Intrathecal baclofen treatment in children with neurological disorders

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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.