt{((1-\rho) \Sigma w_i^2 + \rho(\Sigma w_i)^2)}$; W_i is the weight assigned to the goal, x_i is the numerical value achieved (between −3 and +2), ρ (rho) is the expected correlation of the goal scales, which is normally 0.3.[13,14]

Secondary outcome measures

Dystonia

Videos of all patients will be made using the video protocol described by Monbaliu et al.[20] Blinded therapists or physicians will assess all videotapes and rate dystonia using the Barry-Albright dystonia (BAD) scale and the Dyskinesia Impairment Scale (DIS).

The BAD scale is a five point ordinal severity scale to assess secondary dystonia in eight body regions (eyes, mouth, neck, trunk, each upper and lower extremity).[21] Raters score dystonia as none, slight, mild, moderate or severe. A reduction of 25% or more, in comparison with the baseline score, is considered clinically significant. In our experience, interrater variability is high, but BAD scores are generally accepted as a measurement of dystonia and are widely used to assess dystonia.

Recently, a new instrument to measure dystonia in dyskinetic CP became available, the DIS.[20] It consists of two subscales: dystonia and choreoathetosis. Scoring is carried out

in 12 body regions all in two conditions (rest and activity). Both duration and amplitude are evaluated. Since this is a new instrument, we will use the DIS in addition to the BAD.

Electromyography

The DIS has no external validation. We decided that Surface Electromyography (EMG) might provide an impression of muscle activity level underlying dystonia. Therefore, surface EMG measurements will be carried out to determine mean EMG activity in individually determined muscle groups and in multiple conditions such as rest and during activities.

Spasticity

The soleus Hoffmann-reflex (H-reflex) represents excitability of the neural components of the stretch reflex arc.[22] The H/M-ratio of the H-reflex represents an increased excitability of soleus motor neurons. The H/M-ratio is increased in subjects with spasticity due to various origins,[23] and it has been shown that the H_{max} decreases significantly after ITB administration in children with spastic cerebral palsy when compared with baseline measurements. This represents a decrease in motor neuron excitability. Furthermore, the response appears to be dose-dependent[22]. Although not all children tolerate the measurements, feasibility of the H-reflex was 93% in a study by Hoving and co-workers.[22]

For clinical assessment of spasticity in children with central motor disorders, the spasticity test (SPAT) is used during standard physical examination. When using the SPAT, we will follow a standardized protocol as described in the guideline for standard physical examination of children with central motor disorders.[24,25] The difference between the range of motion and the angle of catch will be used as the outcome measure for spasticity.[26] The test takes approximately 5 to 8 minutes per limb to perform.[25] This test might be difficult to perform in children and adolescents with severe dystonia and its usefulness will become evident during the study.

Pain and comfort

Parents will score pain and comfort on a visual analogue scale (VAS). The VAS is a straight 10 cm long horizontal block consisting of 10 smaller blocks with anchor points at 0 and 10. For pain, a score of 0 represents ‘no pain’ and a score of 10 represents ‘the worst possible pain’. For comfort, a score of 0 will represent being ‘very uncomfortable’ and a score of 10 is having ‘no problems at all’. If patients are able to indicate their mood, it will be scored by pointing out the applicable happy face, with choices of six faces ranging from very happy to very sad.

Sleep-related breathing disorders

Children with CP have a higher risk of sleep-related disorders than typically developing children.[27] Bensmail et al. showed that patients with severe spasticity due to spinal cord injury and multiple sclerosis, treated with ITB by bolus administration, showed an increased respiratory disturbance index (the number of apneas/hypopneas per hour of sleep).[28,29] Polysomnography is the gold standard when measuring sleep-related breathing disorders (SRBD). However, this time-consuming and burdensome diagnostic test is not practical for children participating in research.[30] A subscale of the Pediatric Sleep Questionnaire was developed to measure SRBD. This scale consists of 22 items and can be completed in five minutes. Sensitivity and specificity are high (81% and 87%). The scale is positive for a high risk of SRBD when there are 8 or more positive answers to the 22 question items (≥33%).[30] As the burden of a questionnaire is low for the patients and their families, as compared to polysomnography, we will use this questionnaire to determine if ITB changes the risk of SRBD.

Classification

For classification of the severity of motor abilities we will use the GMFCS [31,32] and the Manual Ability Classification System (MACS).[33,34] GMFCS and MACS classification will be scored at baseline, 3 months and at twelve months. In a study by Voorman and co-workers, 74% of children with CP had restrictions in communication [35]. Since many children with severe CP (GMFCS IV and V) cannot speak, assessment of language abilities cannot be based on speech production. In addition, language comprehension skills are difficult to assess in children with severe CP. Therefore, we will use the Computer-Based Instrument for Low motor Language Testing (C-BiLLT) to measure comprehension of spoken language at baseline. The validity of this instrument has been tested.[36] We do not expect changes in outcomes on the C-BiLLT with ITB treatment since comprehension of spoken language is highly correlated with cognition, and cognition is not effected by ITB treatment. We will use the outcome of the C-BiLLT as a patient characteristic.

Magnetic resonance imaging (MRI) will be used to classify the severity of damage to the gray matter structures (cortex and basal ganglia) and white matter (loss of white matter and gliosis). The severity of brain damage on MRI can be classified in three groups; mild, moderate and severe. The mild pattern includes involvement of nucleus lentiformis and ventro-lateral thalamus, the moderate pattern includes additional involvement of the peri-central region and the severe pattern includes additional involvement of the entire thalamus and hippocampus. In the mild and moderate damage groups, infants suffer from the dyskinetic form of cerebral palsy, whereas the severe type of damage frequently produces purely spastic paresis.[3] MRI studies of the brain are necessary to

confirm the diagnosis of cerebral palsy. If MRI studies have been conducted previously, these studies will be critically assessed. If the quality is good, the MRI will be accepted and no further imaging is needed. If the quality of the MRI images is poor, the patient will undergo a new MRI including diffusion tensor imaging (DTI). If a patient had not yet undergone a MRI, one will be made including DTI. Adding DTI images to a regular MRI scan will require an extra scanning time of approximately four minutes. In this patient category MRI imaging has to be done under general anesthesia, since dystonic movements interfere with MRI quality.

Other study parameters

To assess the safety of ITB treatment, side effects and complications will be closely monitored. The complication rate will be calculated by dividing the number of complications by the duration in years of pump implantation.

Functional abilities at baseline will be assessed by the Paediatric Evaluation of Disability Inventory (PEDI) and will be repeated after three and twelve months. The PEDI was developed for children from six months to seven and a half years of age and assesses skills in mobility, self-care and social function. It can also be used for older children if their functional abilities are expected to be below the level of a child of seven and a half years old. The functional scales indicate if children with disability are able or unable to perform certain activities. Separate measures assess the degree of caregiving assistance and equipment modification that is needed to accomplish complex functional skills. Scores on the caregiver assistance scale are noted on a range from independent to maximal assistance and modification scores are scored as none, child-oriented, rehabilitation-oriented or extensive.[37,38] The PEDI will be administered through direct assessment by a therapist.

Randomization, blinding and treatment allocation

Subjects will be randomized in two groups by block randomization. Randomization will be done by the pharmacies of the VUMC and the MUMC. The pharmacist will be the only holder of the code for randomization. In case of emergency, the code will be accessible 24 hours per day and 7 days per week via either the pharmacist of the VUMC or MUMC or by opening a sealed envelope containing the subject's group, available at the departments concerned. Allocation will be concealed, and the researchers, assessors and the physician responsible for pump filling will be blinded.

Premature termination

Withdrawal of individual subjects

Subjects can end participation in the study at any time without providing a reason and without consequences for their future treatment in the clinic. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Subjects withdrawn from the study will continue their regular follow-up outside of the study protocol. Subjects will be replaced if they withdraw before pump implantation has taken place. Subjects who withdraw after pump implantation has taken place will not be replaced. With subject agreement, a final assessment will take place before definite ending of participation. These subjects will not be included in the analysis but we will present a fact sheet including their information.

Data safety monitoring board

A data safety monitoring board will be formed and will meet periodically to review aggregate and individual subject data related to safety, data integrity and overall conduct of the trial. They will assess the risk/benefit balance, including a statistical analysis if necessary. Depending upon this assessment, the board will provide recommendations to continue, adapt or terminate the trial.

Statistics

Descriptive statistics

Patient characteristics will be described. Gender distribution will be compared between the ITB and placebo group using a Chi-square test. Mean age between the ITB and placebo group will be compared using an independent samples t-test. Means and standard deviation (SD) of the PEDI scores, C-BiLLT scores, GAS t-score, BAD score, SPAT score and mean EMG activity at baseline will be tabulated. Means and SD of the GAS t-score, BAD score, DIS score, SPAT score and mean EMG activity at follow up will be separately tabulated per group.

Univariate analysis

The GAS t-scores, BAD score, SPAT score and EMG activity in the placebo and ITB group will be compared using an independent samples t-test. If the assumption of normality appears not to be valid, the non-parametric Mann–Whitney test will instead be used. A p-value of 0.05 is considered statistically significant for this primary analysis. To assess within-group changes in means between follow-up times and baseline GAS t-scores, BAD score, DIS score, SPAT score and EMG activity, a paired t-test or non-parametric Wilcoxon test will be used (depending on whether the normality assumption is valid). In these analyses, a p-value of 0.05 is considered to be statistically significant.

Multivariate analysis

A multivariate analysis will be used to determine the effect of ITB treatment (primary: functional outcome; secondary: dystonia and the interaction with GMFCS, MACS, MRI classification and use of co-medication).

DISCUSSION

We anticipate that the results of this study will allow evidence-based use of intrathecal baclofen in dystonic cerebral palsy.

ABBREVIATIONS

CP: Cerebral palsy; GMFCS: Gross motor functioning classification system; VUMC: VU University medical center; MACS: Manual ability classification System; EMG: Electromyography; MUMC: Maastricht University medical center; ITB: Intrathecal baclofen; MRI: Magnetic resonance imaging; SD: Standard deviation; PEDI: Pediatric evaluation of disability inventory; RM: Repetitive movements; GAS: Goal attainment scaling; BAD: Barry Albright dystonia scale; DIS: Dyskinesia impairment scale; C-BiLLT: Computer based instrument for low motor language testing; dti: Diffusion tensor imaging; VAS: Visual analogue scale; ICF: International classification of functioning, disability and health.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Phelps Stichting voor Spastici (nr 2011037), the Johanna KinderFonds and the Kinderrevalidatie Fonds de Adriaan Stichting (both nr 2011/0035) and the RevalidatieFonds (nr R2011032) for funding of this project.

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CHAPTER 5

The effect of intrathecal baclofen in dyskinetic cerebral palsy: the IDYS trial

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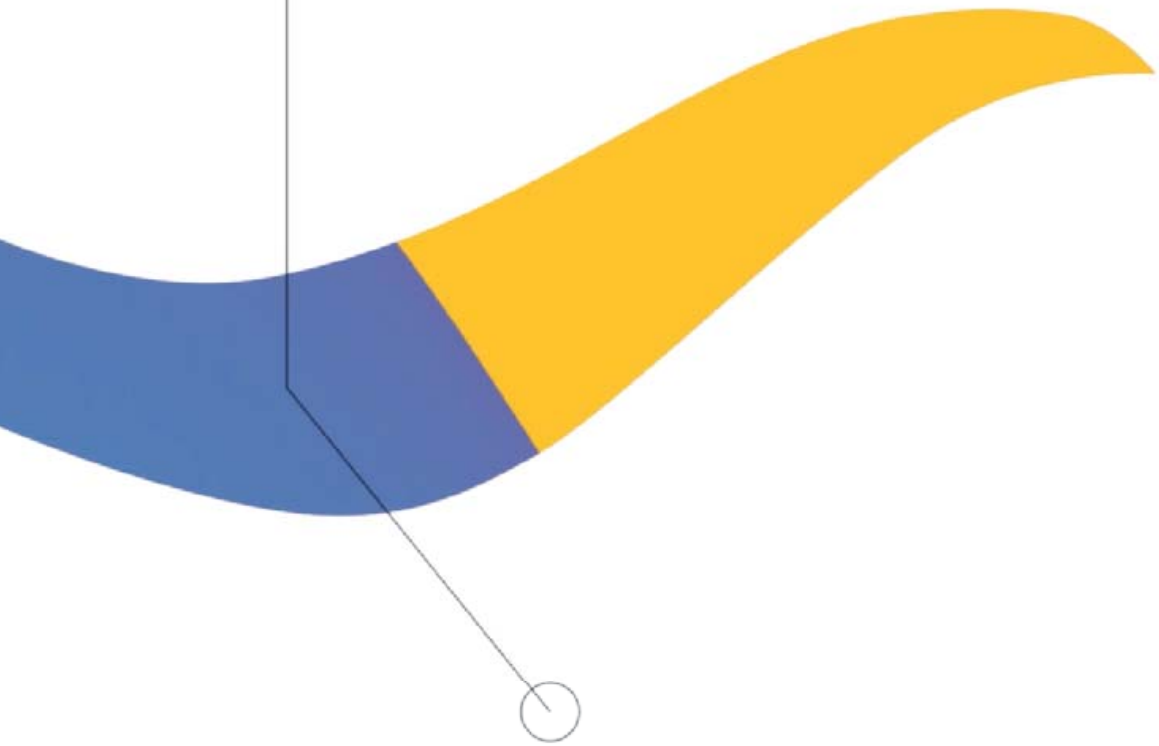
Ann Neurol 2019; epub ahead of print



ABSTRACT

Objective Intrathecal baclofen treatment is used for the treatment of dystonia in patients with severe dyskinetic cerebral palsy, however, the current level of evidence for the effect is low. The primary aim of this study was to provide evidence for the effect of intrathecal baclofen treatment on individual goals in patients with severe dyskinetic cerebral palsy.

Methods This multi-centre, randomized, double-blind, placebo-controlled trial was performed at two University Medical Centres in the Netherlands. Patients with severe dyskinetic cerebral palsy (Gross Motor Functioning Classification System level IV-V), aged 4 to 24, eligible for intrathecal baclofen, were included. Patients were assigned by block randomization (2:2) for treatment with intrathecal baclofen or placebo during three months via an implanted micro-infusion pump. The primary outcome was Goal Attainment Scaling of individual treatment goals (GAS T-score). A linear regression model was used for statistical analysis with study site as a covariate. Safety analyses were done for number and type of (serious) adverse events.

Results Thirty-six patients were recruited from January 1st 2013 to March 31st 2018. Data for final analysis were available for 17 in the intrathecal baclofen group and 16 patients in the placebo group. Mean (SD) GAS T-score at three months was 38.9 (13.2) for intrathecal baclofen and 21.0 (4.6) for placebo (regression coefficient 17.8, 95% CI 10.4 to 25.0, $p<0.001$). Number and types of (serious) adverse events were similar between groups.

Interpretation Intrathecal baclofen treatment is superior to placebo in achieving treatment goals in patients with severe dyskinetic cerebral palsy.

INTRODUCTION

Cerebral palsy (CP) is defined as a group of developmental disorders of movement and posture, attributed to non-progressive disturbances that have occurred in the developing fetal or infant brain. Motor impairments are often accompanied by non-motor symptoms such epilepsy, secondary musculoskeletal problems, and disturbances of sensation, perception, cognition, communication, and/or behaviour.[1] The reported prevalence is 2.11/1000 live births (95% confidence interval (CI) 1.98 to 2.25) in high income countries, and 2.9 to 3.7 /1000 live births in low income countries.[2-4] Based on the predominant motor disorder, CP is classified in three types: spastic, dyskinetic, and ataxic. After spastic CP (80%), dyskinetic CP is the second most common type of CP.[1]

Dyskinesia is the predominant motor disorder in 9-15% of CP patients.[2,4] It is characterised by involuntary, uncontrolled, recurring, occasionally stereotyped movements with fluctuating muscle tone.[5] Dyskinesia is subdivided into dystonia and choreo-athetosis. Dystonia is characterised by slow involuntary movements, distorted voluntary movements and abnormal postures due to sustained or intermittent muscle contractions. Tone is fluctuating but easily increased (hypertonia).[5] Choreo-athetosis is featured by fast hyperkinetic movements and tone fluctuation (mainly hypotonia).[5]

The majority of dyskinetic CP patients are severely affected and classified in Gross Motor Functioning Classification System (GMFCS) levels IV and V. These GMFCS levels correspond with having no walking ability.[6] Dystonia and choreo-athetosis are frequently present simultaneously in dyskinetic CP but dystonia is usually more prominent.[6] Most treatment options for dyskinetic CP are aimed at decreasing dystonia.[6]

When efficacy of oral medication is insufficient, options requiring neurosurgical intervention such as intrathecal baclofen (ITB) treatment or deep brain stimulation (DBS) are the next step in treatment of dyskinetic CP.[6,7] DBS is effective in primary dystonia but results in dyskinetic CP have been conflicting.[6,7] While there is some evidence for the effectiveness of ITB in reducing spasticity in CP, mainly from short term single bolus trial studies, to date, there are only low quality, non-controlled studies, producing low-level evidence for ITB in the reduction of dystonia.[7,8] Most dyskinetic CP patients for whom ITB is considered aim to gain improvement of dressing, positioning, transfers, pain, and comfort.[9] There is currently inadequate evidence for the effect of ITB in dyskinetic CP on achievement of individual goals related to quality of life, activities of daily life and participation.[7]

The primary aim of this study is to provide evidence for the effect of ITB on individual treatment goals in patients with severe dyskinetic CP. Secondary aims are to address the effect on dystonia, spasticity, range of motion, pain, comfort, and treatment related complications.

METHODS

Study design

We conducted a multi-centre, randomized, double-blind, placebo-controlled trial at the Amsterdam UMC, location VU University Medical Center (VUMC), Amsterdam, and the Maastricht University Medical Center (MUMC), Maastricht, the Netherlands. The study was approved by institutional review boards at both sites and by the Medical Ethical Review Committee (MERC) of the VU University. The study protocol was previously published and provides additional information about the methods employed.[10] This trial is registered with the Dutch Trial Register, number NTR3642.

Participants

Participants were recruited from the paediatric rehabilitation and/or child neurology outpatient clinic at both sites. In- and exclusion criteria are summarized in table 1. Patients and/or parents/legal guardians gave written informed consent. Measurements were discontinued at signs of discomfort due to the measurements.

At the start of the study in January 2013, participation in the study was with the result that not all eligible patients were included in the trial, though received ITB treatment. The Data Safety Monitoring Board (DSMB) advised the MERC that the study involved an experimental pharmaceutical therapy, since the effect of ITB in dyskinetic CP patients was not conclusively established. The MERC decided that from December 2014, ITB treatment for dyskinetic CP patients could only be provided in the study context, by which all eligible patients were automatically included in the trail, and ITB was not offered as regular treatment.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Dyskinetic cerebral palsy • GMFCS IV or V (wheelchair users) • Lesions on MRI (cerebral white matter, basal ganglia, central cortex) • Aged 4 to 25 years old • Eligible for ITB treatment using criteria of common practice: o Preferably known etiology o Optimal management of aggravating factors (e.g. pain) o Insufficient effect of oral treatment or unacceptable side effects o Dyskinesia interferes with activities of daily life or quality of life o Treatment goals are clear and applicable o Patients and parents are sufficiently motivated to adhere to requirements of treatment o Patients have sufficient body size to allow pump implantation • Able and willing to complete study protocol • Consensus about inclusion	• Contra-indications for general anesthesia • Contra-indications for baclofen • Oral pharmacological treatment is sufficient • Inadequate knowledge of Dutch language • Deep brain stimulation • Ventriculoperitoneal drain • Other disorders interfering with treatment

GMFCS=gross motor functioning classification system. ITB=intrathecal baclofen treatment. MRI=magnetic resonance imaging.

Randomization and masking

Patients were assigned by block randomization (2:2) to receive either ITB or intrathecal placebo via an implanted micro-infusion pump (Medtronic Synchromed® II pump, Minneapolis, MN, USA). Randomization was stratified by study site. The last four patients combined from both sites were randomized in one block to assure even groups. All but the pharmacist preparing the study medication were masked for group allocation. A list of group allocation was stored at the pharmacy. Closed envelopes were provided for the study staff to be used for unmasking in case of emergency and after final measurements. Outcome assessors remained masked until after statistical analysis was completed.

Procedures

The pump was implanted in a subfascial or subcutaneous pocket in the lower abdomen depending on local routines and patient characteristics (mostly nutritional status). Considering previous clinical observations suggesting that the site of action for ITB in dyskinetic CP is intracranial,[11] the catheter tip was aimed to be placed at the mid cervical level (C4). Best practice surgical techniques were applied, including techniques to

minimize complications such as cerebrospinal fluid (CSF) leakage (48 hours of horizontal bed rest, pressure bandage post-surgery) and infection (pre-operative washing with anti-bacterial soap (until 2017) and from 2018 impregnation/bathing of pump, catheter and pocket with vancomycin, combined with 24 hours intravenous cephazolin starting 30 minutes before first skin incision).[12,13]

During three months after pump implantation the placebo group received Sodium Chloride (0.9%), and the ITB group received baclofen in the intrathecal pump system. Patients were instructed to continue taking their regular oral medication influencing muscle tone, such as baclofen or trihexyphenidyl, at the pre-operative dose during the whole study.

The starting dose of intrathecal treatment was 50µg/24h for all patients. Dose increments were applied by the treating physician, who were not study assessors, guided by a dosing schedule developed for the study and based on clinical experience (table 2, figures 1 and 2). Dose was increased at least ten times, except if the effect was deemed satisfactory earlier and personal goals were achieved at a fewer number of increments.

Measurements were performed prior to pump implantation and three months after. Unmasking was done by the treating physician right after finalization of the three-month measurements.

Table 2. IDYS trial dosing schedule for ITB in dyskinetic cerebral palsy

Phase of dose finding	8 years and older (figure 3)	7 years and younger (figure 4)
1. Start treatment at simple continuous mode at 50µg/day	• No effect: raise with 20% • Some effect: raise with 10%	• No effect: raise with 10% • Some effect: raise with 5%
2. Starting to notice effect	• When improvement continuous > 2 weeks after a 10% raise in dosage, gradually raise dosage further by 10% steps in simple continuous mode • When after a few days the effect disappears, raise dosage, 1-2 weeks after last alteration, with 10% (repeat 3 times when needed) • When the effect persistently decreases or disappears within 2 weeks of last alteration: start bolus 1 hour before awakening, 15% of the daily dose	• When improvement continuous > 2 weeks after a 5% raise in dosage, gradually raise dosage further by 5% steps in simple continuous mode • When after a few days the effect disappears, raise dosage, 1-2 weeks after last alteration, with 5% (repeat 3 times when needed) • When the effect persistently decreases or disappears within 2 weeks of last alteration: start bolus 1 hour before awakening, 10% of the daily dose
3. Bolus added	• Continue to raise bolus with 10% until hypotonia at awakening • Ask when the effect starts to decrease during the day • Add a 2nd bolus of 15% 1 hour before the effect of the bolus decreases • More boluses can be added to a maximum of 4 boluses per day	• Continue to raise bolus with 10% until hypotonia at awakening • Ask when the effect starts to decrease during the day • Add a 2nd bolus of 10% 1 hour before the effect of the bolus decreases • More boluses can be added to a maximum of 4 boluses per day

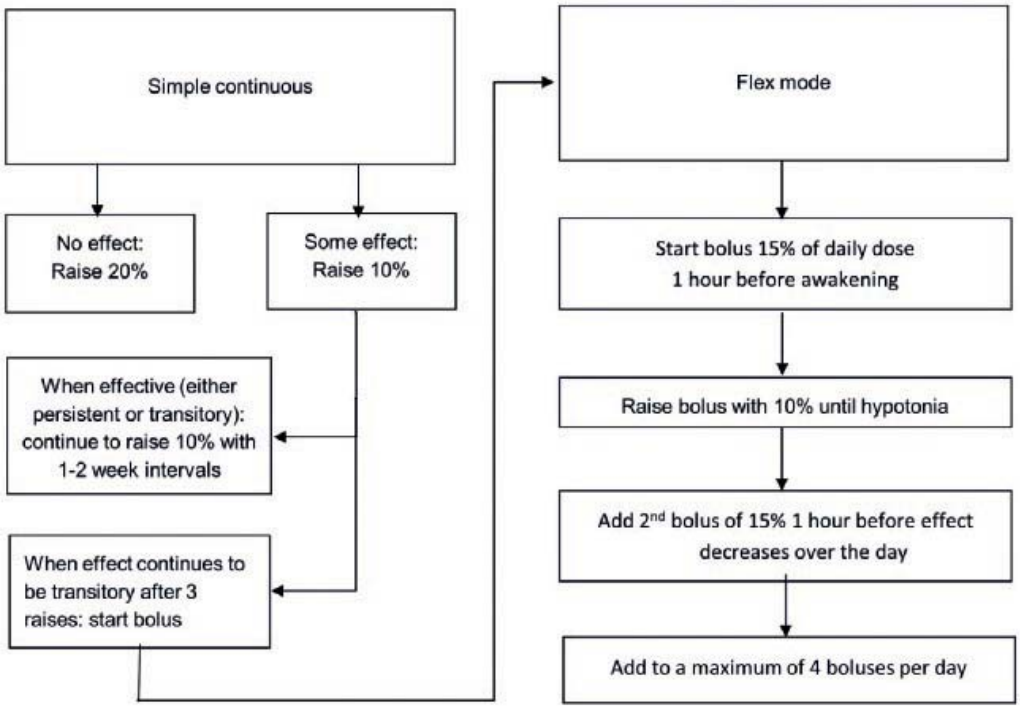


Figure 1. **Dosing Schedule for age 8 years and older**

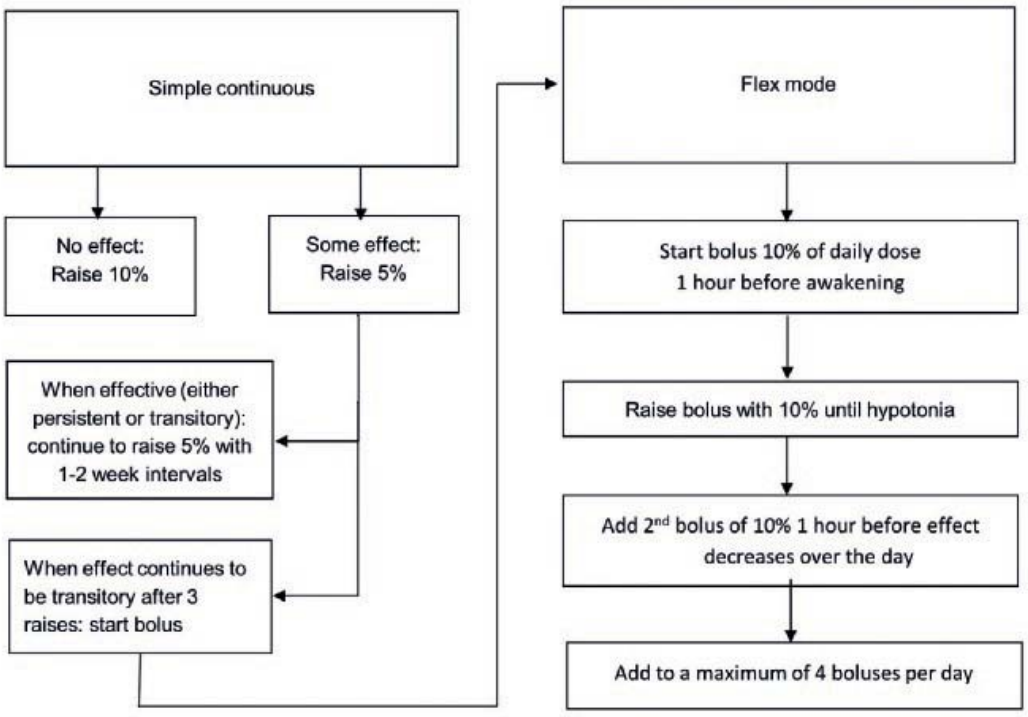


Figure 2. **Dosing schedule for age 7 years and younger**

Outcomes

The following patient characteristics were registered: age, sex, GMFCS level, Manual Ability Classification System (MACS) level, level of comprehension of spoken language (determined with the Computer Based instrument for Low motor Language Testing (C-BiLLT),[14] and brain Magnetic Resonance Imaging (MRI) classification.[10] Treatment characteristics registered were catheter tip position and dosage after three months.

The primary outcome measure, achievement of individual goals, was assessed with Goal Attainment Scaling (GAS).[10] Before pump implantation, individual goals were identified by questioning parents and patients. The current situation and the desired outcome for two to three goals were determined and used to extrapolate all other possible outcomes on the GAS scale. An example of a GAS scale is given in table 3. At follow up after three months, goal attainment was assessed, by the same blinded assessor, questioning parents and patients about the current situation of the previously set goals. The outcome was scored for each separate goal. From these separate scores, a single aggregated T-score was produced using a standardized mathematic formula.[10] Subjects who attain a GAS T-score ≥50 achieved their goals.[10] Furthermore, the number of achieved and partially achieved goals was assessed. Clinical relevance was defined as achievement of at least one goal.[4]

Treatment goals were classified in the domains defined by the International Classification of Functioning, disability and health - Children and Youth version (ICF-CY), developed by the World Health Organization (WHO): body functions and structures, activities and participation, and environmental factors.[15]

Secondary outcome measures were assessed both at baseline and at three months after pump implantation.

Dyskinesia was measured using the Barry-Albright dystonia scale (BADS) and Dyskinesia Impairment Scale (DIS). The BADS measures dystonia in different body regions and provides a total dystonia score (range 0-32). A difference of ≥25% compared to baseline values, has been described to be clinically significant.[10] The DIS measures both dystonia and choreo-athetosis during rest and activities. A total DIS score and subscores for dystonia and choreo-athetosis (total, rest, action) can be computed (range 0-100%).[16] It is not known what the clinically significant cut-off values for the DIS (sub)scores are. There are no test-retest reliability studies or data on responsiveness for either measure.[17] All of our assessors were trained to distinguish dystonia and choreo-athetosis. Studies show moderate interrater reliability.[17] Surface electromyography

was initially performed with the aim to quantify dystonia by recording activation of individual muscles,[10] but was discontinued after interim evaluation. Technical issues made reliable assessment difficult, and measurements appeared to be stressful for patients.

Spasticity was assessed clinically and electrophysiologically. The spasticity test (SPAT) was used to assess spasticity clinically in hip adductors, knee flexors and extensors, ankle plantar flexors, elbow extensors and flexors.[10] With the SPAT, spasticity is elicited by a passive stretch of the muscle with fast velocity, and scored present when a catch is felt by the examiner. The H/M ratio of the soleus Hoffmann-reflex (H-reflex) was determined, representing the spinal cord neuronal response to an afferent electric stimulus.[10,18]

The degrees of passive range of motion (ROM) were measured for hip abduction, knee flexion, popliteal angle, ankle dorsiflexion (with flexed and extended knee), elbow flexion and elbow extension.[10]

Pain and comfort were scored by parents, using a visual analogue scale (VAS) with scores ranging from 0 to 10. For pain, a score of 0 corresponded with 'no pain' and 10 with 'unsustainable pain'. For comfort, a score of 0 corresponded with 'very uncomfortable' and 10 with 'no discomfort'. If possible, children scored their level of comfort using a faces pain scale corresponding with scores from 0 to 6.[10]

The Pediatric Evaluation of Disability Inventory (PEDI) questionnaire was used to assess skills in mobility, self-care and social function.[10,19]

Participants were asked about their thoughts about group allocation after the measurements, right before unmasking (ITB/placebo/don't know).

All (Serious) Adverse Events (S)(AE)s were assessed. SAEs were submitted to an online research database (toetsingonline.nl), automatically informing the MERC. We furthermore evaluated the change in symptoms related to sleep related breathing disorders (SRBD) using a specific subscale of the Pediatric Sleep Questionnaire [10,20]

Statistical analysis

Sample size was calculated on the basis of the primary outcome measure, the difference in GAS T-score between the placebo and ITB group after three months.[10] It was hypothesized that the ITB group would attain a GAS T-score of 50, whereas the score

for the placebo group would not differ from baseline (GAS T-score 22.7). To guarantee a statistical power of 90% at a significance level of 5%, a total of 13 patients per group was needed. Because several complications occurred during the study, inclusion was expanded to 18 patients per group to prevent the study from becoming underpowered.

Baseline data were described with summary statistics. For normally distributed outcome data, linear regression methods were used to compare groups. Baseline values (only applicable for secondary outcome measures) and study site were included as covariates. Where normal distribution was not found, nonparametric methods (Mann-Whitney U test) were used. Safety analysis for number and type of (S)AEs were performed with Pearson Chi Square Test or Mann-Whitney U test. All statistical analyses were performed before group allocation was revealed. Data were analyzed using IBM© SPSS© Statistics Version 22. GAS T-scores and (S)AEs were regularly monitored during the study by an independent DSMB.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the article. The corresponding author had full access to all study data and all main authors (LB, JB, JV, RJV, AB) had final responsibility for the decision to submit for publication.

RESULTS

From January 1st, 2013 to March 31st, 2018, a total of 36 patients (30 in Amsterdam UMC, 6 in MUMC) were randomized over the two groups providing 18 patients per group. The trial profile is presented in figure 3. One patient was unmasked before the end of the study period during presentation at the emergency room because of swelling over the pump, possibly due to liquor leakage, 10 days post implantation. Since knowledge on group allocation could influence outcome, GAS, pain and comfort scores were not rated for this patient and therefore were not included in the final analysis. For this patient, all other outcome measures were assessed by a still masked assessor and used for analysis. Brain MRI was available for all patients at the moment of inclusion but for two patients imaging was not present for scoring due to technical problems. Two patients (one in each group) did not tolerate the H-reflex and this measurement was not repeated at their follow up. The catheter tip was placed at a lower level than the aimed C4 due to technical surgical issues in two patients in the ITB group, and four patients in the placebo group.

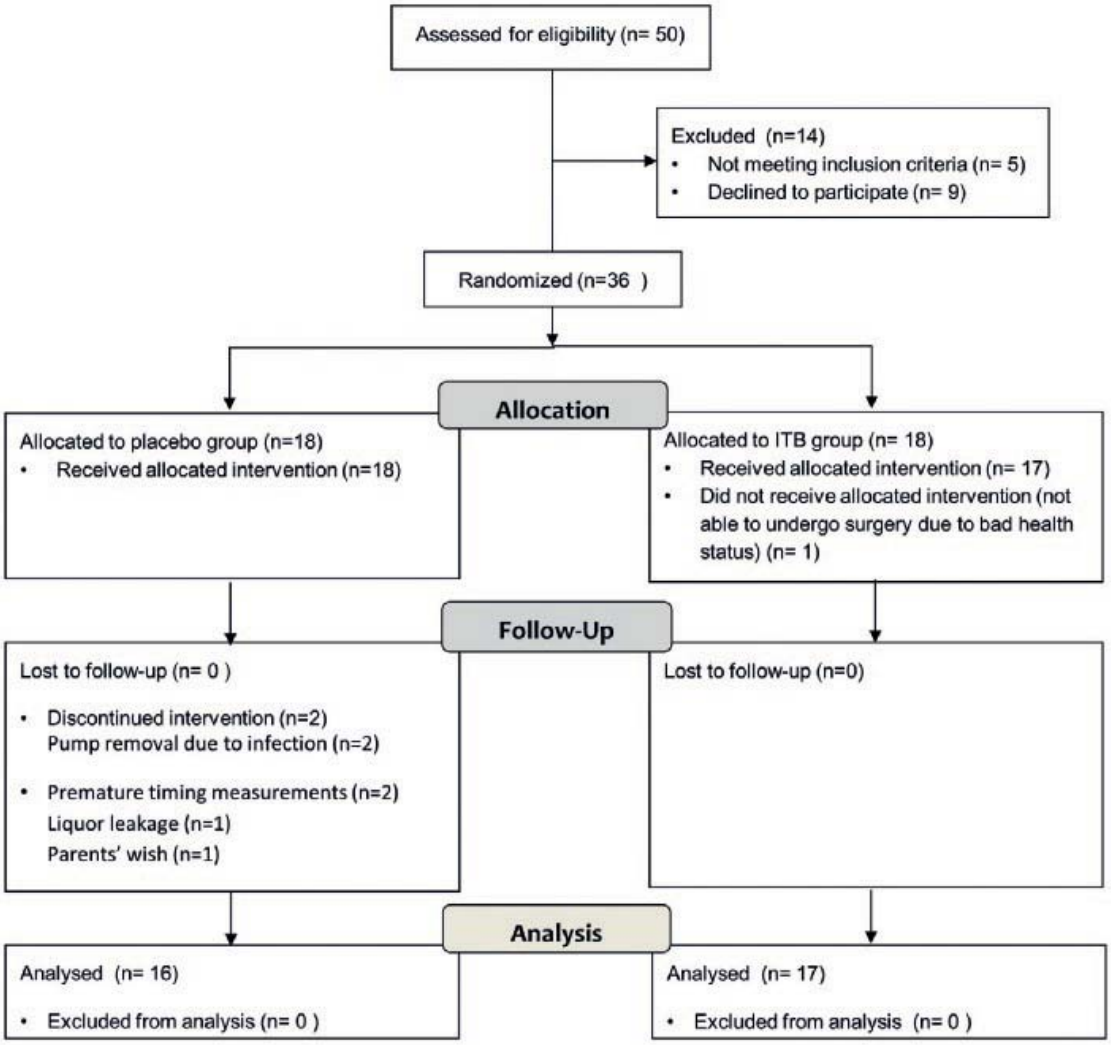


Figure 3. **Trial profile**

Patient characteristics were similar across groups (table 4). Treatment characteristics were similar across groups, except for a significant difference between groups in usage of bolus dosing (p=0.02). Bolus dosing was more frequently applied in ITB (59%) compared to placebo (6%). Mean dosage after three months was 179 µg/24h (SD 206, range 80-966 µg) for ITB compared to 170 µg/24h (SD 70, range 55 to 300 µg) for placebo (p =0.24).

Table 4. Baseline characteristics of the intrathecal baclofen treatment and placebo group

		ITB group (n=18)	Placebo group (n=18)
Sex	Male	13 (72%)	12 (67%)
	Female	5 (28%)	6 (33%)
Age (years)		13·8 (4·3)	14·7 (4·3)
GMFCS	IV	8 (44%)	5 (28%)
	V	10 (56%)	13 (72%)
MACS	III	2 (11%)	1(5%)
	IV	4 (22%)	5 (28%)
	V	12 (67%)	12 (67%)
C-BiLLT [a]		65 (16)[c]	64 (25)[d]
Catheter tip [b]	Th3 or higher	15 (88%)	13 (72%)
	Th4 or lower	2 (12%)	5 (28%)
MRI pattern [a]	Basal ganglia / thalamic lesions	12 (70%)	10 (59%)
	Kernicterus/ globus pallidus	2 (12%)	2 (12%)
	Multicystic encephalomalacia	0 (0%)	1 (6%)
	Periventricular leukomalacia	3 (18%)	4 (23%)

Data are presented as number (%), or as mean (SD). ITB=intrathecal baclofen. n=number. GMFCS=Gross Motor Functioning Classification System. MACS=Manual Ability Classification System. C-BiLLT=Computer Based instrument for Low Motor Language Testing. Th=thorecal. [a]Data not available for all randomized patients. [b]Data available for all implanted pumps. [c]Age equivalent of 53 to 55 months. [d]Age equivalent of 50 to 52 months.

AS T-scores at three months were significantly different between groups in favor of ITB (Regression Coefficient (RC) 17.8, 95%CI 10.4 to 25.0, Effect size (Beta) 0.672, p<0.001) (table 5). Significant differences were found between groups for percentages of number of goals achieved (figure 4A, p=0.005) and partially achieved (figure 4B, p<0.001). In the ITB group 59% achieved at least one goal, which was considered to be clinically relevant, compared to 13% in the placebo group. Number needed to treat to achieve at least one goal is 2.2. Age and sex as confounders, did not influence the effect. The type of treatment goals was similar in both groups (table 6).

Table 5. Differences in outcomes between intrathecal baclofen treatment and placebo group

			ITB group (n=17)		Placebo group (n=16)		RC (95%CI)	Effect size (Beta)	p value
			Baseline	3 months	Baseline	3 months			
Primary outcome									
GAS T-score [a]			n.a.	38·9 (13·2)	n.a.	21·0 (4·6)	17·8 (10·4 to 25·0)	0·672	^^0·00
Secondary outcomes									
DIS	Total		43% (9%)	40% (10%)	41% (13%)	45% (11%)	-6% (-12% to 0%)	-0·28	^^0·045
	Dystonia	Total	67% (11%)	64% (15%)	66% (18%)	72% (11%)	-8% (-14% to -2%)	-0·29	^^0·017
		Rest	58% (16%)	55% (23%)	59% (22%)	68% (12%)	-12% (-22% to -2%)	-0·32	^^0·013
		Activity	73% (12%)	70% (14%)	72% (15%)	75% (12%)	-5% (-13% to 3%)	-0·20	^^0·19
	Choreo-athetosis		19% (15%)	15% (13%)	15% (17%)	17% (20%)			+0·83
BADS			20·6 (8·9)	19·1 (5·9)	19·9 (7·5)	20·4 (4·4)	-1·50 (-4·9 to 1·9)	-0·146	^^0·38

Data are presented as mean (SD). Not all patients were able to perform all items of the DIS standardized video-protocol. When at one measurement moment an item could not be scored, this item was excluded from analysis. ITB=intrathecal baclofen. n=number. RC=Regression Coefficient. CI=confidence interval. GAS=goal attainment scaling. n.a.=not applicable. DIS= Dyskinesia Impairment Scale. BADS=Barry Albright Dystonia Scale. [a]Data not available for all patients. ^^Linear regression analysis +Mann Whitney U test.

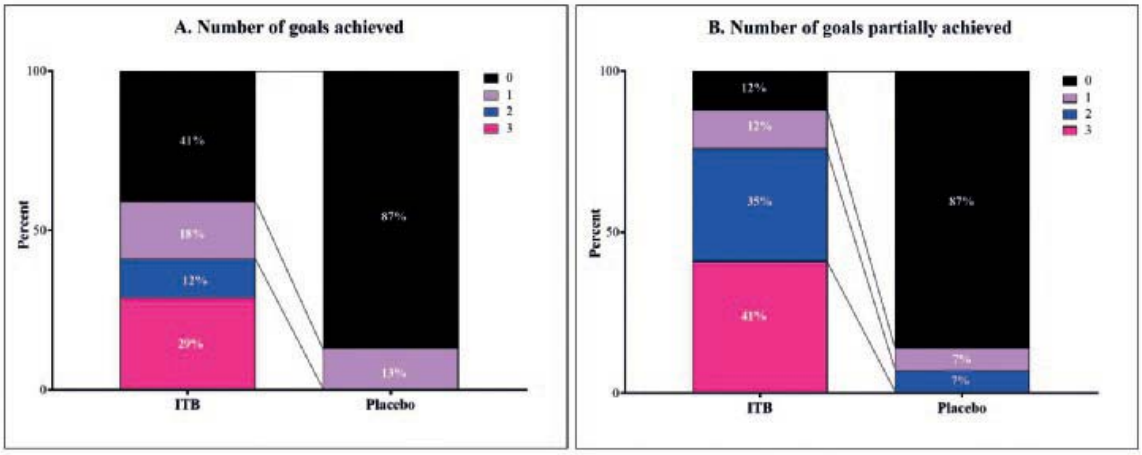


Figure 4. A. Differences in percentage of GAS goals achieved; B. Differences in percentage of GAS goals partially achieved for intrathecal baclofen treatment (ITB) and placebo group
ITB=intrathecal baclofen. 4A, p=0·005. 4B, p<0·001. The percentage of patients (partially) achieving zero, one, two or three goals is shown for the ITB and placebo group.

Table 5 shows the results for DIS and BADS (sub)scores. At three months, no significant difference between groups was seen for the BADS. The total DIS (RC -6%, ES -0.28, p=0.045), DIS dystonia subscale (RC -8%, ES -0.29, p=0.017) and dystonia during rest subscale (RC -12%, ES -0.32, p=0.013) were significantly more favorable with ITB.

There was no significant correlation between DIS (sub)score(s) and GAS T-scores, and between changes (pre-post) in DIS (sub)score(s) and GAS T-scores.

There were no significant differences between groups for any of the other secondary outcome measures, neither in the domain of body functions and structures (spasticity, pain, comfort) nor in the domain of activities and participation (PEDI). Parents' thoughts on group allocation were correct for most patients in both groups (ITB 76%, placebo 87%).

There were a total of 23 AEs and 6 SAE's in 22 patients. There was no significant difference between groups for total number or type of (S)AEs (table 7). There was also no significant difference between groups for the change in parent reported symptoms related to SRBD.

Table 6. Treatment goals

ICF-CY level Goal	Total	ITB group (n=18)		Placebo group (n=18)		p-value
	Total/ evaluated nr of goals	Total/ evaluated nr of goals	Nr (partially) achieved goals	Total/ evaluated Nr of goals	Nr (partially) achieved goals	
Body functions and structures						
	16/14	6/6	5 (83%)	10/8	1 (13%)	p=0·01[+]
Sleep	5/5	1/1	1 (100%)	4/4	1 (25%)	
Pain/comfort	7/6	4/4	3 (75%)	3/2	0 (0%)	
Alertness	2/1	0	n.a.	2/1	0 (0%)	
Weight	1/1	1/1	1 (100%)	0	n.a.	
Wearing AFO	1/1	0	n.a.	1/1	0 (0%)	
Activities and participation						
Communication	6/6	2/2	0 (0%)	4/4	1 (25%)	n.a.
Using communication device	6/6	2/2	0 (0%)	4/4	1 (25%)	
Mobility	36/32	18/18	12 (67%)	18/14	1 (7%)	p=0·001[+]
Changing position	5/5	3/3	2 (67%)	2/2	0 (0%)	
Sitting	8/5	3/3	3 (100%)	5/2	0 (0%)	
Moving around	11/11	7/7	5 (71%)	4/4	0 (0%)	
Hand and arm use	12/11	5/5	2 (40%)	7/6	1 (17%)	
Environmental factors						
Care giving by others	46/41	26/23	18 (78%)	20/18	0 (0%)	p<0·001[+]
Dressing	28/25	14/12	9 (75%)	14/13	0 (0%)	
General care giving	1/0	0	n.a.	1/0	n.a.	
Washing	4/4	4/4	3 (75%)	0	n.a.	
Hygienic care	13/12	8/7	6 (86%)	5/5	0 (0%)	
Total	104/93	52/49	35 (71%)	52/44	3 (7%)	

Data are presented as number, or number (%). ICF-CY=International Classification of Functioning, disability and health – Children and Youth version. ITB= intrathecal baclofen. n=number. AFO=ankle foot orthosis. n.a.=not applicable. [+]comparison of number of partially achieved goals between groups with Mann-Whitney U Test.

Table 7. **Adverse events**

			ITB group	Placebo group	P-value
Number of (S)AE		Total	16	13	+1·00
		AE	14	9	+1·00
		SAE	2	4	+1·00
Type of AE / SAE	Surgery/pump implantation related	Liquor leakage	6 / 1	5 / 1	^0·84 / ^0·29
		Pump infection	0	0 / 2	
		Catheter related	0	0 / 1	
	Possibly adverse drug effects	Nausea or vomiting	2	1	
		Obstipation	0 / 1	0	
	Other[a]		6	3	

Data are presented as number. ITB=intrathecal baclofen. AE=adverse event. SAE=serious adverse event. +Mann-Whitney U test. ^Pearson Chi Square test. [a]Other complications mainly involved infections (e.g. urinary tract infection, gastrointestinal infection).

DISCUSSION

We report the results of the first multi-centre, randomized, double-blind, placebo-controlled trial, that we are aware of, on continuous ITB treatment in dyskinetic CP. Compared to placebo, ITB shows a superior effect on attainment of individual treatment goals. Furthermore, outcome for dystonia, as measured with the DIS, is slightly more favorable with ITB compared to placebo.

Individual goals are achieved significantly more often with ITB compared to placebo. Our study population involves severely affected dyskinetic CP patients with little to no motor skills (GFMCS IV and V). Treatment goals for these patients are mostly to increase comfort, decrease pain, ease caregiving and facilitate mobility (e.g. transfers and positioning)[9]. Standardized questionnaires on quality of life or activities and participation, that were available at the time of the study, do not adequately capture the individual problems in daily life of these patients, and attainment of individual goals is therefore the most useful and meaningful way to determine treatment effects. When looking at the different categories of set goals, we saw a difference between groups in (partial) achievement of goals on the ICF-CY level of body functions and structures, activities and participation (mobility), and environmental factors (caregiving by others). The findings from our study are in line with previous case control and case series studies and add significantly to the level of evidence for the use of ITB to improve goals in these domains.[6,7]

There were significant differences between ITB and placebo for the DIS total dystonia subscale and the DIS dystonia rest subscale in favor of ITB. However, we were not able to confirm results of previous studies, which found a decrease in BADS scores with ITB.[12,21,22,24] Previous studies had a lower level of evidence because of the non-randomized non-blinded study designs. We used standardized videos, and assessors were both masked for treatment allocation and timing of measurements (baseline or follow-up). The reason for finding a difference between dystonia measured by DIS and BADS might be that the situation of measurement in the DIS is better defined than the BADS, which hypothetically can lead to better reliability and less variation in scores. However, there are no test-retest reliability studies for either the BADS or the DIS. Considering the fluctuation of dystonia in individual patients, test-retest reliability and sensitivity to change could be problematic for both scales.[17,21]

A significant difference between groups was found for the dystonia during rest subscale, but not for the dystonia during activity subscale. This may be explained by dystonia being subject to fluctuation and aggravated by non-specific stimuli such as emotion, stress and intentional movement.[6,22] It is likely that, despite treatment, dystonia is still aggravated during periods of activity, and possibly also stress and emotions. The exact clinical implications of the small differences within and between groups are unclear.

Choreo-athetosis scores were similar between groups. We found mean choreo-athetosis scores to be lower than mean dystonia scores which is accordance with previously published findings.[22,23]

DIS (sub)score(s) at three months and changes in DIS (sub)score(s) were not correlated with GAS T-scores. A previous study by Monbaliu et al. showed lower functional abilities for children with higher levels of dystonia and in addition poorer scores on participation and quality of life questionnaires.[23] Our hypothesis was that the effect on goal attainment would be caused by a reduction of dystonia, but this was not confirmed in our study. Fluctuation of dystonia and reliability of currently available instruments, as discussed above, might be of influence on this finding.

Both clinical and electrophysiological spasticity measures were not significantly different between groups. In many patients with a predominant dyskinetic movement disorder, spasticity is also present.[1] In patients with spastic CP, the H-reflex is found to be a feasible and objective measure to identify spinal cord neuronal response to ITB.[18] Considering the findings of previous studies, spasticity was expected to decrease with ITB.[18] In our patients however, spasticity was often difficult to assess reliably since both

measures used, are subjective to the degree of relaxation of the patient.[24] Relaxation was very difficult for most due to involuntary muscle contractions and movements which characterize dyskinesia, and therefore spasticity measures might be less reliable in this group.

Changes in range of motion (ROM) were similar between groups which corresponds with previous studies.[25] This is not surprising because when contractures occur, due to changes in bony structures or to muscle shortening, these problems will not improve on the short term with a decrease of muscle tone established by ITB. On the long term however, contractures might be less progressive or stabilized with ITB, preventing (worsening of) contracture related problems in daily life.

Pain and comfort scores at three months were similar between groups. As most patients in our study did not report pain or comfort as a problem, improvement was not expected for these patients. However, 3 out of 4 patients on ITB who did report pain or discomfort as treatment goals, (partially) achieved this goal compared to non in the placebo group. These last results correspond with previously published studies.[25-28]

Most parents were correct about group allocation which shows that changes due to ITB are indeed favorable, and significantly noticeable. Parents' thoughts on group allocation might bias outcome for goal attainment scaling. We limited this effect by asking parents to describe the current situation without telling them how the baseline situation was.

Baclofen did not have an additional adverse effect on the known serious complications of pump implantation since AE and SAE were similar between groups in types and number. In comparison with previous studies, the frequency of adverse drug effects as constipation and nausea or vomiting were low in our study.[29] The majority of severely affected CP patients already experience constipation before pump implantation. Bedrest after surgery can increase this problem further. In our study, constipation worsened in one of the patients on ITB requiring prolonged hospital admission. Nausea and vomiting occurred in three patients (two ITB, one placebo). Anesthesia, surgery, the period of bedrest after surgery in patients prone to reflux might all elicit nausea and vomiting in addition to the possible adverse drug effect of baclofen. Several surgery-related complications were seen, with symptomatic CSF leak and infection being the most frequent. We found a higher occurrence of CSF leak compared to literature and a lower incidence for infection.[6] We observed one catheter related problem. Comparison with previous studies is not possible since catheter related problems often occur after a longer follow up time.

No difference was found between ITB and placebo in parent reported symptoms related to risk of sleep related breathing disorders. Apnea or hypopnea during sleep is increased with ITB in adult patients with spinal cord injury and multiple sclerosis.[10] Children with CP already have a higher risk of sleep-related disorders than typically developing children.[10] Hypothetically, this risk might increase even more by placing the catheter at the mid cervical level, close to the breathing centre. To be able to fully reject this hypothesis, studies using polysomnography are needed.

Total dosage was similar between groups. This was to be expected as both groups were required to have at least 10 dose increments during the study. More patients in the ITB group were on a bolus schedule. This can be explained by the dosing schedule we used (table 1, figures 1 and 2). If no effect is noticed, the daily dose is increased in the simple continuous mode, providing a fixed infusion rate throughout the day. Only when effect is noticed, but the effect decreases over time, a bolus will be added. Consequently, some of the patients on ITB were on the simple continuous mode, while others were on a "flex mode" in which a bolus can be included.

The study has several limitations. First, the study was powered on the primary outcome measure resulting in a relatively low number of patients needed. This limits the possibility for subgroup analysis on effect modifying factors. It was not possible to place the catheter tip at the aimed C4 level in some patients due to technical surgical issues. Considering the hypothesis that ITB in dyskinetic patients works intracranially, the effect in these patients might be less than when placed on a higher level. Another limitation is the short follow up period of three months. In our clinical experience it takes at several weeks up to several months to find the right dosage for the individual patient. We aimed to approach the optimum dosage by requiring at least 10 increments. Still, some patients might not be on the most adequate dosage yet and others only for a short period of time. However, we did find a clear difference for our primary outcome measure. Furthermore, a longer period of placebo was felt to be unethical. We will perform an additional 9 month open label follow-up period for all patients. Last, assessors were blinded for treatment allocation, but we did not test whether this was successful (i.e. whether they personally had an idea about treatment allocation which could have influenced their judgement). Retrospectively we asked assessors to recall whether they had thoughts on group allocation. They responded that they had no opinion on group allocation during measurements, including scoring of the GAS. During scoring of the videos, which were provided coded and in random order (mixing patients and measuring moments), they also had no idea on group allocation.

Future studies should assess long-term effects and complications using a prospective longitudinal cohort study design. An (inter)national register, like the Australian ITB audit, could provide a good basis for such a study, ensuring sufficient patient numbers and harmonization of outcome measures.[30] The achievement of individual treatment goals should have the primary focus. With a larger sample size, patient- and treatment characteristics and factors on the level of body functions and structures, influencing goal attainment, can hopefully be identified. Furthermore, it might provide us with additional insights in optimal dosage and provide evidence for the usefulness of our dosing schedule designed for patients with dyskinetic CP, which is now based on clinical observation.

Considering the described problems in reliable measurement of dystonia, test-retest reliability studies of the DIS and BADS are needed, and furthermore, it would be useful to examine whether a shortened version of the DIS, perhaps limiting to the most responsive and clinically relevant items, makes the DIS more feasible for severely affected patients with dyskinetic CP in both research and clinical practice. In addition, other measurement methods of dystonia should be explored, such as instrumented measures, which are not dependent on assessors, and which can easily be applied at home or at day-care/school to decrease provocation of stress and ensure correspondence with the daily situation.

In conclusion, we were able to provide level II evidence for the effect of intrathecal baclofen in paediatric and adolescent patients with severe dyskinetic CP (GMFCS IV and V) on the achievement of individual treatment goals. ITB should be considered as a treatment option in patients with severe dyskinetic CP in whom oral medication is insufficient. Treatment goals should be on the level of body functions and structures (such as pain or discomfort), on the level of activities and participation for mobility (such as transfers and sitting), and/or goals on the level of environmental factors (caregiving by others). Studies into the long term effects of ITB and factors influencing outcome, and on reliable measurement of dystonia in severe dyskinetic CP are future perspectives.

ACKNOWLEDGEMENTS

This study was funded by the Phelps Stichting voor Spastici (project number 2011037 and project number 99.047), het Revalidatiefonds (project number R2011032/), Kinderrevalidatie Fonds de Adriaanstichting (project number 11.02.17-2011/0035) and het Johanna KinderFonds (project number 2011/0035-357). We thank Sanne van der Vossen, MD for her help in conducting measurements during the absence of LB, Tamara van Ams and Sharony de Vries for taking care of the logistics around study medication,

appointments and pump fillings, and Helga Haberfehlner for her enthusiastic and innovative ideas.

CONFLICTS OF INTEREST

There are no potential competing interests to report.

AUTHOR CONTRIBUTIONS

The members of the IDYS study group are, from the Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands: Laura A. Bonouvrié MD, Prof Jules G. Becher MD, Annemieke I. Buizer MD, Karin Boeschoten, Johanna J.M. Geytenbeek PhD, Prof Vincent de Groot MD (Rehabilitation Medicine), Laura A. van de Pol MD (Child Neurology), Willem J.R. van Ouwerkerk MD, K M Slot MD, Prof S M Peerdeman MD (Neurosurgery), Rob L.M. Strijers MD (Clinical Neurophysiology), Elisabeth M.J. Foncke MD (Neurology), Jos W.R. Twisk PhD, Peter van de Ven PhD (Epidemiology and Biostatistics), and from Maastricht University Medical Center, Maastricht, the Netherlands: Prof R Jeroen Vermeulen MD, Prof Johan S.H. Vles MD, Dan Soudant MANP, Sabine Fleuren (Neurology) and Onno P. Teernstra MD (Neurosurgery).

LB, JB, JV, RJV, KB, JG, VG, WO, SP, RS, EF, and PV contributed to the conception and design of the study; LB, JB, RJV, AB, KB, DS, SF, JG, RS, LP, and JT contributed to the acquisition and analysis of data; LB, JB, JV, JT, RJV, and AB contributed to drafting the text and preparing the figures.

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CHAPTER 6

Intrathecal baclofen for progressive neurological disease in childhood: a systematic review of literature

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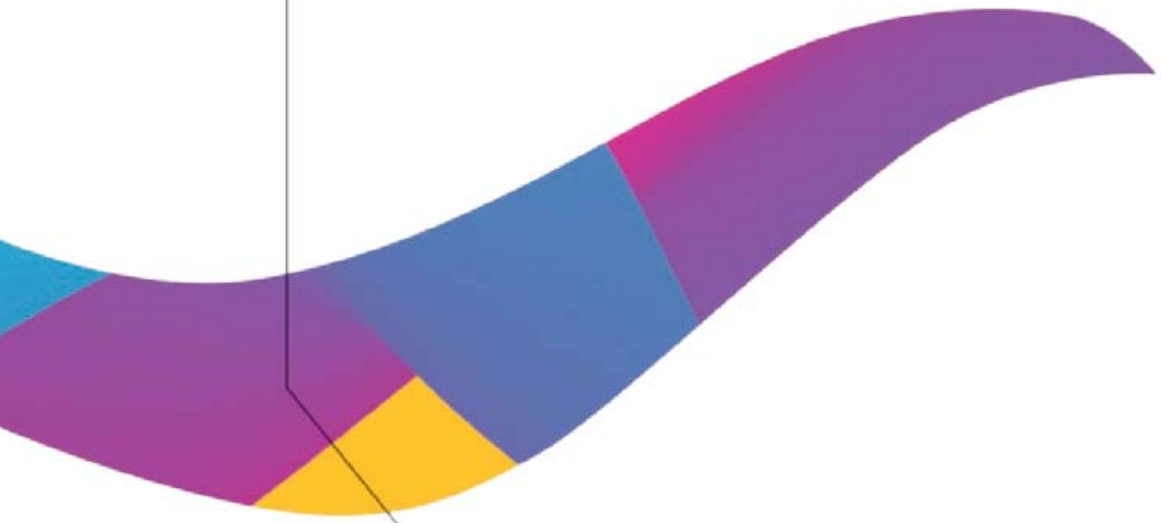
Eur J Paediatr Neurol 2012; 16(3): 279-284



ABSTRACT

Background Intrathecal baclofen (ITB) treatment is frequently used for individuals with severe, but non-progressive, spasticity refractory to oral treatment. However, experiences with ITB in patients with progressive neurological disorders of childhood causing spasticity are limited.

Aim To investigate whether ITB is an option in patients with progressive neurological disorders causing spasticity in childhood.

Design A systematic literature search in Embase, Pubmed and the Cochrane Library was performed.

Results We identified six eligible studies considering patients with progressive neurological disease in childhood and receiving ITB treatment. The studies included a total of seven paediatric patients and four adult patients. Improvement was reported in spasticity, spasms, pain, gait, activities of daily life and providing care. High satisfaction is described.

Conclusions ITB has beneficial effects in paediatric patients with progressive neurological disease. However, the level of evidence is limited due to the small number of available studies and due to the poor quality of these studies

Keywords Intrathecal baclofen, Progressive neurological disease, Spasticity

INTRODUCTION

Intrathecal baclofen treatment (ITB) has been used since the 1980s for the treatment of spasticity.[1] Baclofen is a GABAagonist[2,3] and inhibits neuronal transmission[3-5] at the level of the spinal cord.

ITB is an effective treatment for individuals with severe spasticity refractory to oral, or other non-invasive, spasticity reducing treatments.[3,6-8] ITB is effective especially in patients with stable underlying conditions such as cerebral palsy (CP),[3,4,6,8] traumatic brain injury[4,6] and spinal cord injury.[1,3,5] In these patients ITB decreases spasticity and spasticity related pain, improves functional activities related to activities of daily life[3,9-11] and facilitates ease of care.[8-10] Although complications occur frequently,[6,8,9] most individuals and their caregivers are satisfied with ITB treatment.[11]

The experiences with ITB in patients with progressive neurological disorders of childhood causing spasticity are limited. We will therefore present a systematic review of literature to investigate if ITB is a treatment option in patients with progressive neurological disorders causing spasticity in childhood.

METHODS

Search strategy

A systematic literature search in Pubmed, Embase and the Cochrane Library, was conducted on April 15th 2010. The search strategy used for Pubmed is shown in Table 1. For Embase and the Cochrane Library comparable search terms are used (available as additional material). Titles and available abstracts identified in the searches were reviewed to identify relevant studies. References of relevant studies were searched to identify studies not found in the electronic searches.

Study selection

We included all studies in which: 1) spasticity was caused by progressive neurological disorders with a presentation in childhood (<18 years), 2) the intervention was ITB administration by either a bolus injection by lumbar punction (LP) or continuous infusion by an implanted pump.

We excluded the following studies in which: 1) non-progressive diseases causing spasticity were described; 2) mixed progressive and non-progressive disease in which progressive neurological diseases causing spasticity were not

further specified or not separately analysed.

Table 1. Search strategy PubMed

Search number	Search terms	Results
#1	"baclofen"[Mesh]	4232
#2	"baclofen"[tiab] OR "pcp gaba"[tiab] OR "beta p chlorophenyl gamma aminobutyric acid"[tiab] OR "chlorophenyl gaba"[tiab] OR "beta aminomethyl 4 chlorobenzenepropanoic acid"[tiab] OR clofen[tiab] OR genbaclofen[tiab] OR atrofen[tiab] OR lioresal[tiab] OR "nubaclo"[tiab] OR nubaclo[tiab] OR apobaclofen[tiab] OR "ba 34 647"[tiab} OR "ba34 647"[tiab] OR "ciba 34 647 ba"[tiab] OR "ciba34 647ba"[tiab OR "ba 34647"[tiab] OR ba34647[tiab] OR baclospas[tiab]	4987
#3	#1 OR #2	5723
#4	"Injections, Spinal"[Mesh]	11400
#5	(Intrathecal[tiab] OR intraspinal[tiab] OR spinal[tiab]) AND (injection*[tiab] OR infusion*[tiab])	15525
#6	#4 OR #5	23652
#7	#3 AND #6	751
#8	Child*[tw] OR schoolchild*[tw] OR infan*[tw] OR adolescen*[tw] OR pediatri*[tw] OR paediatr*[tw] OR neonat*[tw] OR boy[tw] OR boys[tw] OR boyhood[tw] OR girl[tw] OR girls[tw] OR girlhood[tw] OR youth[tw] OR youths [tw] OR baby[tw] OR babies[tw] OR toddler*[tw] OR "Mental Disorders Diagnosed in Childhood"[MeSH] OR teen [tw] OR teens[tw] OR teenager*[tw] OR newborn*[tw] OR postneonatal*[tw] OR postnat*[tw] OR OR puberty[tw] OR preschool*[tw] OR suckling*[tw] OR picu[tw] OR nicu[tw] OR	2884776
#9	#7 AND #8	239

Assessment

Two researchers (RJV, LAB) independently reviewed the selected studies and produced summary data tables (level of evidence,[12] study-type, patient-characteristics, intervention, outcome measurements and results). Findings were discussed and consensus was achieved for final analysis of the data. Outcome data extracted from the selected studies included spasticity scores (Ashworth scale, Penn scores), range of motion (ROM), spasticity associated pain (no specified method), gait (velocity, stride length, step width), functioning (no specified method), satisfaction and ease of providing care (no specified method).

RESULTS

Description of studies

Six eligible studies were found in the electronic databases.[13-18] One study was level 4 evidence (case-series),[17] five studies were level 5 evidence (expert opinion/case report)[13-16,18] as defined by the Oxford Centre of Evidencebased Medicine levels of evidence.[12] Study characteristics and outcomes are presented in Table 2.

Description of results

Spasticity, spasms and pain

Three studies described spasticity (Ashworth score) (all level 5 evidence).[14,15,18] ITB treatment decreased spasticity in all studies.[14,15,18] ITB also decreased disabling extensor spasms in one patient, This patient noticed subsequent improvement of pain and sleep.[13] Two other patients reported subjective pain relief.[14,18]

Mobility

In one patient improvement of gait velocity, step length and a decrease in step width was reported (level 5 evidence).[16] Subjective improvement in ease of assisted transfer was reported in one paediatric patient (level 5 evidence).[14]

Activities of daily living and providing care

Four studies (level 4 and 5) described patients who were reliable on others for personal care.[13,14,17,18] In three studies, caregivers report improvement in dressing, hygienic care and positioning in a wheelchair.[14,17,18] One adult patient experienced facilitation of positioning in his wheelchair.[13]

Furthermore, after starting ITB two patients were reported to be more alert and more interactive during the day.[14,18] Caregivers of one patients reported a subsequent improved quality of life.[18]

Side effects and complications

Complications were not reported in the level 5 studies (n = 5). In one study, two of six patients experienced cerebrospinal fluid (CSF) leak during the test phase of treatment. One patient experienced catheter related problems requiring surgery.[17]

Table 2. **Study characteristics**

Ref	*LOE*	*Study type*	*Number of patients*	*Patient characteristics (Diagnosis, age)*	*Ambulation*	*Intervention*	*Duration FU*	*Outcome measures and results*
[13]	5	CR	1	Friedreich's ataxia 39-yr-old male	Non-ambulatory	Bolus ITB[a] (50, 75, 100 µg) Continuous ITB[b] (100 µg/24u)	6 months	• Decreased extensor spasms (subjectively and electrophysiologically measured) • Decreased associated pain (subjectively) • Improved sleep (subjectively) • Facilitated positioning in wheelchair (subjectively) • High satisfaction (subjectively)
[14]	5	CR	1	X-linked adrenoleukodystrophy 8-yr-old male	Non-ambulatory	Continuous ITB[b]	10 months	• Decreased spasticity (2 points ASH) • Increased ROM UE and LE • Elimination of pain (parental assessment) • Improved hygienic care and dressing (parental assessment) • Improved transfer and positioning (parental assessment)
[15]	5	CR	1	FSP 41-yr-old male	Non-ambulatory	Bolus ITB[b] (75 µg)	n.a.	• Decreased spasticity (2 points ASH)
[16]	5	CR	1	HSP 31-yr-old male	Ambulatory	Continuous ITB[b]	24 months	• Improvement in gait (Increased step length, increased self-selected speed in stride, decreased step width)
[17]	4	CS	6	Multiple progressive neurological diseases 4 to 18-yr old 50% male	Ambulatory and non-ambulatory	Continuous ITB[b]	6 months to 6.7 year	• Four caregivers were satisfied with ITB treatment, one was partially satisfied, one was not satisfied (caregiver questionnaire by VAS) • Dissatisfaction due to unfulfilled goals or negative effects (caregiver questionnaire)
[18]	5	CR	1	Rett syndrome 32-yr-old woman	Non-ambulatory	Continuous ITB[b]	6 months	• Increased range of motion LE • Decreased spasticity UE and LE (1point ASH) • Improvement in ease of care including hygienic care and positioning (caregivers assessment) • Decreased pain and increased quality of life (caregivers assessment)

[a] administration via lumbar puncture. [b] administration via implanted pump. ASH, (modified) Ashworth scale of spasticity. CR, case report. CS, case series. FSP, familial spastic paraplegia. FU, follow-up. HSP, hereditary spastic paraparesis. LOE, level of evidence. Level 4 evidence: case-series (and poor quality cohort and case-control studies). Level 5 evidence: expert opinion. LE, lower extremity. OL, open label. Ref, reference number. ROM, range of motion. UE, upper extremity. VAS, visual analog scale. Yr, year.

Baclofen related side effects were also reported in this study. In two patients, caregivers reported progressive scoliosis. In two other patients caregivers reported ITB-tolerance. Other reported side effects (all reported once) included constipation, hypotension, somnolence, increased drooling, decreased head control, swallowing difficulties, abdominal discomfort, back pain, withdrawal symptoms due to a nearly empty pump and iatrogenic overdose.[17]

Satisfaction

One level 4 evidence study scored satisfaction in six paediatric patients. Satisfaction was measured with a modified visual analog scale (VAS) with 0 being the poorest score and 10 the most optimal score. Four of six caregivers were satisfied with

the treatment. In one patient the caregiver was only partially satisfied due to improvements but also side effects and complications. In one patient the caregiver scored satisfaction as a score of 7.0, however he was not satisfied with the ITB treatment due to unfulfilled goals.[17]

DISCUSSION

Data on ITB in patients with spasticity due to progressive neurological disorders with clinical presentation during childhood are limited. In our systematic review of literature, we found six studies reporting seven paediatric patients and four adult patients with manifestation of their disease during childhood. The level of evidence was low in all studies (one level 4 case-series,[17] five level 5 expert opinion/case report).[13-16,18]

ITB treatment decreases spasticity caused by non-progressive diseases such as cerebral palsy.[1-6,8,19] This review shows ITB also decreases spasticity and spasms due to progressive diseases.[13-15,18]

In one ambulant adult patient, improvement of gait was reported during continuous ITB treatment.[16] Other studies showed similar effects on gait in adult patients with progressive neurological disease.[20-22] Improvement in gait may lead to functional improvement as one study showed a decreased need for walking aids.[22]

Most patients in this review were non-ambulatory. Also, in spastic CP patients, the positive effect of ITB is most frequently described in non-ambulatory patients (GMFCS IV or V). For ambulatory CP patients (GMFCS levels I-III) only limited data on improvement of mobility are available.[8]

In this study most patients were dependent on caregivers for mobility and personal care (seven paediatric patients and one adult patient). Three studies reported improvement of ease of care, including dressing, hygienic care, positioning and transfer.[14,17,18] These findings are in line with the goals and effects of ITB treatment on function and caregiver assistance in GMFCS IV and V CP patients.[8,11]

Side effects and complications of ITB treatment are common.[2,4,6,8,23] The most frequent complications are infections, cerebrospinal fluid (CSF) leaks and catheter problems.[2-4,8] In this review, only one study mentioned a total of three complications in six patients[17] comparable to the most frequent reported side effects in CP patients receiving ITB treatment.

Constipations is the most common chronic side effect of ITB in CP patients.[2-4] Though constipation was reported only once in the progressive disease patient population. In two patients progressive scoliosis was reported during ITB treatment.[17] Since ITB treatment causes muscle weakness, including weakness of the paraspinal muscles, it is hypothesized that ITB might elicit scoliosis.[24] In addition to others, we think that scoliosis is a common complication in severe neurological disease, also without ITB treatment.[25,26] Therefore, as well in patients with non-progressive disease as in patients with progressive neurological disease and spasticity, the development and progression of scoliosis should be monitored closely.

Tolerance to ITB is an important complication and results in increased muscle tone over time.[6] We found two patients who suffered from tolerance.[17] We must realize that tolerance is not common in patients with CP.[2,4] Presumably, unresponsiveness to ITB in these patients is usually caused by an underlying system malfunction. Physiological adaptation is common in the first years of treatment, Albright et al. showed increasing baclofen dosages during the first one to three years of ITB treatment in children with cerebral palsy.[6] In our review population, patients had spasticity due to progressive neurological disease. It is not inconceivable that in these patients spasticity worsens as disease progresses, requiring increasing dosages of ITB.

Side-effects and complications can lead to dissatisfaction with ITB treatment. Other reasons for being unsatisfied or being only partially satisfied with continuous ITB treatment are unfulfilled goals. Fortunately, most patients with spasticity due to progressive neurological disease and their caregivers are satisfied with continuous ITB treatment as are patients with stable underlying disease.[11,13,17,18,27]

CONCLUSION

In patients with progressive neurological disease causing spasticity, ITB improves not only spasticity, spasms and pain but furthermore has positive effects on mobility, facilitation of care including dressing, hygienic care, positioning and transfer. Despite the widespread use of ITB, the few available studies and the poor quality of these studies (level 4 and mostly 5) is low, limits our conclusion.

We think that ITB should be considered as a treatment option in patients with progressive neurological disease when other treatment options fail. Further research is needed to establish the beneficial effect of ITB in patients with progressive neurological disease using a range of outcome measures addressing multiple domains of the International Classification of Functioning, Disability and Health (ICF) and furthermore quality of life and long term outcomes.

ACKNOWLEDGEMENTS

We are grateful to J.C.F. (Hans) Ket, medical information specialist of the VU University Medical Center Library for his assistance with the literature search.

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CHAPTER 7

Satisfaction with intrathecal baclofen treatment in paediatric patients with progressive neurological disease

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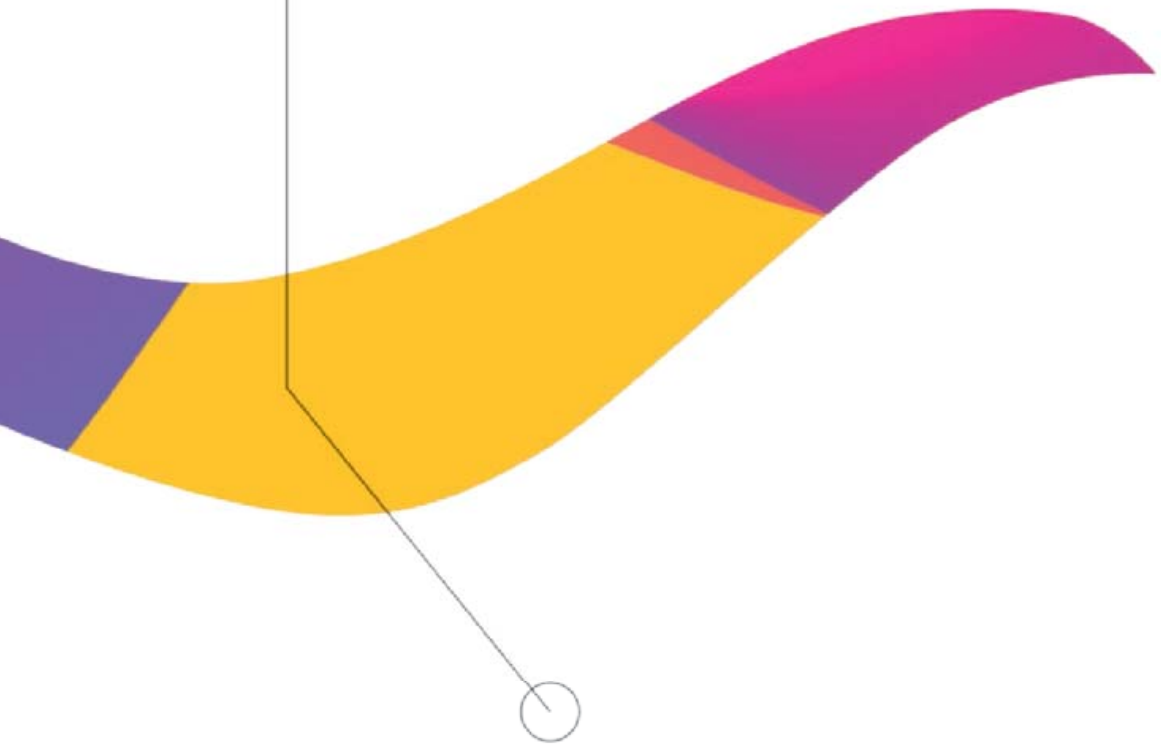
Dev Med Child Neurol 2008; 50(8): 636-638



Intrathecal baclofen (ITB) treatment could be a beneficial treatment option in paediatric patients with progressive neurological disorders causing spasticity. Since its introduction in the 1980s,[1] ITB has been mainly recommended for individuals with severe spasticity refractory to oral treatment[2–4] and is proven to be effective for reduction of spasticity, especially in patients with stable underlying conditions such as cerebral palsy,[2,3,5–7] traumatic brain injury,[2,5,6] and spinal cord injury.[1,3,6] We noticed that the experiences with ITB in paediatric patients with progressive neurological disorders are limited. In addition, although minor complications occur frequently,[2,7] most individuals and their caregivers are satisfied with ITB treatment.[7,8]

We retrospectively studied the overall satisfaction of caregivers with ITB treatment in a group of children and adolescents from our center with progressive neurological disorders causing spasticity. For this purpose, we selected six patients from a total cohort of nine paediatric patients with ITB treatment (Medtronic Inc, Minneapolis, MN, USA; three males, three females; mean age 11y 8mo, [SD 4y 5mo]), with progressive neurological disorders (Table I) starting in childhood. The remaining three patients from the total cohort were not using ITB at the time of the survey. We analyzed whether the treatment effects met the expectations of the caregivers and how they would score the level of overall satisfaction on a scale from 0 to 10 (0 being the poorest score and 10 being the most optimal score). For this purpose we used standard questionnaires.[9] Medical records were checked for complications related to surgery and ITB treatment and for treatment goals.

The mean time since pump implantation was 3 years 4 months (SD 2y 11mo, range 6mo–6y 8mo) and the mean age at time of pump insertion was 8 years 4 months (SD 3y, range 4–13y).

Reduction of spasticity or spasms, facilitation of care, and reduction of pain were the main goals for initiating ITB treatment. Medical records of the six patients still using ITB reported several complications related to ITB hardware, and surgery, including catheter migration in two patients (Table I). One of the patients experienced an overdose of ITB due to a mistake in programming the pump while having his dosage adjusted. The same patient experienced increase of spasticity due to a nearly empty ITB 10ml pump.

The following side effects of ITB treatment were reported in the questionnaires: increased drooling, increased swallowing difficulties, decreased head balance, abdominal discomfort, and constipation (Table I). Each of these complaints was reported once.

Back pain due to worsening scoliosis was reported twice. In two patients, the caregivers reported increased tolerance of ITB with frequent pump adjustments consequently.

Overall satisfaction scored 7.5 (SD 1.6, range 6–10). For detailed results, see Table I. The caregivers of four patients were satisfied with ITB (nr 1–4), mean satisfaction score 8.0 (SD 1.8, range 6–10). The caregiver of patient 5, stated that they were not satisfied although a score of 7.0 was reported. This dissatisfaction was due to not being able to see full results of ITB yet, because of a short follow-up since pump implantation. The caregiver of patient 6 was partially satisfied due to improvement in dressing, personal hygiene spasms, and pain; but on the other hand noted worsening of swallowing, constipation, head balance, trunk stability, back pain, and worsening scoliosis (satisfaction score 6.0).

We are aware of the fact that this is a retrospective study and we only present a small number of patients. Still, we think this study shows clearly and similar to other studies[3,8,10,11] that most caregivers are overall satisfied with the effects of ITB treatment. Dissatisfaction was related to unfulfilled goals or related to negative effects of ITB on functioning.

Considering the present results with moderate to good satisfaction, ITB is, in our opinion, a valuable treatment option in patients with progressive neurological diseases.

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Table 1. ITB treatment: complications, side effects and satisfaction scores

	Diagnosis	*Sex*	*Age (y)*	*Time since pump (y:mo)*	*Goals*	*Dosage (µg/24h)* start	FU	*Complications*	*Side effects*	*Satisfaction Score* Satisfied
1	Neuronal ceroid lipofuscinosis type1	M	8	0:6	Reduction of contractures UE and spasms facilitation of care	100	182		Tolerance	9 Yes
2	Progressive neurodegenerative disease of unknown origin	F	10	1:4	Reduction of spasticity and hyperkinesias	100	202	Temporary hypotension (trial) Catheter migration and re-implantation	Scoliosis Tolerance	7 No
3	Spastic tetraplegia of unknown origin	F	8	4:1	Reduction of spasticity LE	50	150	CSF leak (trial)		6 Yes
4	Spinocerebellar degeneration	M	4 9*	6:8	Reduction of spasticity LE and ataxia	75	155	CSF leak (trial) Back pain (trial)	Abdominal discomfort Increase drooling	7 Yes
5	Progressive leukoencephalopathy	M	13 18*	6:6	Reduction of pain	135	367	Catheter migration Withdrawal symptoms (early empty pump) Overdose of ITB Pneumonia	Progressive scoliosis Loss of head balance Swallowing difficulties Constipation	6 Partially
6	Metachromatic leukodystrophy	F	7	0:8	Reduction of pain Facilitation of care	65	70	Temporary somnolence (trial) Hypotension (trial)		10 Yes

Abbreviations used: CSF, cerebrospinal fluid; F, female; FU, last follow up during clinic visit; h, hour; ITB, intrathecal baclofen; ; LE, lower extremities; M, male; mo, month; PEG, percutaneous endoscopic gastrostomy; UE, upper extremities y, year; * pump replacement.

CHAPTER 8

The effect of intrathecal baclofen treatment on activities of daily life in children and young adults with cerebral palsy and progressive neurological disorders

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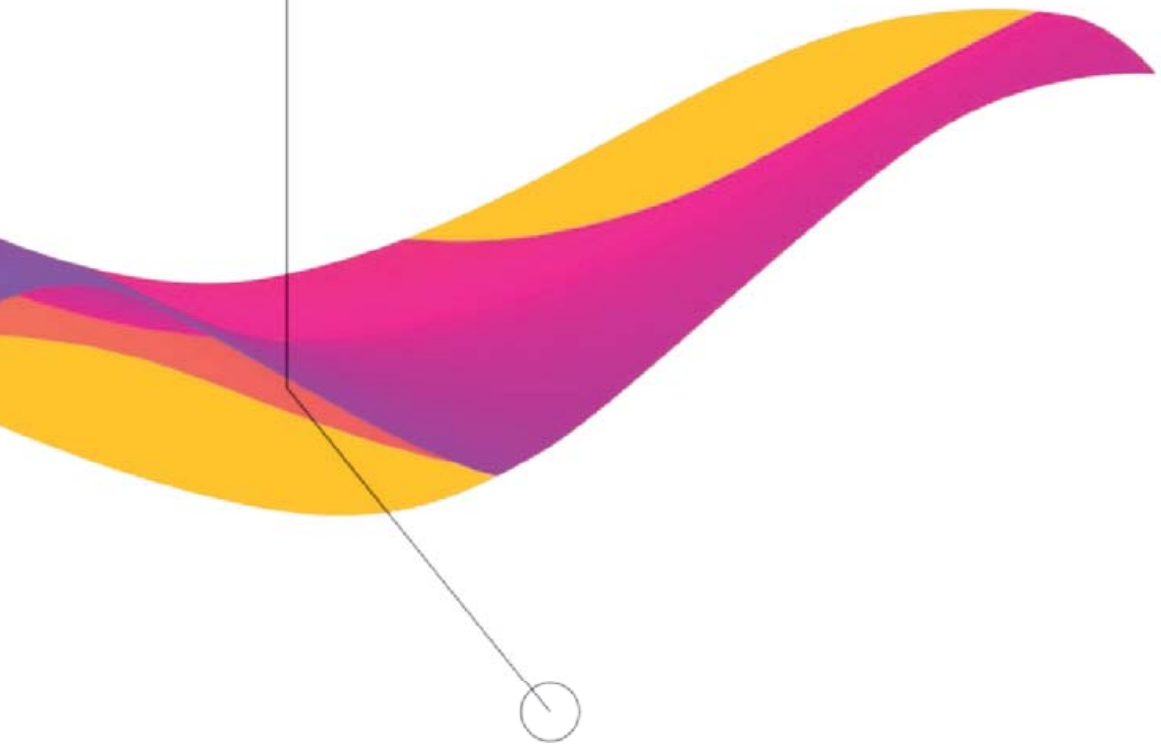
Eur J Paediatr Neurol 2016; 20: 538-543



ABSTRACT

Introduction Intrathecal baclofen (ITB) treatment is applied in patients with spastic cerebral palsy (SCP), dystonic cerebral palsy (DCP) and progressive neurological disease (PND). Our aim was to investigate whether ITB treatment has a different effect on activities of daily life (ADL) in these groups.

Method A retrospective and cross-sectional survey was conducted using a questionnaire to assess the qualitative effect of ITB (Likert scale) on different domains of functioning (mobility, personal care, communication, comfort) and satisfaction with the results. Groups were compared using non-parametric statistics.

Results Questionnaires were completed for 68 patients (39 SCP, 13 DCP, 16 PND). Satisfaction scores were relatively high in all groups (7e8) and the positive effect on personal care and communication was similar in all groups. The PND group had the shortest follow-up and scored significantly less favorably for the effect on mobility and comfort.

Discussion This is the first study to show that ITB treatment has similar effects on personal care and communication in stable and progressive neurological disease. The decrease in mobility in the PND group is likely due to the progressive nature of the disease. The different effect on comfort between groups is mainly due to the smaller effect on startles in the PND group.

Keywords Baclofen, Child, Cerebral palsy, Nervous system diseases, Muscle spasticity, Dystonia

INTRODUCTION

Intrathecal baclofen (ITB) treatment is a well-known and widely used treatment for individuals with severe spasticity due to stable underlying conditions. Studies describe a profound decrease of spasticity in patients with spastic cerebral palsy (SCP) during ITB treatment.[1,2] ITB also seems to have an effect in patients with secondary dystonia.[3]

The effect of ITB on spasticity CP and other neurological disorders is mediated by inhibition of the GABA receptor located on the spinal interneuron. In contrast, how ITB affects dystonia is unclear.

In conjunction with the reduction of spasticity and/or dystonia, it has been shown that individual problems of daily life, such as pain, transfers, sitting and ease of care improve with ITB treatment.[4-6] In 70% of patients with SCP or dystonic cerebral palsy (DCP), with predominantly Gross Motor Function Classification System (GMFCS) level IV and V, goals on activity and participation level are attained.[7]

Other effects of ITB treatment in patients with DCP are also comparable with the effects of ITB treatment in patients with SCP but fewer studies are available. Studies show that care is facilitated and that individual problems of daily life improve.[7-9] Additionally, ITB treatment decreases dystonia in patients with DCP.[8,10]

The experiences with ITB treatment in patients with progressive neurological disorders of childhood (PND) are limited. A previously published review found only six case studies which describe ITB treatment in patients with spasticity caused by PND[11]. The review reported a decrease of spasticity and pain and an improvement in several activities of daily care.

Caregivers of both CP and PND patients are generally satisfied with ITB treatment.[1,5,9,12] It is, however, unknown if patients with these different conditions experience the same problems in daily life and if they benefit from ITB treatment in the same way. Therefore, the aim of this study was to compare the effect of ITB treatment on activities of daily life in patients with SCP, DCP and PND.

METHOD

Design

Combined retrospective and cross-sectional survey.

Patients

In 2007 and 2011 patients were selected from a list of patients who underwent ITB pump implantation since 2001. Patients who were using ITB treatment for less than two years at the time of the first survey in 2007 were again sent the questionnaires in 2011. They were included if they: 1) had undergone pump implantation (Medtronic, Inc., Minneapolis, MN, USA) in the VU University Medical Center in Amsterdam or the Maastricht University Medical Center in Maastricht, the Netherlands and/or were followed up in one of these centers; 2) were using ITB treatment at the time of the survey; and 3) suffered from SCP, DCP (both with onset before the first birthday) or PND (onset before the age of 18 years). Patients were excluded if their knowledge of the Dutch language was insufficient to complete the questionnaires or if >10% of the questions were left unanswered. Patients were contacted by phone (by LB and DS) and after agreeing to participate they were sent the questionnaires by mail.

Medical charts were checked for gender, diagnosis, GMFCS level, age at pump implantation and time since pump implantation. For PND a GMFCS level was estimated on basis of chart information about functioning.

The medical ethical committee of the VU University Medical Center in Amsterdam approved the use of the current questionnaires, without the use of a formal informed consent.

Questionnaire

A questionnaire (Appendix I and II) was sent to caregivers of the included patients. The questionnaire consists of several items (questions), which are divided into four domains of functioning: mobility (fine and gross motor skills), personal care, communication and comfort. Each domain consists of multiple questions focusing on tasks within that domain. For example, within the domain mobility one is asked about transfer, sitting and hand use, within the domain of personal care there are questions about dressing, hygienic care and eating/feeding, for communication about the interaction with other children and the ease of being understood. For comfort there are questions about pain and wellbeing. Since we had a clinical observation that startle reactions often occur,

we also included a question about startles. We defined a startle as generalized motor reaction upon auditory, tactile or visual stimulation.[13]

The caregivers were asked to compare the current situation (with ITB treatment) with the situation before pump implantation (without ITB treatment). Changes due to ITB treatment were classified using a five point Likert scale. Possible outcomes were: much better, somewhat better, no change, somewhat worse or much worse. Furthermore, satisfaction was scored on a Visual Analogue Scale (VAS), in which "0" was the worst score and "10" was the best score.

We chose not to use existing scales as the Pediatric Evaluation of Disability Inventory (PEDI) or the WeeFIM for two reasons: 1. Our study is a retrospective study looking into the effect of ITB treatment, therefore we cannot compare pre and post inventories for our patients. 2. Our patients are mostly GMFCS 4 and 5. The PEDI and WeeFIM are not suitable to evaluate the current situation for these severely affected patients and compare between groups since they will have minimal scores (floor effect).

Statistics

Group characteristics were compared for mean age, time of follow up, age of pump implantation, gender and GMFCS level using a Chi-squared test. Scores for the effect of ITB treatment were divided in three categories: improvement (much better, somewhat better), no change, or deterioration (much worse, somewhat worse). Scores were compared between groups per domain and per item using a non-parametric independent samples (Kruskal-Wallis) test. If significant differences were found with the non-parametric independent samples (Kruskal-Wallis) test, a Mann-Whitney test was used to determine individual group differences. $p<0.05$ was considered statistically significant. All analyses were performed with IBM SPSS version 20.

RESULTS

Patients

Eighty-three patients met the inclusion criteria in 2011. Four patients refused to participate when contacted by phone. Therefore, questionnaires were sent to 79 patients. Seventy patients returned the questionnaires. Two questionnaires were incomplete (>10% missing answers) and were excluded from analysis. Questionnaires of 68 patients (82% overall response rate) were included in the analysis. The mean age of the patients was 17.3 years (standard deviation [SD] 5.9; range 5.5-31.9), GMFCS II n=1, GMFCS III n=7, GMFCS IV n=15, GMFCS V n=45, mean age at implantation was

12.9 years (SD 5.0; range 4.6-28.2), follow-up 4.4 years (SD 2.7; range 0.3-9.3) male to female ratio, 40:28. In 2007 the same questionnaires had been sent to six patients with PND. Three of these patients were treated with ITB for less than two years at that time. At follow up two of these three patients deceased in the previous year due to respiratory problems. A new questionnaire was sent to the other patient. For this patient the most recent questionnaires were used in data analysis. For the other three previously included patients the questionnaire available from 2007 was used. Of those three patients, two were still using ITB at the time of the new survey. One pump was explanted after nine years due to insufficient effect of ITB treatment.

Of the 68 patients, 39 were diagnosed with SCP, 13 with DCP and 16 with PND. The PND group included patients with hereditary spastic paraparesis (HSP, n=5), metachromatic leukoencephalopathy (n=2), Leigh's disease (n=1) neuronal ceroid lipofuscinosis type 1 (n=1), mitochondrial encephalopathy (n=1), progressive primary dystonia (n=1), spinocerebellar syndrome (n=1), neurodegenerative disease (n=1), progressive bilateral spastic paresis (n=1), motor neuron disease (n=1). Patient characteristics are presented in Table 1.

Table 1. Patient characteristics

Diagnosis	N	Mean age, yrs (SD; range)	GMFCS II	III	IV	V	Mean age implantation, yr (SD; range)	Mean follow up, yrs (SD; range)	Gender M:F
SCP	39	17.4 (5.0; 8.4-28.5)	0	5	12	22	12.4 (4.0; 5.0-24.1) *2	5.0 (2.5; 0.5-9.3) *3	25:14
DCP	13	20,5 (6.5; 8.4-31.9) *3	1	0	1	11	16.0 (5.3; 7.0-24.4) *1,3	4.5 (3.2; 1.2-9.2)	6:7
PND	16	14,4 (5.9; 5.5-30.4) *2	0	2	2	12	11.7 (6.3; 4.6-28.2) *2	2.8 (1.9; 0.3-6.6) *1	9:7
Total	68	17.3 (5.9; 5.5-31.9)	1	7	15	45	12.9 (5.0; 4.6-28.2)	4.4 (2.7; 0.3-9.3)	40:28

N, number; yrs, years; SD, standard deviation; GMFCS, gross motor functioning classification system; M, male; F, female; SCP, spastic cerebral palsy; DCP, dystonic cerebral palsy; PND, progressive neurological disease; *, $p<0.05$; [1], compared to spastic CP; [2], compared to dystonic CP; [3], compared to progressive neurological disease.

Questionnaire

The effect of ITB treatment on the level of functioning

For the four domains (mobility, personal care, communication and comfort) the SCP and DCP patients show significantly more improvement than the PND patients for mobility and comfort (Fig. 1a-d). When looking into the different items, the only significant difference is found in the effect on startles (domain comfort). The SCP and DCP groups score significantly better for the effect on startles than the PND group. In contrast to the

SCP and DCP group where startles improve in some patients, startles remain unchanged for all PND patients (Fig. 2). Within the PND group, subgroup analysis was done for the HSP group which did not reveal differences for HSP with the rest of the group for any of the outcome measures (data not shown).

Expectations are met in 82.1% of the SCP patients, compared to 84.6% of the DCP patients and 78.6% of the PND patients, which is not significantly different. The SCP and PND groups scored satisfaction as 7.0 on a 10 point VAS scale. The DCP group scored 8.0. Satisfaction scores do not differ significantly between groups.

DISCUSSION

The aim of this study was to compare the effect of ITB treatment on ADL in patients with SCP, DCP and PND. We used a broad questionnaire for these relatively severely affected patients in order to get an impression on the extent of the effect on all relevant domains.

The effect of ITB treatment on the level of functioning

Previous studies showed positive effects of ITB treatment on individual problems of daily life.[4,5,7-9] Treatment goals are often met.[7] The experiences with ITB treatment in PND patients in childhood are limited11 but seem to be comparable to ITB effects in CP patients.[12,14,15] ITB treatment decreases both dystonia and spasticity.[1,2,8,10,16] We compared the effect of ITB treatment on activities of daily life between SCP, DCP and PND and found a significant difference in the effect on mobility and comfort between the PND group and the two CP groups. The PND group is rather heterogeneous. Subgroup analysis was not feasible due to the small numbers, except for the HSP group (n=5), which did not differ from the rest of the PND group on any of the outcome measures.

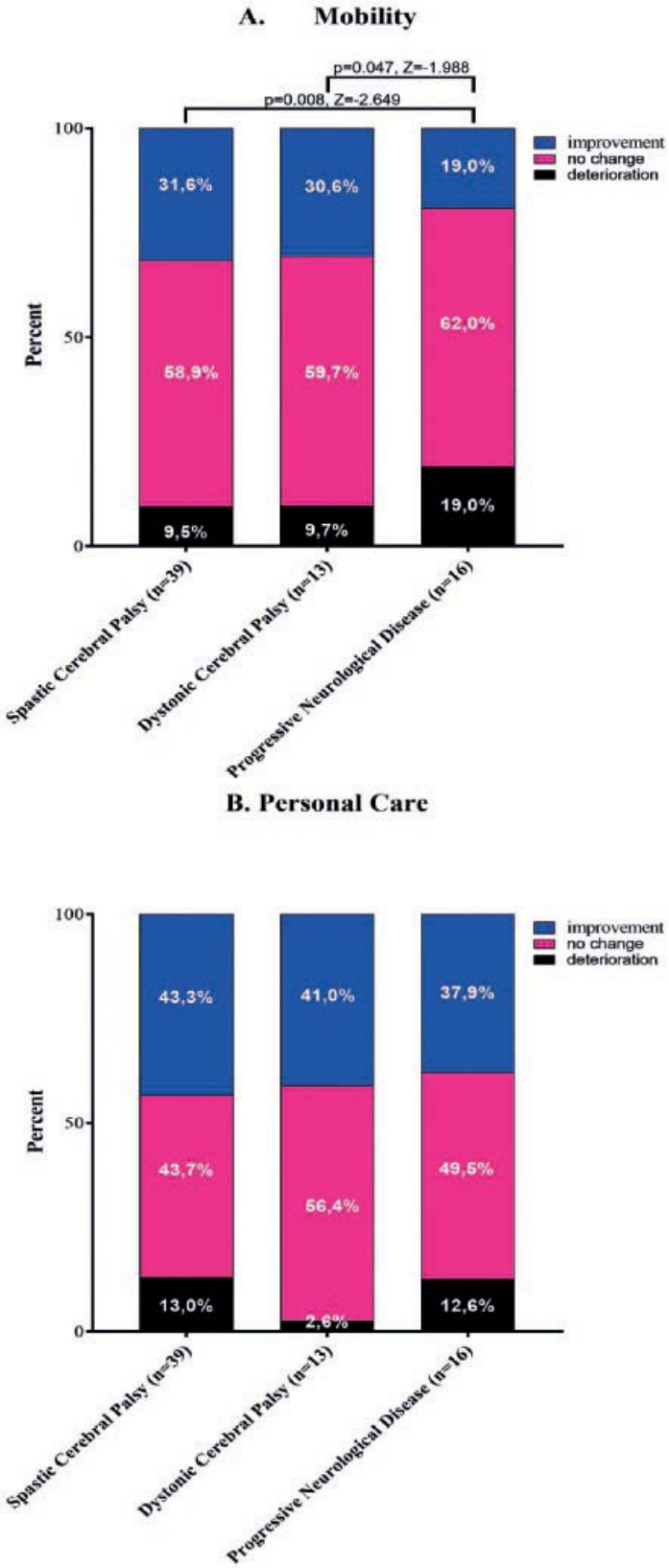
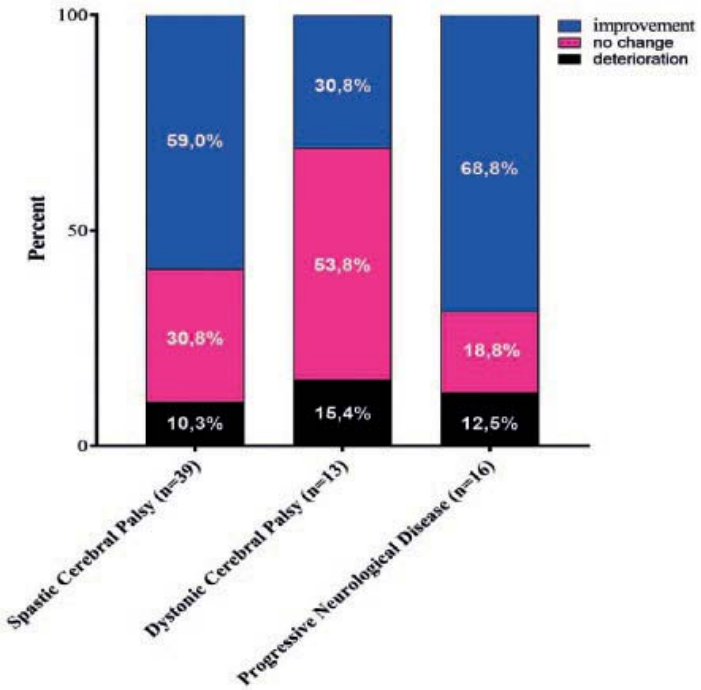
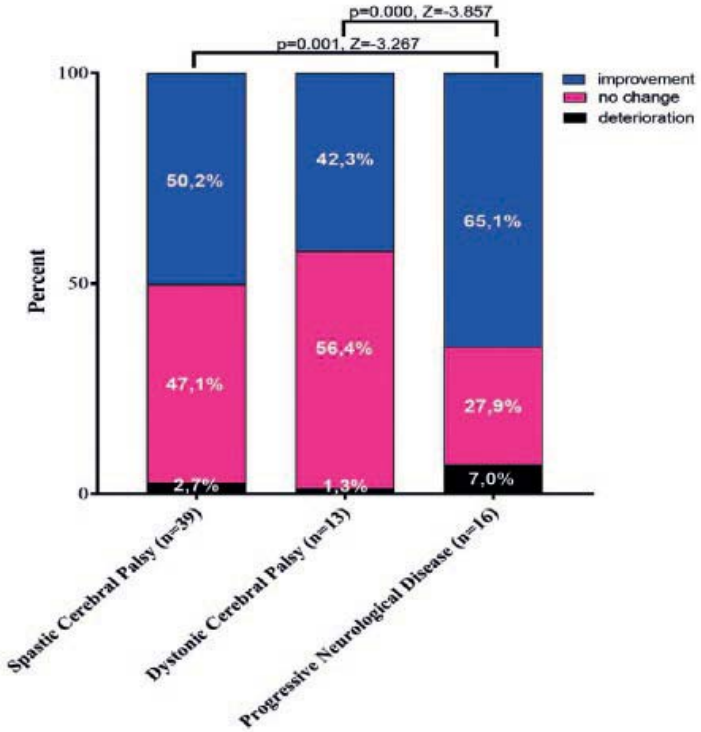


Figure 1. (a) Changes in mobility during intrathecal baclofen treatment (percent of total number of items within domain). There is a statistically significant difference between the CDP group and the PND group with p = 0.047 and Z-score = -1.988 and furthermore between the spastic group and the progressive group with p = 0.008 and Z-score = -2.649 (Mann Whitney). (b) Changes in personal care during intrathecal baclofen treatment (percent of total number of items within domain). There are no significant differences between groups. (c) Changes in communication

C. Communication



D. Comfort



during intrathecal baclofen treatment (percent of total number of items). There are no significant differences between groups. (d) Changes in comfort during intrathecal baclofen treatment (percent of total number of items within domain). There is a statistically significant difference between the DCP group and the PDN group with p = 0.000 and Z-score = -3,857 and furthermore between the SCP group and the PDN group with p = 0.001 and Z-score = -3,267 (Mann Whitney).

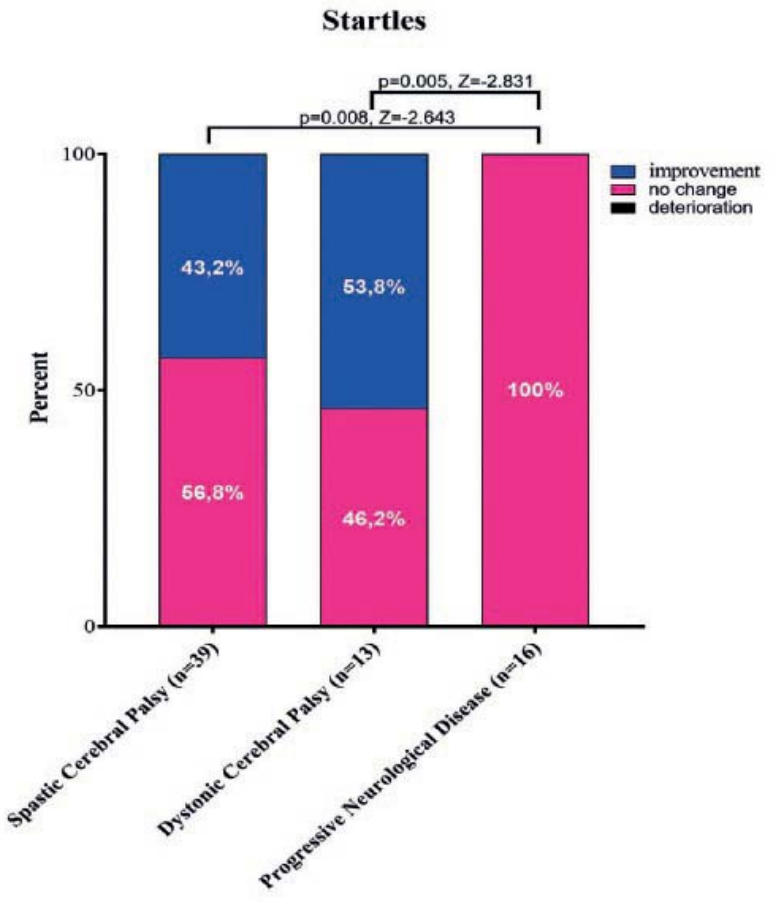


Figure 2. Effect of intrathecal baclofen treatment on startles. (percent of total number of items). There is a statistically significant difference between the DCP group and the PND group with p = 0.005 and Z-score = -2,831 and furthermore between the SCP group and the PND group with p = 0.008 and Z-score = -2,643 (Mann Whitney).

Mobility

Fewer patients showed improvement and more patients showed deterioration in the PND group compared to both CP groups. Deterioration of mobility is to be expected in patients with progressive neurological disease and ITB does not influence this process. In this study, the follow up time for the PND group was significantly shorter than the follow up time of the SCP group. This is partly due to the progressive nature of the disease with early death in some of these patients. For the patients with a longer survival, it is to be expected that over time, the difference between groups will increase even further.

Personal care

The effect on personal care was not significantly different between groups. As a result of decrease of spasticity and/or dystonia, it is presumable that care will be facilitated in all groups. We presume that longer follow up time for the PND group might demonstrate a significant differential effect in the different patient groups.

Communication

The differences between groups on the domain of communication did not reach statistical significance, however there was improvement in more patients in the DCP group than in the other groups (53.8% vs 30.8% (SCP) and 18.8% (PND)) but. Pueyo et al. showed that DCP patients showed better performance in auditory comprehension, visuospatial abilities, immediate visual memory and working verbal memory than SCP patients.[18] Previous studies found that the comprehension of spoken and written language (receptive communication) was influenced by type of motor disorder, with the spastic CP patient being more affected than the dystonic patients.[17] In addition, in severely affected (GMFCS IV and V) bilateral spastic and dystonic CP patients expressive communication is severely hampered.[17,19]

Consequently, in our study we expect that the DCP patients will have better cognitive functions but all groups will have impaired expressive communication due to the severity of the motor disorder. The motor disorder is expected to improve with ITB treatment, resulting in an increased ability for expressive communication in all groups. However, comprehension will not change with ITB treatment. Accordingly, the DCP group, with their pre-existing good understanding, will have more capacities for interaction and communication than the SCP and PND groups, for whom the receptive communication will not change, resulting in a less evident change in interaction/communication.

There are several possible explanations why we did not find a significant statistical difference in the effect of ITB treatment on communication. Firstly, the number of patients is low. Secondly, the domain of communication consisted of only one item. In the questionnaire no distinction is made between receptive and expressive communication. It is possible that with more items, the difference would have been clearer. Thirdly, we omitted to ask for the use of communication aids and as a result we were not able to control for this important factor.

Comfort

The PND group showed more deterioration and less improvement in comfort during ITB treatment than the two CP-groups. The only item in this domain that was different

between groups was the effect on startles. This reflex is more profound in CP children than in typically developing children.[20] It is thought that perceptual disorders are the underlying cause of the startle reflex in children with cerebral palsy.[13] Startles did not change in the PND group in contrast to the SCP group and the DCP group where respectively 43.2% and 53.8% of patients improved. For the CP-groups, this is consistent with the findings of Krach et al. who showed a decrease of startles of 54% with ITB.[21] Patients with significant startles should be counselled before giving ITB treatment that decreasing spasticity does not necessarily mean decreasing startles.

In questioning about satisfaction, some of our patients reported an increase of scoliosis resulting in more discomfort. Scoliosis can occur or progress in patients during ITB treatment but ITB treatment has not been proven to influence the development or progression of scoliosis,[22] also when compared to a control group of similar patients without ITB.[23] Scoliosis is a common complication that may develop during growth in severe neurological disease.[11] Our study did not ask about scoliosis specifically and only a few patients spontaneously reported scoliosis and related problems. We cannot draw conclusions for our patient group but we feel that counselling before ITB treatment is recommended. Patients must know that scoliosis can deteriorate or occur despite the treatment, and that monitoring for scoliosis is needed.

Satisfaction

There is no difference in satisfaction between groups. Previous studies show that most patients are satisfied with ITB treatment.[7,12,21] A score of 7.0 on a VAS scale was given for overall satisfaction in PND patients[12] and 88% of patients with CP would choose for ITB treatment again if they had the choice.[21] In both patient groups daily care improved, which in our opinion resulted in similar satisfaction scores.There are few treatment options for severe spasticity or dystonia and patients and parents might be content with every little improvement they experience, especially in PND where we do not expect much improvement over time given the progressive character of the disease. In PND, complaints are alleviated only temporarily and will worsen as time progresses. Parents and patients are counselled and are aware of the foreseen future progression, which is unrelated to ITB treatment. Therefore, they might be able to put things in perspective and see how ITB treatment benefits their daily lives.

Limitations

This study has several limitations. The main limitation is the retrospective setup of the study, which resulted in different numbers of the patient groups and different follow-up timing.

Due to the limited number of patients we were not able to perform a multivariate analysis to correct for multiple factors. However, this is the largest multicenter study addressing these issues.

The parents were responsible for the responses in the majority of questionnaires (66 of 68 questionnaires). Two questionnaires were filled in by caregivers other than the parents. We do not know if caregivers incorporated the patient's opinion in their answers. Furthermore we asked caregivers to recall the situation at the time of the pump implantation, a few weeks to a few years before this survey. Nevertheless, caregivers reported detailed information on both amelioration and deterioration after starting ITB treatment.

Scales used in the questionnaires have not been validated. No other validated scales were available at the time of this survey to measure ADL in GMFCS level 4 and 5 patients. Outcome measures of the questionnaire were chosen on basis of previous papers[10,24,25] and the expertise of our clinic's health care professionals with the main problematic areas and therapeutic goals for children and young adults with spasticity.

CONCLUSION

With regard to the effect of ITB treatment on the level of functioning, ITB treatment results in almost similar improvement of ADL for patients with SCP, DCP and PND. The PND group shows a less favorable effect on mobility and comfort. In all groups we noticed variation of the effects, some show improvement, others deterioration and many show no change. Current residual difficulties are comparable for all groups. We would expect to find a larger difference between the PND group and the two CP groups since the PND group is expected to worsen over time. It will be interesting to evaluate these patients after a similar follow up time as the CP groups even though this will not be possible for some of the patients due to the progressive nature of their disease with an early death. We expect that there will be more significant differences between the PND group and the CP groups over time.

Prospective, maybe even randomized controlled, trials are needed to obtain higher scientific evidence about the effect of ITB treatment on activities and participation and furthermore to determine which patients are most likely to benefit.

ACKNOWLEDGEMENTS

Patients and caregivers are gratefully thanked for their cooperation.

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APPENDIX I. Questionnaires Part 1

De effecten van intrathecale baclofen behandeling

VOORBEELD INGEVULDE VRAGENLIJST

Naam van kind: Jan

Deze vragenlijst is ingevuld door: de moeder van Jan

1. Kan uw kind zich verplaatsen?

Zelfstandig | *Met hulp* | *In rolstoel* | **Anders**

• Zo ja, doet hij/zij dat **

Evt. nadere toelichting ... met hulp/ondersteuning van één persoon .....
.....

• Is dit veranderd door de baclofen behandeling via de pomp ?

Ja | **Nee**

• Zo ja, gaat het verplaatsen *

Veel beter | *Iets beter* | *Iets slechter* | **Veel slechter**

2. Zijn onderstaande verzorgingspunten veranderd door de baclofen behandeling?

Aankleden*	*Ja*		**Nee**	
Zo ja gaat dit nu*	Veel beter	Iets beter	Iets slechter	Veel slechter
Voeden/eten*	Ja		Nee	
*Zo ja, gaat dit nu**	Veel beter	Iets beter	Iets slechter	Veel slechter

Naam van kind: .....

Deze vragenlijst is ingevuld door: .....

Huidige dosering (zie uitdraai pomp: daily dose): .....

1. Kan uw kind zich verplaatsen?* *Ja* **Nee**

   • Zo ja, doet hij/zij dat** *Zelfstandig* *Met hulp* *In rolstoel* **Anders**

   Evt. nadere toelichting .....
   .....

   • Is dit veranderd door de baclofen behandeling via de pomp ?* *Ja* **Nee**

   • Zo ja, gaat het verplaatsen nu* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

2. Kan uw kind zelfstandig zitten?* *Ja* **Nee**

   • Is dit veranderd door de baclofen behandeling via de pomp?* *Ja* **Nee**

   • Zo ja, is dit nu* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

3. Gebruikt uw kind zijn of haar handen?* *Ja* **Nee**

   • Is dit veranderd door de baclofen behandeling via de pomp ?* *Ja* **Nee**

   • Zo ja, is dit nu* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

4. Kan uw kind zijn/haar hoofd zelfstandig goed rechtop houden?* *Ja* **Nee**

   • Is dit veranderd door de baclofen behandeling via de pomp ?* *Ja* **Nee**

   • Zo ja, is dit nu* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

*** omcirkelen wat van toepassing is.**
**** omcirkelen wat van toepassing is, meerdere antwoorden mogelijk.**

5. Krijgt uw kind eten via de mond? * *Ja* **Nee**

• Zo nee, hoe krijgt uw kind voeding binnen? Is dat via een PEG-sonde /anders* nl .....
.....

• Is het eten/voeden veranderd door de baclofen behandeling via de pomp? * *Ja* **Nee**

• Zo ja, is dit nu* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

6. Is uw kind bij de verzorging volledig afhankelijk van anderen? *

• Zo niet, wat kan hij of zij zelf doen?
.....
.....
.....

• Vindt u de verzorging makkelijker gaan sinds de baclofen behandeling? * *Ja* **Nee**

• Zijn onderstaande verzorgingspunten veranderd door de baclofen behandeling?

Aankleden*	*Ja*			**Nee**
Zo ja gaat dit nu*	Veel beter	Iets beter	Iets slechter	Veel slechter
Voeden/eten*	Ja			Nee
Zo ja, gaat dit nu*	Veel beter	Iets beter	Iets slechter	Veel slechter
Wassen/baden/douchen*	Ja			Nee
Zo ja, gaat dit nu*	Veel beter	Iets beter	Iets slechter	Veel slechter
Ontlasting (poepen)*	Ja			Nee
*Zo ja, gaat dit nu**	Veel beter	Iets beter	Iets slechter	Veel slechter

***omcirkelen wat van toepassing is**

Blaascontrole (plassen)*	*Ja*		**Nee**	
*Zo ja, gaat dit nu**	Veel beter	Iets beter	Iets slechter	Veel slechter

7. Is de mogelijkheid tot transfer (verplaatsen vanuit bed naar (rol)stoel en andersom) veranderd door de baclofen behandeling?* *Ja* **Nee**

- Zo ja, is transfer* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

- Kunt u toelichten wat er precies veranderd is?

.....

.....

8. Is er communicatie mogelijk tussen u en uw kind? * *Ja* **Nee**

- Zo ja, hoe communiceert u met uw kind?

.....

.....

.....

- Is dit veranderd door de baclofen behandeling? * *Ja* **Nee**

- Zo ja, gaat de communicatie nu* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

9. Hoe zou u de stemming van uw kind over het algemeen omschrijven?

.....

- Is de stemming van uw kind veranderd door de baclofen behandeling?* *Ja* **Nee**

- Zo ja, is de stemming van uw kind*

Veel beter *Iets beter* *Iets slechter* **Veel slechter**

***omcirkelen wat van toepassing is.**

10. Heeft uw kind last van plotselinge spierschokken (spasmen)? * *Ja* **Nee**

• Zijn deze spierschokken veranderd in hoeveelheid of ernst door de baclofen behandeling?* *Ja* **Nee**

• Zo ja, is het * *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

11. Heeft uw kind last van schrikken (bv hevige reactie op geluid)? * *Ja* **Nee**

• Is dit veranderd door de baclofen behandeling? * *Ja* **Nee**

• Zo ja, is het schrikken* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

12. Heeft uw kind problemen met slapen s'nachts? * *Ja* **Nee**

• Is daar een bekende reden voor? * *Ja* **Nee**

• Zo ja, welke?

.....

.....

• Is de slaap van uw kind veranderd door de baclofen behandeling? * *Ja* **Nee**

• Zo ja, is de slaap* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

• Kunt u vertellen wat er precies aan veranderd is?

.....

.....

***omcirkelen wat van toepassing is.**

13. Heeft u het idee dat uw kind last heeft van pijn? * *Ja* **Nee**

• Zo ja, waardoor heeft uw kind pijn?

.....

.....

• Is dit veranderd door de baclofenbehandeling? * *Ja* **Nee**

• Zo ja, is de pijn* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

14. Heeft u het idee dat uw kind lekker in zijn/haar vel zit? * *Ja* **Nee**

• Is dit veranderd door de baclofenbehandeling? * *Ja* **Nee**

• Zo ja, hoe zit uw kind nu in zijn/haar vel* *Veel beter* *Iets beter* *Iets slechter* **Veel slechter**

15. Ondervindt uw kind ook problemen van de baclofenbehandeling? * *Ja* **Nee**

• Zo ja, welke problemen?

.....

.....

16. Heeft de baclofen behandeling de verbeterig gebracht die u verwacht/gehoopt had? * *Ja* **Nee**

• Hoe tevreden bent u over de baclofenbehandeling?
Geef een cijfer van 1 tot 10

1	2	3	4	5	6	7	8	9	10

• Kunt u dit toelichten?

.....

.....

*** omcirkelen wat van toepassing is.**

APPENDIX II. Questionnaires Part 2

Probleem scoring

VRAGENLIJST DEEL 2: PROBLEEMSCORING

Naam van kind:.....

Naam van verzorger: .....

Datum:.....

Wilt u hieronder aangeven hoe gemakkelijk of moeilijk het voor u of uw kind is om elk van de volgende taken uit te voeren. Op de onderstaande balken staan cijfers. Omcirkel het cijfer dat volgens u overeenkomt met de pijn, beperkingen of klachten **op dit moment**. Als een vraag niet van toepassing is, omcirkel dan NVT.

VOORBEELD INGEVULDE VRAGENLIJST

Luiers verwisselen?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

Uitleg: Dit kind draagt geen luiers

Heeft uw kind pijn?

Geen pijn Onhoudbare pijn

0	1	2	3	4	5	6	7	8	9	10	NVT

Uitleg: Dit kind heeft geen erge pijn

Het gemak van transfers (verplaatsen vanuit bed in de (rol)stoel en andersom)?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

Uitleg: Het is erg moeilijk om dit kind te verplaatsen maar het lukt nog wel

Persoonlijke verzorging

1. Het aan- en uitkleden?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

2. Luiers verwisselen?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

3. Bips schoon maken?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

4. Gemak van toiletgang (poepen)?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

5. Gemak van baden/douchen/wassen?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

6. Gemak van eten c.q. voeren?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

7. Hoe tevreden bent u met de vooruitgang van uw kind betreffende persoonlijke verzorging door de intrathecale baclofen?

Zeer tevreden Helemaal niet tevreden

0	1	2	3	4	5	6	7	8	9	10	NVT

Positioneren/ verplaatsen

8. Het gemak van positioneren in de rolstoel?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

9. Het gemak van positioneren buiten de rolstoel?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

10. Het gemak van transfers (verplaatsen vanuit bed in de (rol)stoel en andersom)?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

11.Het gemak van het aantrekken van braces of het positioneren van hulpmiddelen?

Niet moeilijk Heel erg moeilijk

0	1	2	3	4	5	6	7	8	9	10	NVT

12. Hoe tevreden bent u met de vooruitgang van uw kind op het gebied van positionering en transfers door de intrathecale baclofen?

Heel tevreden — Helemaal niet tevreden

0	1	2	3	4	5	6	7	8	9	10	NVT

Comfort

13. Mijn kind is meestal gezond en actief

Mee eens — Mee oneens

0	1	2	3	4	5	6	7	8	9	10	NVT

14. Hoe is de stemming van uw kind?

Zeer goede stemming — Zeer slechte stemming

0	1	2	3	4	5	6	7	8	9	10	NVT

15. Heeft uw kind pijn?

Geen pijn — Onhoudbare pijn

0	1	2	3	4	5	6	7	8	9	10	NVT

16. Heeft uw kind last van plotselinge spierschokken

Nooit — Zeer vaak

0	1	2	3	4	5	6	7	8	9	10	NVT

17. Heeft uw kind last van schrikken (bv van geluiden)

Nooit — Zeer vaak

0	1	2	3	4	5	6	7	8	9	10	NVT

Interactie/ communicatie

18. Hoe gemakkelijk is het voor uw kind om met andere kinderen te spelen?

Zeer gemakkelijk Onmogelijk

0	1	2	3	4	5	6	7	8	9	10	NVT

19. Hoe gemakkelijk is het voor uw kind om helemaal begrepen te worden door anderen die uw kind goed kennen (broertjes/zusjes, uzelf)?

Zeer gemakkelijk Onmogelijk

0	1	2	3	4	5	6	7	8	9	10	NVT

20. Hoe gemakkelijk is het voor uw kind om helemaal begrepen te worden door iemand die uw kind niet kent?

Zeer gemakkelijk Onmogelijk

0	1	2	3	4	5	6	7	8	9	10	NVT

21. Hoe tevreden bent u met de mogelijkheden van uw kind voor interactie en communicatie?

Zeer tevreden Helemaal niet tevreden

0	1	2	3	4	5	6	7	8	9	10	NVT

22. Beschrijf uw kind

Zeer gelukkig Zeer ongelukkig

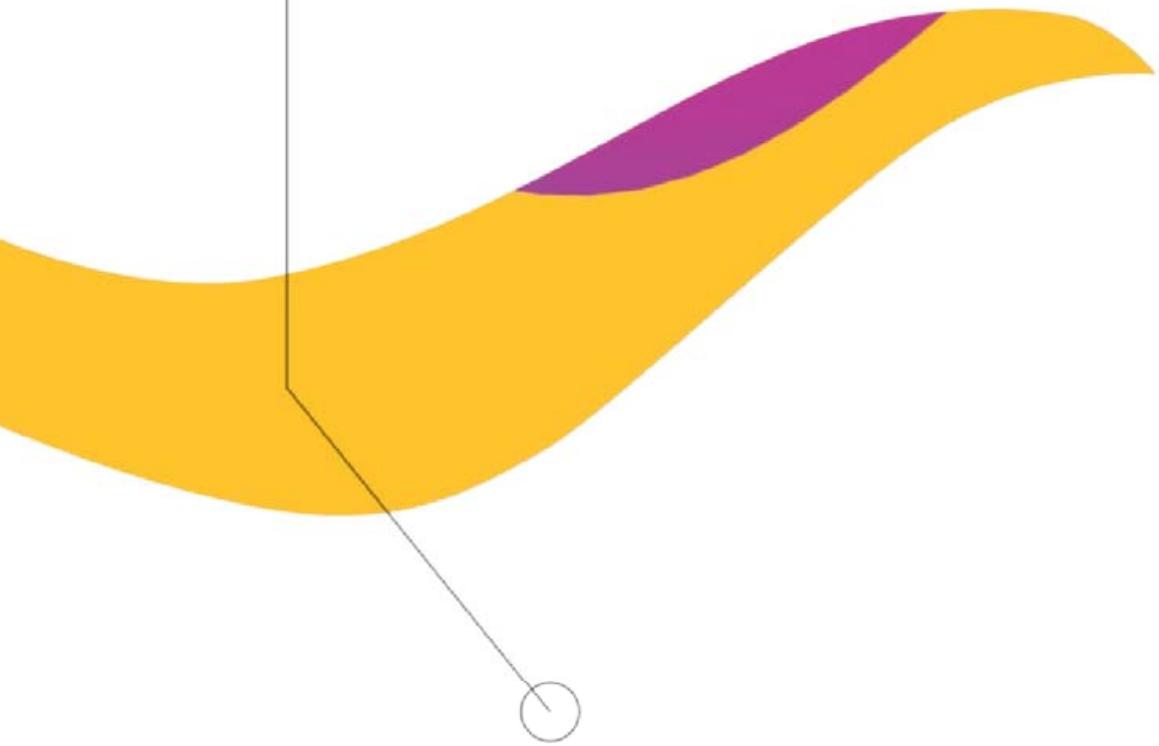
0	1	2	3	4	5	6	7	8	9	10	NVT

Hartelijk dank voor het invullen van de vragenlijst.

U kunt deze nu in de bijgaande envelop aan ons terugsturen.

CHAPTER 9

General Discussion



The studies in this thesis focus on the effect of intrathecal baclofen (ITB) in severely affected children on different levels of the International Classification of Functioning, disability and health for Children and Youth (ICF-CY).

1. The first aim was to investigate the effect of ITB in the treatment of dyskinetic cerebral palsy (CP). The focus was primarily on the effect on individual treatment goals, mostly on the levels of activities and participation, and environmental factors. The secondary focus was on the level of body functions and structures (dystonia, choreoathetosis, spasticity, pain, comfort).

2. The second aim was to describe the effect and the current level of evidence of ITB treatment in progressive neurological disease (PND) of childhood on all ICF-CY levels.

In this chapter the main findings of this thesis are critically appraised. Subsequently, implications for clinical practice and directions for future research are provided.

ITB IN DYSKINETIC CEREBRAL PALSY

The majority of patients with dyskinetic CP are severely disabled with 59-80% of patients being classified in Gross Motor Functioning Classification System (GMFCS) level IV or V.[1-3] When pharmacological treatment is considered in order to decrease functional problems, the first step is oral medication such as baclofen, trihexyphenidyl, or gabapentin.[4] The evidence for the use of oral pharmacological agents for treatment of dystonia and functional problems in dyskinetic CP is limited, and the level of evidence of the reported studies low.[5-7] Efficacy of the different agents ranges from low to possibly ineffective.[5-7] The second step in treatment of dystonia are advanced treatment options, such as ITB and Deep Brain Stimulation.[5-7] These treatment options can possibly be effective, however evidence is limited due to lack of high quality studies.[5,6,8]

Treatment goals for ITB in patients with severe cerebral palsy (GMFCS IV-V) are mostly to improve activities of daily living (e.g. ease of caregiving and sitting), decrease pain and improve quality of life.[9,10] There are no selection criteria for ITB specifically formulated for patients with dyskinetic CP. In clinical practice, selection criteria analogous to those for spastic CP can be used.[9] Following these criteria, ITB can be considered in patients with dyskinetic CP in whom dystonia interferes with activities of daily life or quality of life, and in whom other pharmacological treatment options are insufficiently effective.[9]

Only few previous studies have reported on the effect of ITB in children with severe dyskinetic CP.[10-13] The scientific quality of these studies is low (one case series study, one small retrospective cohort study, and two (small and/or low quality) prospective cohort studies).[10-13] In these studies, severity of dystonia is the most commonly used outcome measure.[10-13] The Barry Albright Dystonia Score (BADS) is the most frequently used outcome measure to report the effect on the severity of dystonia.[10-12] Dystonia decreases in all studies.[10-13] In addition to the effect on dystonia, structured interviews or questionnaires have been used to evaluate the effect on multiple levels of the ICF-CY.[10-12] On the level of body functions and structures improvement has been reported for quality of life, pain, mood, and sleep.[10-12] On the level of activities and participation improvement has been reported for feeding and swallowing, sitting and posture control, upper limb use and communication/speech.[10-12] In the majority of patients no change in autonomy of carrying out daily activities was seen.[12] Furthermore, there was no change in gross motor function.[10] On the level of environmental factors, ease of care has been reported to improve in most patients.[10-12] Treatment goals were reported to be fully reached in the majority of patients.[10] Furthermore, most patients reported to be satisfied with ITB treatment.[12]

Despite the apparent positive outcomes of these studies for the effect of ITB in dyskinetic CP on dystonia and functional problems (e.g. sitting, burden of care giving), the level of evidence provided by these studies is low. Further high quality studies were required to determine the treatment effects of ITB in this population.

The IDYS trial which is presented in chapter 4 and 5 of this thesis, is the first multi-center, double blind, placebo controlled, randomized trial addressing the effect of ITB in patients with severe dyskinetic CP (GMFCS IV-V), primarily on the attainment of individual treatment goals. Thirty-six patients participated in the trial, providing the study with sufficient power. Considering the complex multi-morbidity of patients with dyskinetic CP, a multi-disciplinary team consisting of (pediatric) physiatrists, (child) neurologists, neurosurgeons, clinical neurophysiologists, pharmacists, occupational therapists, physiotherapists, speech therapists and epidemiologists were involved in designing and executing the study.

In the IDYS trial we found that the ITB group scored significantly better on attainment of individually defined treatment goals compared to the placebo group. Our findings are in line with the previously described studies using structured interviews or questionnaires on different areas of daily life.[10-12] Additionally, this randomized controlled study adds substantially to the level of evidence, which was previously low.[5,8]

Secondary outcome measures of the IDYS trial included the severity of dystonia (Dyskinesia Impairment Scale (DIS), BADS).[14-16] We found a significant difference between groups in favor of the ITB group for the dystonia subscale and the dystonia in rest subscale of the DIS. The ITB group remained stable on these scores whilst the placebo group showed slight worsening. We did not find a significant difference between groups on the BADS. This is different from the findings of our pilot study (chapter 3) and other previously published studies, where the BADS showed a clinically significant decrease (decrease of 25% or more).[10-13] These differences might be explained by the double-blind, placebo-controlled, randomized design of the IDYS trial, eliminating bias from the outcome assessments. Furthermore, we used a structured video-protocol for scoring, which was new compared to previous studies.

Individual treatment goals

ITB in dyskinetic CP is a symptomatic, and not curative, treatment to reduce the level of involuntary muscle activity, mainly in order to improve daily functioning and caregiving.[5,6] Standardized questionnaires and outcome measures, available at the time of this thesis, such as the Pediatric Evaluation of Disability Inventory (PEDI) or Gross Motor Functioning Measure (GMFM), do not adequately capture the individual problems in daily life of severely affected patients with very limited motor skills (GMFCS IV and V), who were the focus in the studies in this thesis. Improvement of autonomy of carrying out daily activities is not likely to be achieved with ITB in most of these patients.[12] Gross motor function, measured with the GMFM, has been reported to improve slightly in some dyskinetic patients receiving ITB but on a group level no significant difference was found for the overall GMFM score.[10] In a group of patients with spastic CP, mostly GMFCS IV-V, the sitting domain of the GMFM was reported to improve after one year of ITB.[17] We would expect this to be similar for dyskinetic CP patients. Considering the severity of motor problems in GMFCS IV-V patients, improvement of other domains of the GMFM (e.g. rolling, crawling, standing and walking/running) are not expected to change with ITB and subsequently, were these motor functions were not reported as individual treatment goals.

ITB treatment goals for patients with dyskinetic CP were on multiple levels of the ICF-CY: the level of body functions and structures (e.g. pain and comfort), activities and participation (e.g. mobility including sitting and transfers), and environmental factors (caregiving by others) (Chapter 5). Goal attainment scaling (GAS) is a meaningful measure to determine treatment effects in severely affected patients with dyskinetic CP. Goals are set from a client centered perspective and can include different levels of the ICF-CY.[18,19] Due to the inclusion criteria of the IDYS trial, our population was fairly

homogeneous, but the GAS can also be used in heterogeneous populations where goals differ between patients in type and magnitude.[20] Furthermore, GAS can capture subtle changes that are important for the patient, but difficult to determine using standardized outcome measures. GAS development is, however, time consuming (45 minutes per child) and training is needed before use.[18,19]

Measurement of dystonia and attainment of goals

A previous study by Monbaliu et al. showed lower functional abilities for children with higher levels of dystonia and in addition poorer scores on participation and quality of life questionnaires.[21] Since ITB is aimed to reduce dystonia, we expected that a decrease of dystonia would induce attainment of individual treatment goals. In the IDYS trial we found a significant difference between ITB and placebo for the DIS dystonia subscale and dystonia in rest subscale. However, this difference was based on a slight increase of dystonia in the placebo group whereas dystonia the ITB group remained unchanged. We did not find a difference for the BADS between groups. We furthermore did not find a correlation between changes in dystonia scores and attainment of goals. Based on these findings, the hypothesis that treatment goals are attained due to a decrease of the level of dystonia cannot be confirmed.

As previously described, our findings for the BADS are in contrast with previous studies.[10-13] These studies were not blinded, and as a consequence biased by the knowledge of observer and caregiver, resulting in a lower scientific level.

A limitation of both the DIS and BADS is that there are no test-retest reliability studies available for either scale. In clinical practice we observe that the severity of dystonia fluctuates and can be aggravated by non-specific stimuli such as emotion, stress and intentional movement.[6,22] Test-retest reliability might therefore be limited and the usability of this type of measurement methods in intervention studies questionable. Furthermore, the situation during a clinical consultation or during measurements can cause stress or anxiety, eliciting an increased level of dystonia. As a consequence, the measured level of dystonia might not necessarily correspond to the overall normal daily situation. We do expect that dystonia decreases in the overall normal daily situation, causing attainment of treatment goals, but at this moment, with the current available outcome measures, we are not able to capture this change.

Clinical implications

Conditions for ITB treatment

Patients with dyskinetic CP receiving ITB are often severely affected. With a higher GMFCS level, accompanying impairments such as epilepsy, cognitive impairments, hearing and visual impairments, are more frequently present.[1,3] This makes medical care for these patients complex. As a consequence of this complexity, a multi-disciplinary team consisting of a pediatric physiatrist, child neurologist, neurosurgeon, pediatrician, specialized nurse or physician assistant, occupational therapist, physiotherapist, speech therapist, social worker, and psychologist, is needed for selecting patients for ITB, evaluating ITB treatment effects, treating accompanying impairments and ITB emergency problem solving. Specialized members of the team must be available 24 hours a day, seven days a week, for trouble shooting in case of ITB pump emergencies such as sudden catheter dysfunction which can, without adequate care, result in life threatening withdrawal symptoms. As a result of the possible occurrence of life-threatening complications, patients or caregivers must be able to comply to instructions in case of emergency and adhere to appointments for pump filling. Considering the low prevalence of patients on ITB it might take a long time to travel to a specialized center. When the need for pump filling is frequent, or when traveling is too time consuming and difficult for patients, it should be explored if pump fillings are possible in the home situation, as is the case in the Netherlands. Collaboration between enterprises who perform home-based ITB care and the responsible physicians in specialized clinics must be warranted.

Patient and treatment characteristics

ITB has been shown to be effective for attainment of individual treatment goals in patients with dyskinetic CP (GMFCS IV and V) and is therefore a treatment option in patients in whom oral medication is insufficient and who have goals that can be attained with ITB.

For the treatment of dystonia, baclofen is thought to act on the intracranial level.[11,23] Clinical findings support this hypothesis: in contrast to spasticity, a single intrathecal lumbar bolus of baclofen mostly is not sufficient in decreasing dystonia.[13] In line with what is described in literature, it usually takes several days of continuous intrathecal infusion to see improvement on dystonia and individual problems of daily life. Subsequently, for the treatment of dystonia in CP, catheters in our clinic are usually placed at the level of C4. Drawbacks of this high placement are assumed to be decreased head and trunk control and increased breathing disorders.[24-26] In our study population however, we had only one patient on ITB complaining of decreased trunk control.

Furthermore we did not see a difference in change of risk on sleep related breathing disorders while using ITB compared to placebo, showing that high catheter placement can safely be done.

A test period with ITB treatment via an external micro-infusion pump is conducted in many centers before definitive pump implantation. As described above, a single bolus administration of ITB is not sufficient in patients with dystonia.[13] They require multiple days of continuous ITB infusion via an external lumbar catheter and an external micro-infusion pump. In our clinical experience, we encountered many side effects and major complications during these test periods, including CSF leaks, infection and meningitis (chapter 3). In these cases, ITB treatment had to be stopped prematurely, sometimes before any effect was noticeable. Often, adequate evaluation of the effect of ITB treatment could not be established. For parents and children, it was difficult to separate the effect of complications with the effect of the ITB, making the decision for pump implantation difficult. In the international consensus conference on the appropriate use of ITB, test treatment has been under discussion.[9] It was decided that pump implantation without test treatment can be an option in teams with experience in ITB treatment. For these reasons we no longer include a test period for patients with dyskinetic CP and directly continue to pump implantation.

Dose finding can be troublesome for patients with dyskinetic CP. We developed a dosing schedule, based on clinical experience. We saw that many patients with dyskinetic CP do not respond enough or only temporary to the simple continuous mode in which they receive a stable dosage of baclofen during the day. Patients who do not respond sufficiently or who experience improvement with increments but fading of the effect after several days, are likely to benefit from bolus dosing 3 to 4 times per day and a lower basal rate in between boluses. We suggest using this dosing schedule as a guideline for finding the optimal dosage in patients with dyskinetic CP (schedule is presented in chapter 5, additional information).

Evaluation of ITB treatment

ITB in dyskinetic CP is aimed to decrease dystonia, but current measurement methods for dystonia severity (DIS, BADS) did not show change after three months of ITB treatment (IDYS trial chapter 5). Furthermore, dystonia fluctuates and the measured severity of dystonia does not necessarily correspond to the overall normal daily situation. Therefore, the severity of dystonia as measured with these scales cannot be used to guide optimal dose finding. As described, GAS is a meaningful measure to evaluate the effect of treatment for the individual patient. Attainment of goals,

by interviewing patients and parents, can be used to guide optimal dose finding. For example, when a goal is to facilitate changing a diaper, parents can be questioned about the status of that specific goal. When the goal is attained, further increase might not be needed. However, when the goal is not yet attained, the dosage can be further increased in a stepwise manner, until it is.

During the time of writing this thesis, a new scale was developed, the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD©) Questionnaire.[27] This questionnaire assesses the health status, functional limitations, comfort, wellbeing and ease of caregiving of children with severe CP (GMFCS IV and V).[27,28] Six domains are rated: personal care/activities of daily living (9 items), positioning, transferring and mobility (8 items), comfort and emotions (9 items), communication and social interaction (7 items), health (3 items), overall quality of life (1 item). Domain subscores can be evaluated and a total score can be calculated from these scores. The CPCHILD has an excellent test-retest reliability.[27] In 2015 the Dutch version (CPCHILD-DV) was found to have sufficient reliability and validity to be a representative outcome measure for health status and well-being of non-ambulatory children with CP.[28] A limitation of this scale is that scoring is done from a child-perspective and does not include the burden of care for parents and other caregivers. However, this questionnaire seems to be a useful instrument for children with severe CP, in addition to goal attainment scaling, to evaluate treatment effects.

Future studies

Reliable measurement of dystonia

Current clinical observation scales to rate dystonia are limited in reliability. More reliable measures are needed to measure changes in dystonia in patients on ITB. Future research into the assessment of dystonia should focus on finding reliable outcome measures that are feasible for clinical measurement of dystonia, both in the clinical setting and at home. Instrumented measures of dystonia are future perspectives, which might provide objective assessment during average daily situations. Options to be explored are, for example, automated markerless video tracking, and/or the use of body sensors such as accelerometers and 3D motion trackers with automated pattern recognition. Using these measurements, we can explore the use of machine learning to assess and distinguish dystonia.

Long term effects and characteristics influencing outcome

The IDYS trial evaluated the effect of ITB treatment in dyskinetic CP during the first 3 months of treatment. Several questions on the effect of ITB in dyskinetic CP remain to be answered.

Firstly, the long term effects have yet to be determined. Will the level of dystonia remain stable in the course of time? How often is adjustment of the dose of ITB needed? Will the effect of ITB remain present on the long term? What is the relation between the position of the spinal catheter and the effect of baclofen on dystonia and individual treatment goals?

The use of GAS for evaluation on the long term is questionable. Dystonia will not disappear with ITB. During growth and further into adulthood, it can be expected that other complaints or problems will become more evident for patients. Evaluation of problems from the past will be less relevant. Standardized measurements, sensitive to change, on the level of activities and participation and the degree of external support needed, seem more suitable for long term evaluation.

Secondly, we see that most patients benefit from ITB but not all patients attain their goals. It is important to find out which patients characteristics influence outcome. This knowledge can be used to improve patient selection and counselling.

In order to determine long term effects and which treatment and patient characteristics influence outcome, studies with a large sample size are needed. A randomized clinical trial is not a suitable design to study the effect of ITB over years. A prospective cohort study design is most suitable. National and international networks are important to obtain sufficient sample size. In the Netherlands, a national follow up and treatment register (Nederlands CP Register) has started, providing the opportunity to prospectively register outcomes of ITB on a national level. Another example is the Australian ITB Audit.[29] International harmonization of outcome measures is important to provide the opportunity to pool data of this relatively small patient group.

ITB IN PROGRESSIVE NEUROLOGICAL DISORDERS OF CHILDHOOD

Spasticity and dystonia can be symptoms in children with progressive neurological disorders (PND). ITB has been applied for treatment of severe spasticity or dystonia in patients with PND in order to maintain comfort and decrease the burden of caregiving but the effect and the level of evidence were not clear. In the systematic review presented in chapter 6, we found only six studies, which consisted of five case reports

and one small case series. Between publication of this paper and the present, two more papers (one case report, one case series) were published.[30,31] This means that there is insufficient evidence for the effect of ITB in PND. Despite the low level of evidence of the available studies on the effect of ITB in PND, studies reported improvement of spasticity, spasms, pain, mobility and care giving (chapter 6).[30,31] In the studies in chapter 7 and 8, we found that most patients are satisfied with ITB treatment. Unfulfilled goals and adverse treatment effects are reasons for being unsatisfied or only partly satisfied.

Comparable to severely affected CP patients, ITB treatment goals for PND patients are set on the different levels of the ICF-CY (chapter 6 and 7).[32] On the level of body functions and structures, reduction of spasticity and pain are frequent goals. On the level of activities and participation, goals are mostly related to mobility (e.g. improvement of sitting and transfers). On the level of environmental factors, goals are related to facilitation of care giving. The nature of these goals reflects that most patients with PND receiving ITB are non-ambulatory.

ITB as part of palliative care

Although treatment goals are comparable to those of patients with CP receiving ITB, we questioned whether the effect would be similar. Since PND has a progressive course, we hypothesized that the reported effect would be less evident over time. Chapter 8 presents a cross-sectional questionnaire study. In this study we found that the effect of ITB on caregiving was comparable in spastic or dyskinetic CP and PND. Passive movements of the legs during care giving, transfers and sitting are thought to be facilitated by decreasing spasticity and/or dystonia, independent of the underlying condition, explaining the similar findings between groups.

The effect on comfort and mobility was significantly less favorable for the PND group compared to both CP groups. For CP, spasticity and/or dystonia are expected to be continuously present in more or less similar severity. Thereby the effectiveness of ITB is expected to be maintained on the long term.[8,32] However, the clinical manifestation of PND can be complicated. For diseases such as metachromatic leukodystrophy, demyelination of the peripheral nervous system and the central nervous system can be present in varying ways leading to a clinical picture that changes between patients and within patients over time. Spasticity can be present at first and increase over time due to central nervous system involvement, but when peripheral neuropathy becomes more evident, spasticity decreases and may even disappear. Motor impairments, epilepsy, visual and cognitive impairments will worsen when disease progresses with death as a final consequence. Despite similarity in goals between CP and PND, ITB in PND is part

of palliative care, with the aim to maintain the best achievable level of comfort, delay progressing of contractures and (hereby) facilitate sitting, transfers and care giving.

Clinical implications and advice

Despite the complicated and varying clinical manifestation of PND, a common clinical finding is that discomfort due to pain and spasticity often increases shortly after wheelchair dependency occurs.[30,31] Patients' general health status will also decrease from this moment on. It is advisable to consider ITB at this point in time as part of palliative care, since general health status is still sufficient to allow pump implantation and initiation of ITB will be beneficial for the patient.

Taking the decision for ITB is a difficult one, for patients, parents and caregivers. Decision making should therefore be done in a multidisciplinary team including a pediatric physiatrist, child neurologist, neurosurgeon, pediatrician, specialized nurse or physician assistant, occupational therapist, physiotherapist, speech and language therapist, social worker and psychologist, who have experience with ITB and PND. Follow up should also take place in a multidisciplinary setting since additional problems might occur for which further treatments and comprehensive aids might be needed.

Future studies

Prospective cohort studies are needed to establish the long-term effect of ITB in PND. International collaboration is necessary considering the very limited number of patients with PND who receive ITB. With larger number of patients, a distinction can be made between the effect of ITB in different PNDs. Large international registers using harmonized outcome measures are needed to assure sufficient and adequate data collection. Outcome measures should represent all levels of the ICF-CY. Hereby we can get more insight in the course of symptoms over time when disease progresses. Furthermore, we should gain insight in which patient characteristics, such as type of PND, age of onset, age of loss of mobility, and timing of initiating of ITB, influence outcome. This information can be used to improve patient selection and counselling.

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CHAPTER 10

Samenvatting / Summary

SUMMARY

Movement disorders in childhood are mostly caused by dysfunction of the developing brain due to brain lesions or brain abnormalities. The International Classification of Functioning, disability and health for Children and Youth (ICF-CY) can be used as a framework to categorize personalized treatment goals. The ICF-CY shows that impairments on the level of body functions and structures (e.g. spasticity or dyskinesia) can lead to problems in activities of daily life and participation in society such as mobility, self-care, communication and learning. Activities and participation are furthermore influenced by environmental factors including the availability of assistance for personal care and aids for mobility.

The spectrum of the severity of cerebral movement disorders is broad. This thesis will focus on severely affected children: children with cerebral palsy (CP) classified with the Gross Motor Functioning Classification System (GMFCS) in levels IV and V and children with progressive neurological disorders (PND) who are equally affected. These children are not able to walk unassisted or do not walk at all, and mainly use a (powered) wheelchair for mobility.

The most common cause of cerebral movement disorders and physical disability in childhood is CP. Spastic and dyskinetic CP are the two most common movement disorders (72-91% and approximately 15% of CP respectively). Spastic and dyskinetic movement disorders can also be caused by PND. There are many different diagnoses related to PND in childhood, all of them rare.

When spasticity or dystonia is severe and interferes with comfort, quality of life or activities of daily life, the first step is oral pharmacological treatment. When this is insufficient, the next steps are advanced treatment options. One of these options is intrathecal baclofen (ITB). With ITB, baclofen is administered intrathecally using an implanted micro-infusion pump (Medtronic Synchromed II). The pump is implanted subcutaneously, mostly in the left lower abdomen. A catheter connects the pump with the intrathecal space.

There is some evidence for the short-term effectiveness of ITB for treatment of spasticity in children with spastic CP, provided by single bolus randomized trials. For the effect of ITB in children with dyskinetic CP, the level of evidence is low. For PND, it is unclear what the level of evidence for the effect of ITB is.

The first aim of this thesis was to investigate the effect of ITB in the treatment of dyskinetic cerebral palsy (CP). The focus was primarily on the effect on individual treatment goals, mostly on the levels of activities and participation, and environmental factors. The secondary focus was on the level of body functions and structures (dystonia, choreoathetosis, spasticity, pain, comfort). The second aim was to describe the effect and the current level of evidence of ITB treatment in PND of childhood on all ICF-CY levels.

A narrative review on dyskinetic CP is provided in **chapter 2**. In dyskinetic CP, dystonia and choreoathetosis are often present simultaneously, with dystonia being the dominant feature. Most treatment options focus on the treatment of dystonia, little is reported for the treatment of choreoathetosis. The use of pharmacological treatment in both dystonia and choreoathetosis is not supported by scientific evidence. Neuromodulation interventions such as ITB and deep brain stimulation (DBS) are advanced treatment options. ITB is used to decrease pain, improve comfort, prevent deformities and ease care giving. ITB decreases dystonia but does not lead to changes in functional independence of daily activities. Dystonia shows variable responsiveness with DBS for secondary dystonia (where there is structural damage to the basal ganglia, as in dyskinetic CP), and despite the reported decrease in some patients, the effects on functionality and quality of life are not clear. Multicenter studies are necessary to provide more evidence for the effect for both neuromodulation treatment options.

Chapter 3 describes the results of a pilot study, looking into the effects of ITB in dyskinetic CP, in four patients admitted for ITB test treatment via an external spinal catheter. They received either intrathecal baclofen or intrathecal placebo for four consecutive days after completion of the regular test treatment period. Individual problems of daily life were scored on a visual analogue scale (VAS) from 0 (no problems) to 10 (impossible to do) on three time points: before treatment, during ITB test treatment and during blinded treatment (ITB or placebo). Secondary outcome measures were dystonia (Barry-Albright-Dystonia Scale (BADS)), pain (VAS), and comfort (VAS). The clinically significant difference was determined. Both problems of daily life and dystonia scores improved in all patients during ITB test treatment. Pain and discomfort improved for two patients and worsened in one. This pilot was hampered by several serious complications making reliable assessment during the blinded phase difficult. Despite this limitation and the limited level of evidence of this study, the results of the pilot were promise enough to continue with a clinical trial.

The Intrathecal baclofen in Dyskinetic cerebral palsy (IDYS) trial is a multi-centre, randomised, double-blind, placebo-controlled trial with the aim to provide evidence for the effect of ITB in dyskinetic CP. The study protocol is presented in **chapter 4**. Patients with dyskinetic CP, GMFCS IV and V, who are eligible for ITB treatment were included. They were assigned by blocked randomization (2:2), to receive either placebo or ITB for 3 months via an implanted micro-infusion pump. After three months, outcome measures were assessed and all patients continued on ITB thereafter. The primary outcome measurement was attainment of individual treatment goals using Goal Attainment Scaling (GAS). Secondary outcome measures included dystonia (BADS and Dyskinesia Impairment Scale (DIS)), spasticity (spasticity test (SPAT) and Hoffmann reflex (h-reflex)), range of motion (ROM), pain (VAS), comfort (VAS) and the change in risk of sleep-related breathing disorders (questionnaire). Adverse events were monitored. Power calculations were done and a total of 13 patients per group would provide enough power.

The results of the IDYS trial are described in **chapter 5**. To prevent the study from becoming underpowered due to complications, 18 patients per group were included. Data for final GAS analysis were available for 16 patients in the placebo group and 17 in the ITB group. The mean GAS T-scores at three months were significantly more favourable for ITB, compared to placebo. The DIS dystonia subscore and dystonia rest subscore showed a significant difference in favour of ITB. This difference was caused by an increase of dystonia in the placebo group, compared to no change in the ITB group. On the other secondary outcome measures, no difference between placebo and ITB was found. Number and types of (serious) adverse events were similar between groups. With the IDYS trial, we provide high level of evidence for the effect of ITB on the attainment of individual treatment goals. Current clinical observation scales to rate dystonia are limited in their use due to unknown test-retest reliability. More reliable measures are needed to measure changes in dystonia in patients on ITB.

Chapter 6 presents the results of a systematic literature search on the effect of ITB in patients with PND in childhood. A total of six studies were identified. Five studies were case reports and one study a case series, and therefore of low level of evidence. Outcome measures used were mainly on the level of body functions and structures. On this level, spasticity was objectively measured in three studies and decreased in all during ITB treatment. Furthermore, pain was reported to decrease. On the level of activities and participation no structural outcome measures were used. Subjective improvement of dressing, hygienic care and positioning in a wheelchair were described.

One of the studies included in the review of chapter 2 reported satisfaction on ITB in six patients with PND. This study is described in **chapter 7.** The mean follow up time of these patients was 3.3 years (SD 2.9). Parents were asked if they were satisfied with ITB treatment (yes/no/partially) and asked to score satisfaction on a Visual Analogue Scale (VAS) ranging from 0 (poorest score) to 10 (most optimal score). Four parents reported satisfaction with ITB treatment, one was partially satisfied and one was not satisfied. The mean satisfaction score (VAS) was 7.5 (SD 1.6, range 6–10). Since parents in this study reported moderate to good satisfaction, we conclude that ITB could be a valuable treatment option in patients with PND.

Intrathecal baclofen is used for treatment in spastic CP, dyskinetic CP and PND. CP and PND share symptoms, but the etiology and the course of these disorders is very different. In **chapter 8** the effect of ITB on the domains of mobility, personal care, comfort and communication was assessed. Satisfaction was scored (VAS). Results were compared between groups. Caregivers of 68 patients completed the questionnaire. Thirty-nine patients were diagnosed with spastic CP, 13 with dyskinetic CP and 16 with PND. The PND group had the shortest follow-up time. They scored significantly less favorably for the effect on mobility and comfort. The positive effect on personal care and communication was similar in all groups. Expectations were met in approximately 80% of the patients in all groups. Satisfaction scores were similar between groups as well. Given the progressive nature of PND and the only short follow up period in this study compared to the CP groups, it is interesting to see if the positive effects of ITB found in PND remain present after a longer follow up period.

Chapter 9 presents a critical appraisal of the findings of the studies described in this thesis. ITB seemed promising for treatment of dyskinetic CP but the level of evidence was low. With the results of the IDYS trial we provided high level of evidence for the effectiveness of ITB for attainment of individual treatment goals. Measurement of dyskinesia is troublesome with the current available outcome measures and should not be primarily used for evaluation. Attainment of treatment goals provides more reliable information about the actual treatment effect. Other options for measuring the severity of dystonia should be explored in the future. Furthermore, future research assessing long term effects and the influence of treatment and patient characteristics is needed. An (inter)national register such as the Nederlands CP register (Dutch CP register), will provide a good basis for a prospective longitudinal cohort study, ensuring sufficient patient numbers and harmonisation of outcome measures.

For patients with PND, the level of evidence for the effect on ITB is very low. However, most patients seem to benefit from ITB and ITB should be considered as part of palliative care. International trials with a longer follow up period and larger numbers of patients are needed to provide information about, amongst others, adequate selection of patients and appropriate timing of initiation of ITB.

SAMENVATTING

Cerebrale bewegingsstoornissen omvatten een breed spectrum aan uittingsvormen waarbij ook de ernst erg uiteenlopend is. Dit proefschrift richt zich op ernstig aangedane kinderen. Dit zijn kinderen met cerebrale parese (CP) die geclassificeerd worden op de Gross Motor Functioning Classification System (GMFCS) in niveau IV en V, of kinderen met progressieve neurologische aandoeningen (PND) die net zo ernstig aangedaan zijn in hun motorisch functioneren. Deze kinderen kunen niet zelfstandig lopen, of kunnen helemaal niet lopen, en gebruiken voornamelijk een (elektrische) rolstoel voor mobiliteit.

Bewegingsstoornissen bij kinderen worden voornamelijk veroorzaakt door dysfunctie van het in ontwikkeling zijnde brein door beschadigingen of aanlegstoornissen. De International Classification of Functioning, disability and health for Children and Youth (ICF-CY) kan gebruikt worden als kader om de complexiteit van problemen die optreden bij cerebrale bewegingsstoornissen te omvatten. De ICF-CY maakt verbinding tussen het niveau van lichaamsfuncties en structuren (bijv. spasticiteit of dyskinesie), welke kunnen leiden tot problemen op het gebied van activiteiten in het dagelijks leven of participatie in de maatschappij zoals mobiliteit, zelfverzorging, communicatie en leervaardigheid. Activiteiten en participatie kunen daarnaast nog worden beïnvloed door omgevingsfactoren, waaronder de beschikbaarheid van hulp bij persoonlijke verzorging en hulpmiddelen voor mobiliteit.

De meest voorkomende oorzaak van cerebrale bewegingsstoornissen en lichamelijke beperkingen in de kindertijd is CP. Spastische en dyskinetische CP zijn de twee meest voorkomende bewegingsstoornissen (respectief 72-91% en ongeveer 15% van CP). Spastische en dyskinetische bewegingsstoornissen kunen daarnaast ook veroorzaakt worden door PND. De meeste onderliggende diagnosen van PND zijn zeldzaam.

Wanneer spasticiteit of dystonie ernstig zijn en een negatieve invloed hebben op comfort, kwaliteit van leven of activiteiten in het dagelijks leven, zal als eerste stap orale farmacologische behandeling overwogen worden. Als dit onvoldoende werkt, zal de volgende stap invasieve behandelopties omvatten. Eén van deze opties is intrathecale baclofen (ITB). Met deze behandeling wordt baclofen intrathecaal afgegeven door middel van een geïmplanteerde micro-infusie pomp (Medtronic Synchromed II). De pomp wordt subcutaan geplaatst, meestal in het linker onder kwadrant van het abdomen. Een katheter verbindt de pomp met de intrathecale ruimte waar de baclofen wordt afgegeven.

Er is enig bewijs voor het korte termijn effect van ITB in de behandeling van spasticiteit bij kinderen met spastische CP. Dit bewijs wordt geleverd door gerandomiseerde trials waarbij intrathecale baclofen middels eenmalige bolus wordt toegediend. Voor het effect van ITB bij kinderen met dyskinetische CP, is de bewijskracht laag. Voor PND is het onduidelijk wat het effect is, en wat de bewijskracht voor het effect is.

Het eerste doel van deze thesis was om te onderzoeken wat het effect is van ITB bij patiënten met dyskinetische CP. De primaire focus lag hierbij op het effect op individuele behandeldoelen, in het bijzonder op het niveau van activiteiten en participatie, en omgevingsfactoren. Secundair lag de focus op het niveau van lichaamsfuncties en structuren (dystonie, choreoathetose, spasticiteit, pijn, comfort). Het tweede doel van deze thesis was om het effect en de huidige bewijskracht te beschrijven voor behandeling met ITB bij PND op alle niveaus van de ICF-CY.

Hoofdstuk 2 bevat een beschrijvend review over dyskinetische CP. Bij dyskinetische CP zijn dystonie en choreoathetose vaak simultaan aanwezig. Dystonie is hierin meestal dominant. De meeste behandelopties richten zich op de behandeling van dystonie. Er is slechts weinig bekend over de behandeling van choreoathetose. Het wetenschappelijk bewijs voor het gebruik van orale farmacologische middelen voor zowel dystonie als choreoathetose is zwak. Neuromodulatie met bijvoorbeeld ITB of deep brain stimulation (DBS) zijn een volgende stap in de behandeling. ITB wordt gebruikt om pijn te verminderen, comfort te verbeteren, deformiteiten te voorkomen en de verzorging te vergemakkelijken. Dystonie vermindert door ITB, maar dit leidt niet tot veranderingen in de onafhankelijkheid bij het uitvoeren van dagelijkse activiteiten. Het effect van DBS op dystonie is variabel en meestal slechts zeer beperkt bij patiënten met secundaire dystonie (dystonie veroorzaakt door hersenenschade zoals bij dyskinetische CP). Ondanks dat dystonie bij sommige patiënten verbetert, is het niet duidelijk wat het effect op het functioneren en de kwaliteit van leven is. Multicenter studies zijn nodig om meer bewijs te krijgen voor beide neuromodulatie-opties.

Hoofstuk 3 beschrijft de resultaten van een placebo gecontroleerde pilotstudie naar de effecten van ITB bij vier patiënten met dyskinetische CP. Dit werd gedaan tijdens een ITB proefbehandeling via een externe lumbale katheter. Na het afronden van de reguliere proefbehandeling, ontvingen zij gerandomiseerd en geblindeerd intrathecale baclofen of intrathecale placebo gedurende vier opeenvolgende dagen. Individuele problemen van het dagelijks leven werden gescoord op een visual analogue scale (VAS) van 0 (geen problemen) tot 10 (onmogelijk om te doen). Het scoren werd op drie tijdpunten gedaan: voor het starten van de behandeling, tijdens de proefbehandeling

en tijdens geblindeerde behandeling met ITB of placebo. Secundaire uitkomstmaten waren dystonie (Barry-Albright-Dystonia Scale (BADS)), pijn (VAS), en comfort (VAS). Het klinisch significante verschil werd beoordeeld. Zowel problemen in het dagelijks leven als dystonie verbeterden bij alle patiënten tijdens de proefbehandeling. Pijn en comfort verbeterden bij twee patiënten en verslechterde bij één. Tijdens de pilot waren er enkele serieuze complicaties, waardoor betrouwbare beoordeling tijdens de geblindeerde fase moeilijk was. Ondanks deze beperking en de beperkte bewijskracht van deze studie, waren de resultaten veelbelovend genoeg om een klinische trial te starten.

De intrathecale baclofen bij dyskinetische cerebrale parese (IDYS) trial, is een multicenter, gerandomiseerde, dubbel geblindeerde en placebo gecontroleerde trial met het doel bewijs te leveren voor het effect van ITB bij dyskinetische CP. Het studieprotocol staat beschreven in **hoofdstuk 4**. Patiënten met dyskinetische CP, GMFCS IV en V, die in aanmerking komen voor ITB werden geïncludeerd. Nadat er baseline metingen gedaan waren, werden patiënten gerandomiseerd middels blok randomisatie (2:2) om gedurende drie maanden placebo of ITB te krijgen via een geïmplanteerde micro-infusie pomp. Na drie maanden, werden wederom metingen gedaan. De primaire uitkomstmaat was het behalen van individuele behandeldoelen waarvoor gebruikt gemaakt is van Goal Attainment Scaling (GAS). Secundaire uitkomstmaten waren: dystonie (BADS en Dyskinesia Impairment Scale (DIS)), spasticiteit (spasticiteit test (SPAT) en Hoffmann reflex (H-reflex)), range of motion (ROM), pijn (VAS), comfort (VAS) en de verandering van het risico op slaap gerelateerde ademhalingsproblemen (middels een vragenlijst). Bijwerkingen en complicaties werden gemonitord. Power berekeningen zijn gedaan en er waren 13 patiënten per groep nodig om genoeg power te verkrijgen.

De resultaten van de IDYS trial worden beschreven in **hoofdstuk 5**. Op basis van de power-analyse en rekening houdend met mogelijke uitval werden er 18 patiënten per groep geïncludeerd. Data voor GAS-analyse was beschikbaar voor 16 patiënten in de placebo groep en 17 in de ITB groep. De gemiddelde GAS-score na drie maanden was significant beter voor ITB in vergelijking met placebo. De DIS dystonie subscore en dystonie rust subscore lieten een significant verschil zijn, ten gunste voor ITB. Het verschil werd veroorzaakt door een toename van dystonie in de placebo groep, in vergelijking met een onveranderde score in de ITB groep. Voor de andere secundaire uitkomstmaten, werd geen verschil tussen de groepen gevonden. Bijwerkingen en complicaties, zowel type als aantal, waren gelijk tussen de groepen. Met de IDYS trial, leveren we een hoog niveau van bewijskracht voor het effect van ITB op het behalen van individuele behandeldoelen bij patiënten met dyskinetische CP. Huidige

klinische observatie schalen voor het scoren van dystonie zijn mogelijk beperkt in het gebruik door de nog onbekende test-hertest betrouwbaarheid. Er is behoefte aan betrouwbaardere uitkomstmaten om veranderingen in dystonie bij patiënten met ITB te meten.

Hoofdstuk 6 geeft de resultaten weer van een systematische literatuurstudie naar het effect van ITB bij patiënten met PND in de kindertijd. In totaal zijn zes studies gevonden. Vijf waren case reports en één was een case serie. De bewijskracht is derhalve laag. Uitkomstmaten waren voornamelijk op het niveau van lichaamsfuncties en structuren. Spasticiteit werd in drie studies objectief gemeten en verbeterde in al deze studies tijdens ITB. Daarnaast werd gerapporteerd dat pijn verminderd. Op het niveau van activiteiten en participatie werden geen structurele uitkomstmaten gebruikt. Subjectieve verbetering van kleden, hygiënische verzorging en positioneren in een rolstoel werd beschreven.

Eén van de studies geïncludeerd in het review in hoofdstuk 2 rapporteert de tevredenheid over ITB bij zes patiënten met PND. Dit onderzoek staat beschreven in **hoofdstuk 7**. De gemiddelde follow up tijd van deze patiënten was 3.3 jaar (SD 2.9). Ouders werd gevraagd of zij tevreden waren met ITB (ja/nee/deels) en of ze een rapportcijfer (VAS) konden geven voor hun tevredenheid van 0 (slechtste score) tot 10 (beste score). Vier ouders gaven aan tevreden te zijn met ITB, een was deels tevreden en een was niet tevreden. De gemiddelde tevredenheidsscore (VAS) was 7.5 (SD 1.6, range 6-10). Aangezien ouders matige tot goede tevredenheid rapporteerden, concluderen we dat ITB waardevol kan zijn in de behandeling van patiënten met PND.

Intrathecale baclofen wordt gebruikt voor de behandeling van spastische CP, dyskinetische CP en PND. CP en PND hebben overeenkomstige symptomen, maar de etiologie en het ziektebeloop is erg verschillend. In **hoofdstuk 8** werd het verschil tussen deze groepen voor het effect van ITB op verschillende domeinen (mobiliteit, persoonlijke verzorging, comfort en communicatie) beoordeeld. Tevredenheid werd gescoord (VAS). Verzorgers van 68 patiënten vulden de vragenlijst in. Er waren 39 patiënten met spastische CP, 13 met dyskinetische CP en 16 met PND. De PND groep had de kortste follow-up tijd. De PND groep scoorde significant slechter voor het effect op mobiliteit en comfort. Het effect op persoonlijke verzorging en communicatie was gelijk voor alle groepen. Bij ongeveer 80% voldeed de behandeling aan de verwachtingen. Tevredenheidsscores waren gelijk tussen de groepen. Gezien de progressieve karakter van PND en de korte follow-up tijd voor deze groep in vergelijking met de CP groepen,

is het interessant om te zien op welke manier het effect aanwezig blijft naarmate de follow up langer is.

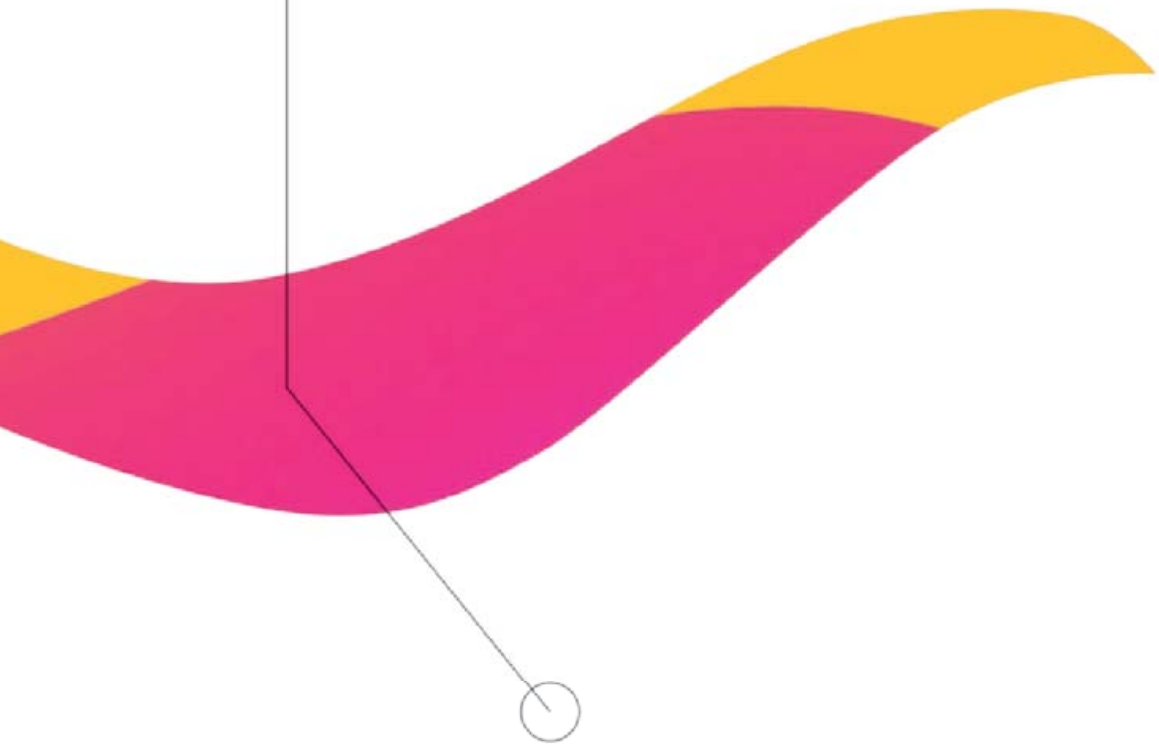
Hoofdstuk 9 bevat een kritische beschouwing van de bevindingen van de studies in dit proefschrift. ITB leek veelbelovend voor de behandeling van dyskinetische CP maar de bewijskracht was laag. Met de resultaten van de IDYS trial leveren we een hoog niveau van bewijskracht voor de effectiviteit van ITB op het behalen van individuele behandeldoelen. Het meten van dyskinesie met de huidig beschikbare methoden is lastig en zou daarom niet primair gebruikt moeten worden voor evaluatie van behandeling. Het behalen van individuele behandeldoelen geeft meer betrouwbare informatie over het werkelijke behandeleffect. Andere opties voor het meten van de ernst van dystonie moeten in de toekomst onderzocht worden. Daarnaast zijn studies nodig die het lange termijn effect en de invloed van behandel en patiënt karakteristieken beoordelen. Een (inter)nationaal register, zoals het Nederlands CP register, zorgt voor een goede basis voor een prospectief, longitudinaal cohort onderzoek waarin voldoende patiënt aantallen en harmonisatie van uitkomstmaten gewaarborgd zijn.

Voor patiënten met PND is de bewijskracht voor het effect van ITB laag. Echter lijken de meeste patiënten wel profijt te hebben van ITB. Op grond van deze bevindingen zijn wij van mening dat ITB overwogen moet worden als deel van het palliatieve beleid. Internationale trials met een langere follow up periode en grote patiënt aantallen zijn nodig om informatie te verschaffen over onder andere adequate selectie van patiënten en het geschikte moment van starten van ITB.

CHAPTER 11

Appendix I.
Dyskinesia Measurement Scales

Appendix II.
IDYS Study Group



Appendix I. Dyskinesia Measurement Scales

A. The Barry-Albright_Dystonia Scale (BADS)

Directions
Assess the patient for dystonia in each of the following regions: eyes, mouth, neck, trunk, and each upper and lower extremity (eight body regions). Write the scores on the lines provided. Rate severity based only on dystonia as evidenced by abnormal movements or postures. When assessing functional limitations, do not score as dystonia-induced functional limitation if other factors such as weakness, lack of motor control, cognitive deficits, persistent primitive reflexes, and/or other movement disorders are contributing to functional limitation.

Definitions of movement disorders:
Dystonia – sustained muscle contractions caused by twisting and repetitive movements or abnormal postures
Spasticity – velocity-dependent resistance to passive movement
Athetosis – distal writhing or contorting movements
Chorea – brief, rapid, unsustained, irregular movements
Ataxia – incoordination of movement characterized by wide based unsteady gait and falling movements

Eyes
Signs of dystonia of the eyes include prolonged eyelid spasms and/or forced eye deviations:
0 – Absent
1 – Slight: dystonia less than 10% of the time and does not interfere with tracking
2 – Mild: frequent blinking, without prolonged spasms of eyelid closure and/or eye movements less than 50% of the time
3 – Moderate: prolonged spasms of eyelid closure, but eyes open most of the time and/or eye movements more than 50% of the time that interfere with tracking, but able to resume tracking
4 – Severe: prolonged spasms of eyelid closure, with eyelids closed at least 30% of the time, and/or eye movements more than 50% of the time that prevent tracking
*Unable to assess eye movements.
Eyes: _____

Mouth
Signs of dystonia of the mouth include grimacing, clenched or deviated jaw, forced open mouth, and/or forceful tongue thrusting:
0 – Absent
1 – Slight: dystonia less than 10% of the time and does not interfere with speech, and/or feeding
2 – Mild: dystonia less than 50% of the time and does not interfere with speechand/or feeding
3 – Moderate: dystonia more than 50% of the time and/or dystonia that interferes with speech and/or feeding
4 – Severe: dystonia more than 50% of the time and/or dystonia that prevents speech and/or feeding
*Unable to assess mouth movements.
Mouth: _____

Neck:
Signs of dystonia of the neck include pulling of the neck into any plane of motion – extension, flexion, lateral flexion, or rotation:
0 – Absent
1 – Slight: pulling less than 10% of the time and does not interfere with lying, sitting, standing, and/or walking
2 – Mild: pulling less than 50% of the time and does not interfere with lying, sitting, standing, and/or walking
3 – Moderate: pulling more than 50% of the time and/or dystonia that interferes with lying, sitting, standing, and/or walking
4 – Severe: pulling more than 50% of the time and dystonia that prevents sitting in a standard wheelchair (e.g. requires special head rest), standing, and/or walking
*Unable to assess neck movements.
Neck: _____

Trunk:
Signs of dystonia of the trunk include pulling of the trunk into any plane of motion – extension, flexion, lateral flexion or rotation:
0 – Absent
1 – Slight: pulling less than 10% of the time and does not interfere with lying, sitting, standing and/or walking
2 – Mild: pulling less than 50% of the time and does not interfere with lying, sitting, standing, and/or walking
3 – Moderate: pulling more than 50% of the time and/or dystonia that interferes with lying, sitting, standing, and/or walking
4 – Severe: pulling more than 50% of the time and dystonia that prevents sitting in a standard wheelchair (e.g. requires adapted seating system), standing, and/or walking
*Unable to assess trunk movements.
Trunk: _____

Upper extremities:
Signs of dystonia of the upper extremities include sustained muscle contractions causing abnormal postures:
0 – Absent
1 – Slight: dystonia less than 10% of the time and does not interfere with normal positioning and/or functional activities
2 – Mild: dystonia less than 50% of the time and does not interfere with normal positioning and/or functional activities
3 – Moderate: dystonia more than 50% of the time and/or dystonia that interferes with normal positioning and/or upper extremity function
4 – Severe: dystonia more than 50% of the time and/or dystonia that prevents normal positioning and/or upper extremity function (e.g. arms restrained to prevent injury)
*Unable to assess upper extremity movements.
Left upper extremity: _____
Right upper extremity: _____

Lower extremities
Signs of dystonia of the upper extremities include sustained muscle contractions causing abnormal postures
0 – Absent
1 – Slight: dystonia less than 10% of the time and does not interfere with normal positioning and/or functional activities
2 – Mild: dystonia less than 50% of the time and does not interfere with normal positioning and/or functional activities
3 – Moderate: dystonia more than 50% of the time and/or dystonia that interferes with normal positioning and/or lower extremity weight bearing and/or function
4 – Severe: dystonia more than 50% of the time and/or dystonia that prevent normal positioning and/or lower extremity weight bearing and/or function
*Unable to assess lower extremity movements
Left lower extremity: _____
Right lower extremity: _____

TOTAL SCORE: _____

B. The Burke-Fahn_Marsden Dystonia Rating scale (BFMDRS)

Region	Provoking factor		Severity factor		Weight		Region Score
Eyes	0-4	x	0-4	x	0,5	=	0-8
Mouth	0-4	x	0-4	x	0,5	=	0-8
Speech/ swallow	0-4	x	0-4	x	1,0	=	0-16
Neck	0-4	x	0-4	x	0,5	=	0-8
R arm	0-4	x	0-4	x	1,0	=	0-16
L arm	0-4	x	0-4	x	1,0	=	0-16
Trunk	0-4	x	0-4	x	1,0	=	0-16
R leg	0-4	X	0-4	x	1,0	=	0-16
L leg	0-4	x	0-4	x	1,0	=	0-16
					Sum	=	0-120

I. Provoking factor

A. General
0 – No dystonia at rest or with action
1 – Dystonia only with particular action
2 – Dystonia with many actions
3 – Dystonia on action of distant part of body or intermittently at rest
4 – Dystonia present at rest

B. Speech and swallowing
0 – No dystonia
1- Occasional, either, or both
2– Frequent either
3– Frequent one and occasional other
4– Frequent both

II. Severity factors

Eyes
0 – No dystonia
1 – Slight: occasional blinking
2 – Mild: frequent blinking without prolonged spasms of eye closure
3 – Moderate: prolonged spasms of eyelid closure, but eyes open most of the time
4 – Severe: prolonged spasms of eyelid closure, with eyes closed at least 30% of the time

Mouth
0 – No dystonia present
1 – Slight: occasional grimacing or other mouth movements (e.g. jaw opened or clenched; tongue movement)
2 – Mild: movement present less than 50% of the time
3 – Moderate dystonic movements or contractions present most of the time
4 – Severe dystonic movements or contractions present most of the time

Speech and swallowing
0 – Normal
1 – Slightly involved: speech easily understood or occasional choking
2 – Some difficulty in understanding speech or frequent choking
3 – Marked difficulty in understanding speech or inability to swallow firm foods
4 – Complete or almost complete anarthria, or marked difficulty swallowing soft foods and liquids

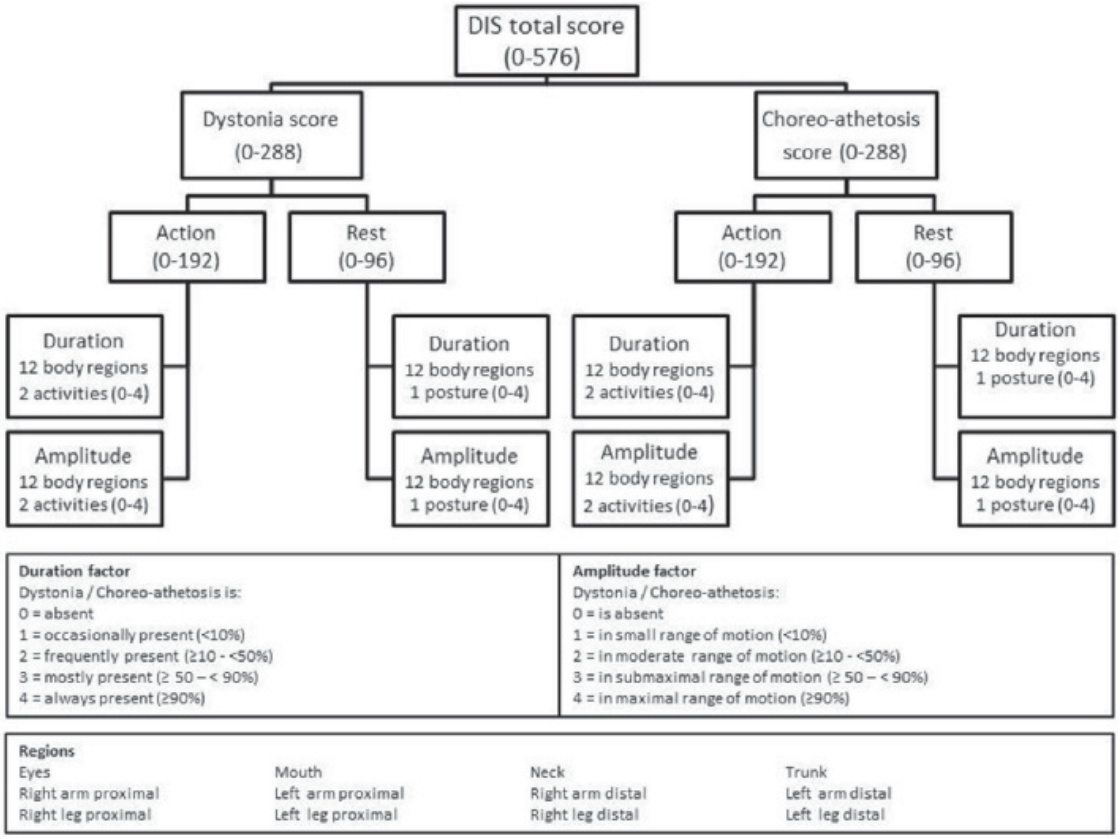
Neck
0 – No dystonia present
1 – Slight: occasional pulling
2 – Obvious torticollis, but mild
3 – Moderate pulling
4 – Extreme pulling

Arm
0 – No dystonia present
1 – Slight dystonia: clinically insignificant
2 – Mild: obvious dystonia, but not disabling
3 – Moderate: able to grasp, with some manual function
4 – Severe: no useful grasp

Trunk
0 – No dystonia present
1 – Slight bending: clinically insignificant
2 – Definite bending: but not interfering with standing or walking
3 – Moderate bending: interfering with standing or walking
4 – Extreme bending of trunk preventing standing or walking

Leg
0 – No dystonia present
1 – Slight dystonia, but not causing impairment: clinically insignificant
2 – Mild dystonia: walks briskly and unaided
3 – Moderate dystonia: severely impairs walking or requires assistance
4 – Severe: unable to stand or walk on involved leg

C. The Dyskinesia Impairment Scale (DIS)



A standardized video protocol is used in which activities and postures are described.

Appendix II. IDYS study group

Department of Rehabilitation Medicine
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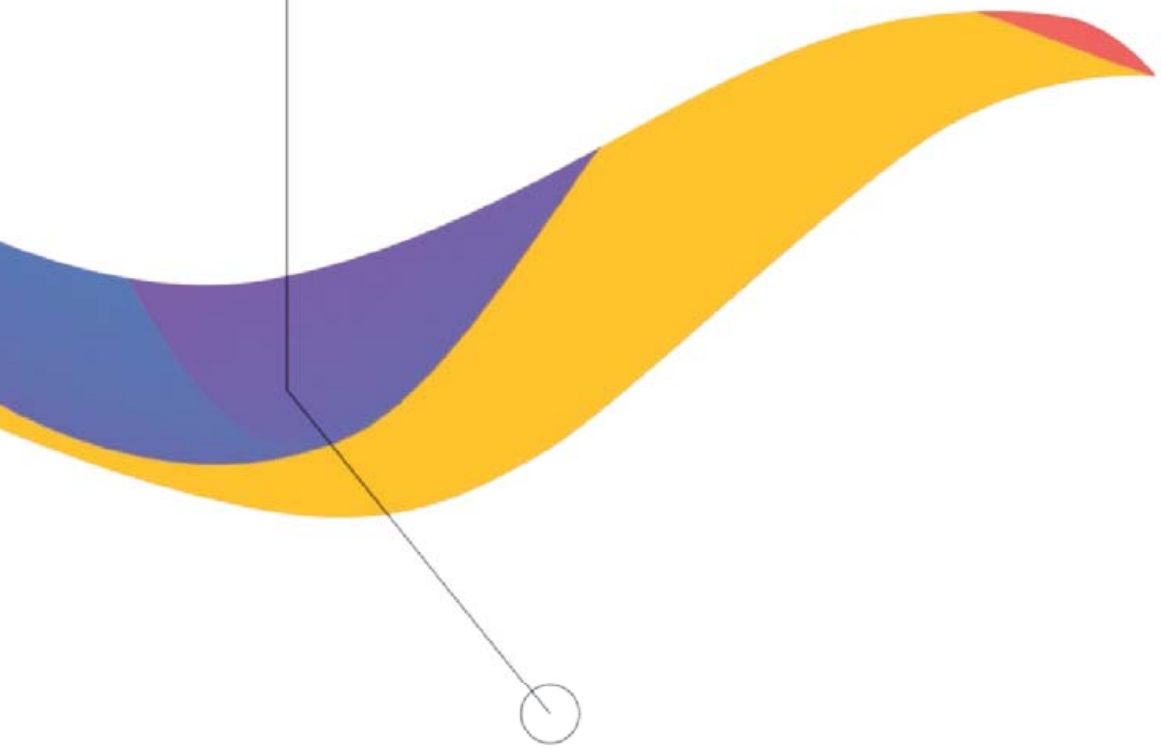
CHAPTER 12

List of abbreviations



ASH,(modified) Ashworth scale

BADS, Barry-Albright dystonia scale

BFMDRS,Burke-Fahn-Marsden dystonia rating scale

C, cervical

cm, centimeters

CSF, cerebrospinal fluid

DCP, dystonic cerebral palsy

DBS, deep brain stimulation

DIS, dyskinesia impairment scale

C-BiLLT, computer based instrument for low motorlanguage testing

CFCS, communication functioning classification system

CP, cerebral palsy

CR, case report

CS, case series

F, female

FSP, familial spastic paraplegia

FU, follow up

GAS, goal attainment scaling

GMFCS, gross motor functioning classification system

h, hour

HSP, hereditary spastic paraparesis

ITB, intrathecal baclofen

kg, kilograms

LE, lower extremities

LOE, level of evidence

LP, lumbar punction

M, male

m(o), month(s)

MACS, manual ability classification system

METC, medical ethical committee

MRI, magnetic resonance imaging

MUmc, Maastricht University medical center

N, number

OL, open label

PEDI, Pediatric Evaluation of Disability Inventory

PEG, percutaneous endoscopic gastrostomy

PND, progressive neurological disease

RCT, Randomized clinical trial

Ref, reference number

ROM, range of motion

SCP, spastic cerebral palsy

SD, standard deviation

SDR, selective dorsal rhizotomy

SPAT, spasticity test

SRBD, sleep related breathing disorders

Th, thoracic

UE, upper extremities

VAS, visual analogue scale

VUmc, VU University medical center

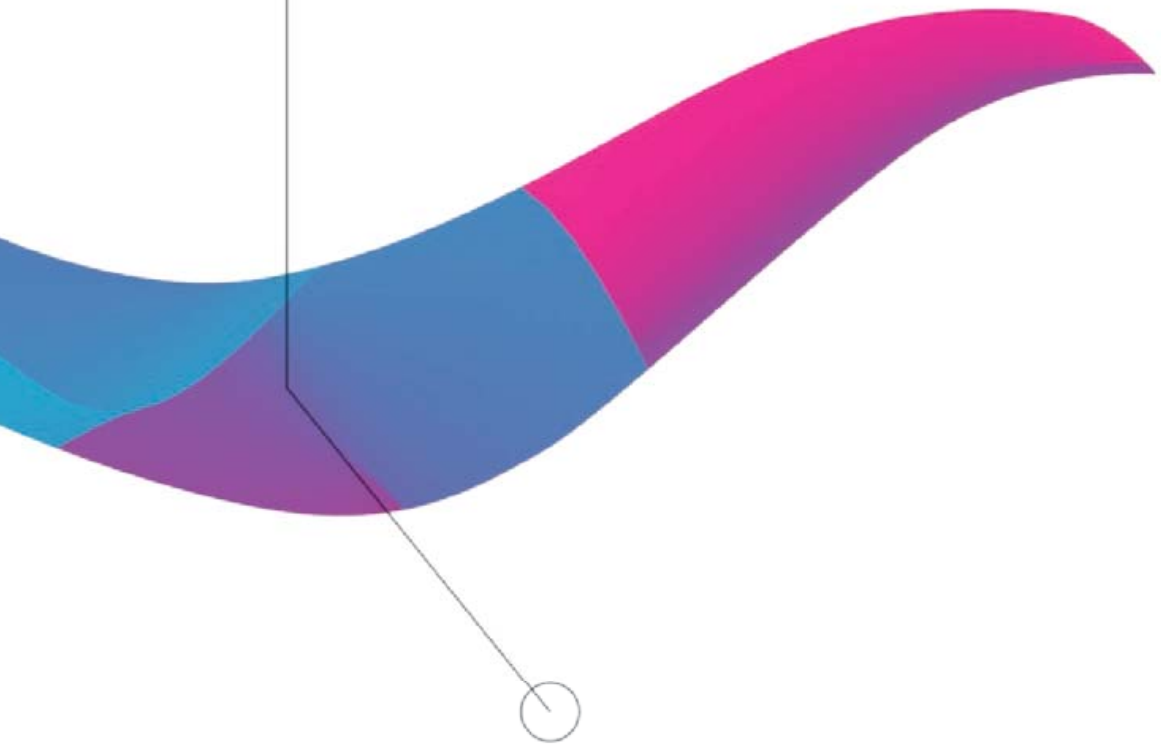
y, year(s)

yr(s), year(s)

µg, microgram

CHAPTER 13

Dankwoord / Word of thanks



DANKWOORD / WORD OF THANKS

Dit kan nog wel eens het langste hoofdstuk van dit proefschrift worden, want zoals het gezegde luidt: “Alleen ga je sneller, maar samen kom je verder”. En een proefschrift schrijven doe je zeker, en gelukkig, niet alleen. Niet alleen tijdens de ruim negen jaar durende weg van het schrijven van mijn proefschrift, maar ook voor de start van mijn promotietraject, ben ik mensen tegengekomen die mijn pad, voor grotere of kleinere delen, met mij mee hebben bewandeld. Zonder deze mensen zou ik niet staan waar ik nu sta, en ik ben velen daarvoor dankbaar.

Als eerst dank aan de **kinderen, jongeren en hun ouders** die meegedaan hebben aan de studies in dit proefschrift, zonder jullie deelname was dit proefschrift er nooit gekomen.

Prof. dr. J.G. Becher, prof. dr. J.G. Vermeulen en dr. A.I. Buizer waren als begeleiders nauw betrokken bij mijn promotie. Beste **Jeroen**, we go back long time! Vanaf 2004 als ik mij niet vergis. Jij was mijn kritische begeleider op afstand terwijl ik als medisch student een wetenschappelijke stage in Canada deed. Het begin van een mooie samenwerking als je het mij vraagt. Je wijze adviezen over zowel mijn loopbaan als andere, meer persoonlijke, toekomstplannen zijn belangrijk geweest in keuzes die ik heb gemaakt. Beste **Jules**, het eerste college wat ik van jou had tijdens mijn geneeskunde opleiding kan ik mij nog levendig herinneren. Ik heb werkelijk geen idee waar het over ging (waarschijnlijk over CP) maar je enthousiasme en levendige manier van presenteren zijn me altijd bij gebleven. Jaren later begon ik onder jouw hoede mijn opleiding tot revalidatiearts. Ik ben blij dat je ondanks je pensioen toch mijn promotor bent gebleven. Dank voor al jouw enthousiasme, steun, kennis en kunde waarop ik altijd heb kunnen vertrouwen. En ook niet onbelangrijk: dat je me hebt geleerd dat ik beter niet kan gaan pokeren. Lieve **Annemieke**, in vele rollen kom ik je tegen en werk(t)en we samen: eerst als een van mijn supervisoren, nu als hoofd van de kinderrevalidatiegeneeskunde, directe collega en copromotor. Ondanks je overvolle agenda mag ik altijd bij je binnen komen voor advies of gewoon om mijn hart te luchten. Dank voor al je begrip, adviezen, steun, begeleiding en geduld de afgelopen jaren. Ik ben trots dat ik met jou verder mag werken in het CP expertise centrum.

Prof. dr. H. van Goudoever, Prof. Dr. V. de Groot, , Prof. dr. M. de Koning-Tijssen, Prof. dr. E. Monbaliu en dr. O. Teernstra, de **leescommissie**, dank voor jullie tijd en kritische blik bij het lezen en beoordelen van mijn proefschrift. Prof. van Goudoever, **Hans**, het is fijn te merken dat jij de kinderrevalidatiegeneeskunde een warm hart toe draagt. Dank dat je voorzitter van de leescommissie wilde zijn. **Vincent**, zonder jou had ik hier niet gestaan want met jou had ik mijn sollicitatiegesprek voor de opleidingsplek tot

revalidatiearts. Ik ben blij dat je me destijds aangenomen hebt en dat ik een aantal jaar later als staflid mocht blijven met jou inmiddels als afdelingshoofd. **Elegast,** bedankt voor het beantwoorden van al mijn vragen over de DIS. We hebben de afgelopen jaren frequent heen en weer gebeld, gemaild en besprekingen gehad. Ik verheug me op de toekomstige Belgisch-Nederlandse en natuurlijk ook de Europese samenwerking die we vorm aan het geven zijn. **Marina**, dank voor de fijne samenwerking binnen het landelijk overleg bewegingsstoornissen bij kinderen en het kijkje dat ik heb mogen nemen in de Groningse DBS keuken.

Speciale dank voor de kerngroep van het **IDYS onderzoeksteam** in zowel het VUmc als MUmc: Prof. dr. J.G. Becher, prof. dr. J.G. Vermeulen, dr. A.I. Buizer, prof. dr. J.S.H. Vles, mw. K. Boeschoten, dhr. D. Soudant, mw. S. Fleuren, dr. H. Haberfehlner. **Hans**, na jouw pensioen heb je het stokje aan Jeroen overgedragen. Je kritische blik heb ik altijd zeer gewaardeerd. Zo ook de hartelijkheid waarmee je me altijd ontvangen hebt tijdens mijn bezoekjes aan Maastricht, en onze mailwisselingen over onderzoek en de goede dingen in het leven. **Karin**, als meet-assistent in het VUmc was jij voor mij van onschatbare waarde. Bedankt voor al je tijd en inzet. Het was veel werk. **Dan** en **Sabine**, voor jullie geldt eigenlijk hetzelfde. Dank voor het plannen en uitvoeren van alle metingen in Maastricht. **Helga**, fijn dat jij als nieuwste lid ons team bent komen versterken. Ik kijk uit naar onze toekomstige projecten. De **IDYS study group** wil ik bedanken voor alle input tijdens de verschillende fasen van het onderzoek. In het **VUmc** waren dit prof. dr. J.G. Becher, dr. A.I. Buizer, mw. K. Boeschoten, dr. J.J.M. Geytenbeek prof. dr. V. de Groot (afdeling revalidatiegeneeskunde), dr. L.A. van de Pol (afdeling kinderneurologie), dr. W.J.R. van Ouwerkerk, drs. K.M. Slot, prof. dr. S.M. Peerdeman (afdeling neurochirurgie), dr. R.L.M. Strijers (afdeling klinische neurofysiologie), dr. E.M.J. Foncke (afdeling neurologie), prof. dr. J. Twisk, en dr. P. van de Ven (afdeling epidemiologie en biostatistiek). In het **MUmc** waren prof. dr. R.J. Vermeulen, prof. dr. J.S.H. Vles, dhr. D. Soudant, mw. S. Fleuren (afdeling neurologie) en dr. O. Teernstra (afdeling neurochirurgie) betrokken. Een deel van de metingen is uitgevoerd op de afdeling klinische neurofysiologie voornamelijk door dr. R.L.M. Strijers en mevr. A. Jongkind en later ook door dr. A. Gouw. **Rob, Anita en Alida**, hartelijk dank voor de fijne samenwerking. Daarnaast is de C-BiLLT afgenomen door dr. J.J. Geytenbeek, mw. J. Bootsma en mw. E. Vaillant. **Joke**, dank voor onze gesprekken onder andere over het wel en wee van het promoveren. **Jaël**, gelukkig blijf je aan de andere kant van het grote water betrokken bij de afdeling. Ik denk met veel plezier terug aan onze gesprekken over vega(n)-recepten en grappen over baby-spinazie. **Emma**, super fijn dat je ons team bent komen versterken. Over een tijdje mag jij jouw proefschrift verdedigen! De MRI's zijn gescoord door de **kinderneurologen** prof. dr. R.J. Vermeulen en dr. L.A. van de Pol.

Beste **Laura**, ik ben blij met onze fijne samenwerking en word erg enthousiast van onze brainstormsessies over wat we in de toekomst allemaal nog willen bereiken met onder andere verder onderzoek. Ik kijk ernaar uit hier verder vorm aan te geven. Grote dank aan de **neurochirurgen**, dr. W.J.R. van Ouwerkerk, dr. M. Slot, en dr. O. Teernstra voor het uitvoeren van de pompimplantaties. **Pim**, zo simpel is dat handwerken van jou niet. Veel dank aan de fantastische ITB verpleegkundigen/P.A. die betrokken zijn geweest: **Tamara**, **Sharony** en **Renske.** Zij zorgden voor het vullen en bijstellen van alle pompen en dat ik op tijd nieuwe onderzoeksmedicatie bestelde. We hebben kritische vragen en goede adviezen gekregen van de **Data Safety Monitoring Board** en de **monitor** van het Clinical Research Bureau, in het bijzonder wil ik prof. dr. P. Huijgens, prof. dr. M. Boers en mw. M. van Leeuwen bedanken.

Naast onderzoeker ben ik natuurlijk ook nog kinderrevalidatiearts waarbij ik in een fantastisch gedreven en bedreven **kinderrevalidatieteam** mag werken. Hier ben ik ontzettend trots op! Lieve Els, Karin, Karen, Mirjam, Eline, Petra, Veronique, Danny, Joke, Emma, Liza, Eefje, Jacqueline, Hestien, dank daarvoor. Ook de lieve dames van de **backoffice, planning en secretariaat**, in het bijzonder Monique, Marit en Heleen, wil ik bedanken voor hun geduld, gezelligheid en creatieve oplossingen.

Een aantal van mijn **mede-onderzoekers** op de afdeling ben ik extra dank verschuldigd. José Maas, Lizeth Sloot en Helga Haberfehlner, dank voor jullie hulp bij mijn EMG vragen en andere onderzoeksperikelen die mijn doktersbrein te boven gingen. Mijn collega **revalidatieartsen in het VUmc**: **Vincent, Annemieke, Louise, Eveline, Carel** en oud-collega's **Mirjam en Renske**, dank voor jullie interesse in de voortgang van het onderzoek en begrip voor mijn afwezigheid als de onderzoekstaken daarom vroegen. **Sanne**, bedankt dat je tijdens jouw fellowship en mijn zwangerschapsverlof de honneurs waar wilde nemen tijdens de metingen. **Eveline,** top dat je mijn kamergenoot bent en ik je ten alle tijden kan storen met al mijn promotie vragen! Dank voor alle goede adviezen. Ik vind het super fijn dat je me bij wil staan als paranimf! We hebben wel een Breezertje verdiend. Het team van het **CP-expertise centrum: Annemieke, Laura, Jaap, Marjolein, Petra, Els, Annet, Pim, Mariam, Melinda, Hans, Agnita en Barend,** wil ik bedanken voor de inspirerende samenwerking binnen onderzoek en onze gezamenlijke patiëntzorg.

Manin Konijnenbelt, **Kirsten** Nienhuis, **Judith** Vloothuis en **Hanneke** Aussems wil ik bedanken voor het enthousiasme waarmee jullie me begeleid hebben bij mijn eerste baan als anios in de revalidatiegeneeskunde. Jullie hebben me enthousiast gemaakt voor ons fantastische vak. De opleiding en het fellowship zouden niet zo leuk geweest

zijn zonder jullie: **Marloes, Francisca, Conny, Olga, Wietske, Irene, Margriet, Maaike, Rimke en Eveline.**

Ook wil ik nog even terug naar het begin van mijn onderzoekscarrière, een wetenschappelijke stage in Canada bij **prof. dr. M. Tarnopolsky**. Mark, I finally am a double doctor, and I owe you many thanks. Without knowing me, you agreed for me to come to Hamilton to conduct a study in boys with Duchenne Muscular Dystrophy. You made me see the beauty of scientific research and how wonderful it goes together with work as a clinician. This has been an inspiration for me troughout my career. Furthermore, I would never have met these lovely ladies if it weren't for you: **Alissa, Erin** and **Michaela**, my dear friends, I so wished you lived closer so we could see more of each other. I really hope we will one day plan a grand reunion together with our families, preferably somewhere on a tropical island!

Mijn lieve vriendinnetjes, ook al zijn we allemaal druk en wonen we niet meer allemaal bij elkaar om de hoek, het is zeker niet uit het oog uit het hart. Het is altijd fijn om jullie te spreken over werk maar vooral ook over de andere dingen in het leven. **Elsbeth**, ik ben zo blij dat we nadat we tijdens onze basisschooltijd en middelbare schooltijd waarin we voor tweeling, stelletje en wie weet wat nog meer zijn aangezien, nog steeds zulke goede vriendinnen zijn. Ik verheug me op het volgende etentje, met of zonder onze mannen. **Carlijn**, ook al waren we jong en hebben we maar een paar jaar bij elkaar in de klas gezeten (groep 2 t/m 4) voordat ik naar het zuiden van het land, we zijn elkaar altijd blijven zien. Ik vind het bijzonder dat we na zoveel jaren, nog steeds zo'n goed contact hebben. Lieve geneeskunde (en bewegingswetenschappen) vriendinnetjes: **Jantina, Nina, Annelies, Tineke en Laurien**, jarenlang hebben we lief en leed gedeeld, dit blijft waardevol. **Jantina,** dank voor alle fijne en gezellige gesprekken tijdens onze eet dates, je steun en enthousiasme. Voor mij ben je goud waard! **Marloes**, jouw blik op zaken levert altijd weer nieuwe verfrissende inzichten op en ik ben blij dat je ook van gedoseerd klagen, wijn, eten en gezelligheid houdt. De andere kant van het land is gelukkig minder ver gebleken dan het lijkt! Andere zeer gewaardeerde vrienden en vriendinnen bedankt voor alle leuke middagen, avonden, (ski)tripjes, de vrolijke en minder vrolijke momenten in het leven die we samen mochten delen en nog mogen gaan delen in de toekomst, in het bijzonder: **Menno** en **Maartje, Lukas** en **Michi, Willemijn** en **Arno, Frits** en **Floor, Kees** en **Lizet, Erik** en **Saskia, Steef** en **Gijs, Tom** en **Eveline**, **Mark** en **Maureen, Liselot** en **Vincent.**

Lieve **familie en schoon familie**, sommigen ver weg en anderen dichtbij, bedankt voor jullie belangstelling in het onderzoek en het meeleven tijdens dit traject. Het is zo

fijn dat ieders deuren altijd open staan voor geplande en spontane familiebezoekjes, etentjes, borrels en noem maar op.

Marleen en **Huub**, wat ben ik blij met jullie als zus en zwager, het is altijd fijn om tijd met elkaar door te brengen. Liefste sis, wie had er in onze tienerjaren ooit gedacht dat wij zij aan zij zouden staan op een dag als deze. Dank dat je mijn paranimf wil zijn. Ik kan altijd op jou, en Huub, rekenen en ben ontzettend trots op wie je bent, en dol op jullie prachtige kinderen, Jack en Kate.

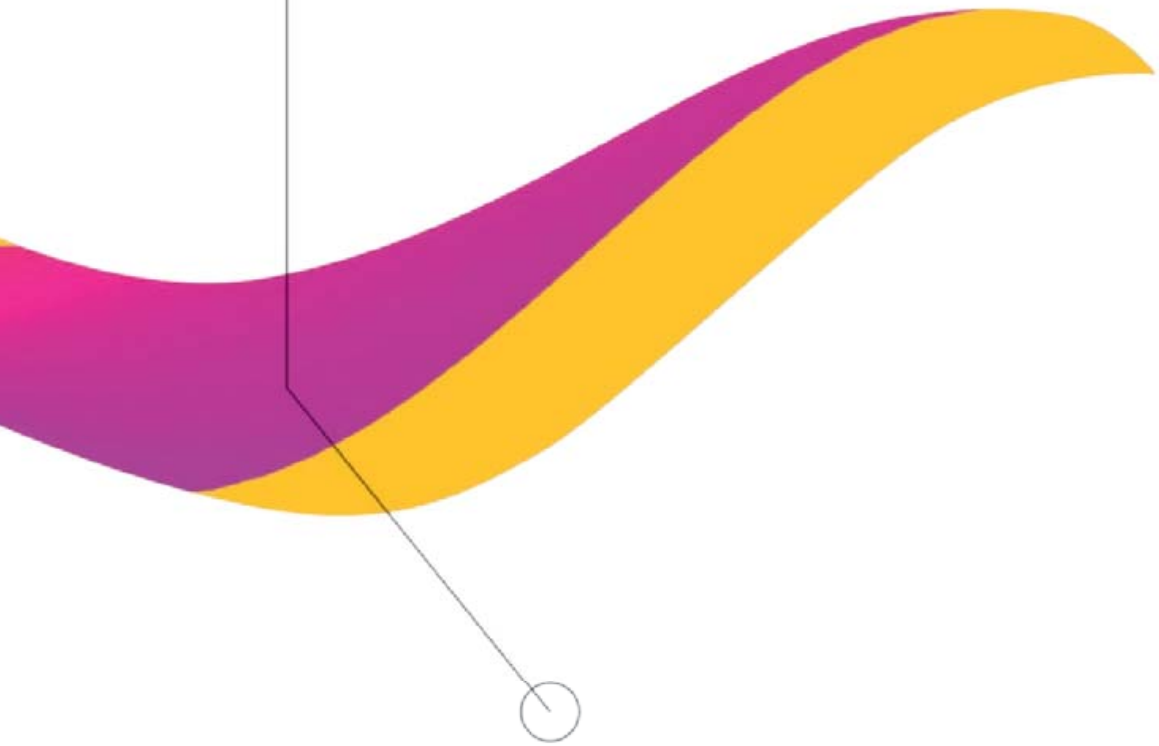
Lia en Ton, papa en mama, ik heb het getroffen met ouders zoals jullie. Door jullie levenslessen, 2 in het bijzonder, heb ik mij altijd gesteund gevoeld maar ook gemotiveerd en vrij om mijn eigen pad uit te stippelen. Dank voor jullie vertrouwen. Speciale dank voor het oppassen op de jongens, helemaal in de laatste fase van mijn proefschrift, hierdoor had ik tijd en rust om mijn boekje af te ronden.

Loek en Quint, mijn jongens, mijn alles. Ik ben zo ontzettend trots op wie jullie zijn en dankbaar dat jullie in ons leven zijn. Jullie maken de wereld mooi.

Lodewijk, mijn liefde, mijn leven. Wat hebben we het goed samen! En wat boffen we met onze jongens! Met jou wil ik later oud worden maar eerst samen nog heel veel mooie momenten beleven.

CHAPTER 14

About the author



fotograaf: Anita Edridge

Laura Alexandra Bonouvrié was born on Sunday March 15th, 1981 in the Military Hospital in Utrecht. Most of her youth she lived in Waalre with her parents and sister Marleen. She completed high school education (VWO) at the Augustinianum in Eindhoven in 1999. After graduation she moved to Amsterdam to study Human Movement Sciences. The year after she was accepted for medical school at the VU University. For her final bachelor thesis, she spend seven months in Hamilton, Ontario, Canada for a research project on the effect of antioxidants in boys with Duchenne Muscular with prof. dr. Mark Tarnopolsky. She obtained her medical degree in 2007 and continued with research, working with dr. Jeroen Vermeulen at the Department of Child Neurology at the VU University medical center (VUmc). Her interest in intrathecal baclofen and dyskinetic cerebral palsy (CP) was aroused during this project.

After working as a resident (not in training) at two neurology departments in Amsterdam, she worked at the rehabilitation center Reade in Amsterdam (formerly Rehabilitation Center Amsterdam) where her interest in rehabilitation medicine was aroused. Laura started her physiatry residency shortly after, in November 2009, at the Department of Rehabilitation Medicine of the VUmc (now Amsterdam UMC). At that time her PhD project also started with writing of the protocol. After completion of her residency in December 2014, she continued with a 2 year fellowship in pediatric physiatry under supervision of prof. dr. Jules Becher and dr. Annemieke Buizer. During this fellowship

she specialized in complex care for patients with spasticity and dystonia (mainly due to CP). Since January 2017, she works as a pediatric physiatrist at the Amsterdam UMC, location VUmc, combining clinical work, research and education.

During her PhD training, as a member of the JOK (young researchers in pediatrics Amsterdam UMC), she organized several trainings for PhD students. She is currently the coordinator of the minor Body in Motion and a member of the national training committee for pediatric physiatry. Furthermore, she is part of the CP center of expertise in the Amsterdam UMC which is led by Annemieke Buizer (www.cpexpertisecentrum.nl), and a promotor of the Dutch National Consultation Group Movement Disorders in Children (LOBBK; Landelijk Overleg Bewegingsstoornissen Bij Kinderen) and the European Dyskinetic CP Network.

Laura lives in Amstelveen with Lodewijk van der Meulen and their two sons, Loek (born Oct 2013) and Quint (born Nov 2015).

LIST OF PUBLICATIONS AND PRESENTATIONS

This thesis is based on the following international peer-reviewed publications:

1. Bonouvrié LA, van Schie PEM, Becher JG, Ouwerkerk WJR, Vermeulen RJ.Satisfaction with Intrathecal baclofen treatment in pediatric patients with progressive neurological disease. *Developmental Medicine and Child Neurology 2008;50(8):636-638*

2. Bonouvrié LA, van Schie PEM, Becher JG, van Ouwerkerk WJR, Reeuwijk A, Vermeulen RJ. Effects of intrathecal baclofen on daily care in children with secondary generalised dystonia:a pilot study. *European Journal of Paediatric Neurology 2011;15:539-543*

3. Bonouvrié LA, van Schie PEM, Becher JG, Ouwerkerk WJR, Vermeulen RJ.Intrathecal baclofen for progressive neurological disease in childhood; a systematic review of literature. *European Journal of Paediatric Neurology 2012;16:279-284*

4. Bonouvrié LA, Becher JG, Vles JS, Boeschoten K, Soudant D, de Groot V, van Ouwerkerk WJ, Strijers RL, Foncke E, Geytenbeek J, van de Ven PM, Teernstra O, Vermeulen RJ. Intrathecal baclofen treatment in dystonic cerebral palsy: a randomized clinical trial: the IDYS trial. *BMC Pediatrics 2013; 13: 175*

5. Bonouvrié L, Becher J, Soudant D, Buizer A, van Ouwerkerk W, Vles G, Vermeulen J. The effect of intrathecal baclofen treatment on activities of daily life in children

and young adults with cerebral palsy and progressive neurological disorder. *European Journal of Paediatric Neurology, 2016 ;20 :538-544*

6. Monbaliu E, Himmelmann K, Lin J-P, Ortibus E, Bonouvrié L, Feys H, Vermeulen RJ, Dan B. Clinical presentation and management of dyskinetic cerebral palsy. *Lancet Neurology 2017;16 :743-749*

7. Bonouvrié LA, Becher JG, Vles JSH, Vermeulen RJ, Buizer AI, on behalf of the IDYS study group. The effect of intrathecal baclofen in dyskinetic cerebral palsy : the IDYS trial. *Annals of Neurology 2019; epub ahead of print*

Other international peer-reviewed publications:

1. Vles GF, Soudant DL, Hoving MA, Vermeulen RJ, Bonouvrié LA, Vles JSH. Long-term follow-up on Intrathecal Baclofen therapy in non-ambulant children with intractable spastic Cerebral Palsy. *European Journal of Paediatric Neurology 2013 Nov;17(6):639-44*

Book chapters:

1. Vermeulen RJ, Bonouvrié LA, Buizer AI, van Ouwerkerk WJR, van Aalst J, Teernstra O, Soudant D, Becher JG (2018). Intrathecal baclofen for dyskinetic cerebral palsy. In: Dressler D, Altenmüller E and Krauss JK (Eds). Treatment of Dystonia (p 229-232). Cambridge: Cambridge University Press.

Invited editorial commentaries:

1. Bonouvrie LA. Intrathecal baclofen in progressive neurological disease: to be considered before all other options fail. Editorial commentary on 'Intrathecal Baclofen Treatment: an option in X-linked Adrenoleukodystrophy' by Helgi Thor Hjartarson, Christoffer Ehrstedt and Kristina Tedroff. *Europ J Paediatr Neurol 2018; 22(1):1*

2. Bonouvrié LA. How to assess goals in intrathecal baclofen therapy. Commentary on: 'Intrathecal baclofen therapy in children: identifying and improving individualised goals' by Peck Yee Liew et al. *Dev Med Child Neurol 2018; 60(4):332*

Contributions to scientific conferences:

Poster presentations:

1. Bonouvrié LA, Becher JG, van Schie PEM, van Ouwerkerk WJR, Reeuwijk A, Vermeulen RJ. Effects of intrathecal baclofen on daily care in children with secondary generalized dystonia: results of a pilot study and a glimpse into the future. Poster. Kindersymposium Amsterdam, 16 februari 2012.

2. Bonouvrié LA, Becher JG, Vles JSH, Soudant D, van Ouwerkerk WJR, Teernstra O, Vles GF, Vermeulen RJ. Comparing the effects of intrathecal baclofen treatment: diagnosis does not matter (much). Poster. VUmc Science Exchange Day, 12 februari 2013.

3. Bonouvrié LA, Becher JG, Vles JSH, Soudant D, van Ouwerkerk WJR, Teernstra O, Vles GF, Vermeulen RJ. The effect of Intrathecal baclofen in spastic cerebral palsy, dystonic cerebral palsy and progressive disease: does diagnosis matter? Poster. Kindersymposium Amsterdam, 6 februari 2014.

4. Bonouvrié LA, Becher JG, Soudant D, Buizer AI, van Ouwerkerk WJR, Vles GF, Vermeulen RJ. The effect of intrathecal baclofen treatment on activities of daily life: does diagnosis matter? Poster. Paediatric Movement Disorders, Barcelona, Spanje, 20 februari 2015.

Oral presentations:

5. Bonouvrié LA, Becher JG, van Schie PEM, van Ouwerkerk WJR, Reeuwijk A, Vermeulen RJ. Intrathecale baclofen behandeling bij dystonie: resultaten van een pilot studie en een blik op de toekomst. Oral presentation. Nederlandse Vereniging voor Kinderneurologie, Middelburg, the Netherlands, April 27th 2012.

6. Bonouvrié LA. Intrathecal baclofen treatment. Invited speaker. European Society for Paediatric Neurosurgeons, Amsterdam, the Netherlands, April 5th 2012.

7. Bonouvrié LA, Becher JG, van Schie PEM, van Ouwerkerk WJR, Reeuwijk A, Vermeulen RJ. Intrathecal baclofen treatment in dystonic cerebral palsy. Oral presentation. 4th International Cerebral Palsy Conference, Pisa, Italy, October 12th 2012.

8. Bonouvrié LA. Intrathecale baclofen bij dystone cerebrale parese. Invited speaker. Medtronic User Day, St. Michielsgestel, the Netherlands, June 13 th 2014.

9. Bonouvrié LA, Becher JG, Vermeulen RJ. IDYS trial: Intrathecal baclofen treatment for dystonic cerebral palsy. Oral presentation. European Society Paediatric Neurology, Boekarest, Roemenia, September 12th and 13th 2014.

10. Bonouvrié L. Oral presentation. Dyskinesieën en tonusregulatie. Invited speaker. Spasticiteits Symposium, Lunteren, the Netherlands, March 27th 2015.

11. Bonouvrié L. Intrathecal baclofen treatment in dyskinetic cerebral palsy. Part of the mini-symposium 'Dyskinetic cerebral palsy: from a better understanding towards a targeted management'. Speakers: Monbaliu E, Himmelmann K, Ortibus E, Bonouvrié L, Lin J-P. European Academy of Childhood Disabilities, Stockholm, Sweden, June 1st-4th 2016.

12. Bonouvrié LA. 1. Clinical patterns and the influence on activities and participation, and 2. Intrathecal baclofen treatment. Parts of the mini-symposium 'Dyskinetic Cerebral Palsy – from movement disorder to targeted treatment'. Speakers: L.A. Bonouvrié, A.I. Buizer, R.J. Vermeulen, Y. Temel. Dutch Congress of Rehabilitation Medicine, Maastricht, the Netherlands, November 9th and 10th 2017

13. L.A. Bonouvrié. Intrathecal baclofen in dyskinetic cerebral palsy. Invited speaker. Symposium "Dystonia and choreo-athetosis in dyskinetic cerebral palsy: clinical presentation and management". Brugge, Belgium, March 17th 2018.

14. L.A. Bonouvrié. Workshop "ITB in dyskinetic CP: clinical cases". Symposium "Dystonia and choreo-athetosis in dyskinetic cerebral palsy: clinical presentation and management". Invited speaker. Brugge, Belgium, March 17th 2018.