Spasticity in children and young people with non-progressive brain disorders: management of spasticity, co-existing motor disorders and their early musculoskeletal complications

Intrathecal baclofen

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment
Authors Krach,L.E., Kriel,R.L., Gilmartin,R.C., Swift,D.M., Storrs,B.B., Abbott,R., Ward,J.D., Bloom,K.K., Brooks,W.H., Madsen,J.R., McLaughlin,J.F., Nadell,J.M. **Year of publication** 2004 **Country of study** USA **Aim of Study** To assess whether reduction in muscle tone by CITB affects the progression of hip subluxation in persons with CP **Ref ID** 56510 **Type of study** Prospective case series (follow-up of Gilmartin 2000)	**Inclusion Criteria** Patients who had a CITB pump implanted in the previous study and also had radiographic evaluation of their hips before and after a year of treatment with CITB and a baseline and 12-month post initiation of therapy comparison **Exclusion Criteria** Failure to respond to the bolus dose of intrathecal baclofen, pregnancy during the year after the pump implantation, infection of the pump or catheter or lack of comparison radiographic information **Participant characteristics** Total: 33 patients Total number of children: 28 < 8 years: 11 8 to 18 years: 17 Cerebral palsy groups(number of patients, including adults) CP 1 and 2 (walks without device; walks with assistive device): 9 (18 hips)	**Intervention** Continuous intrathecal infusion of baclofen (CITB) via the programmable infusion pump Medtronic SynchroMed Infusion System. Two baclofen injection concentrations were available: 500 µg/mL and 2000 µg/mL Maximum refill interval was 90 days. The pump reservoir was refilled every 1 to 3 months as needed **Comparison** N.A **Background treatment** Oral baclofen was stopped prior to study participation unless discontinuation presented a hazard to the patient which happened in 2 cases. In these 2 patients the dose was held constant during phase 1 but it is unclear what happened with them during phase 2	Progression of hip subluxation Measured when: 12 months after pump was implanted Measured by: unclear Instrument/test: radiographic evaluation of hips Unit of measurement: migration percentage (it is a measure of the amount of the ossified femoral head which is uncovered by ossified acetabular roof) Results <u>Absolute migration percentage by age category (%) (mean ± SD):</u> Age category < 8 years Number of hips: 22 Baseline: 27.1 ± 19.7 12-month: 27.2 ± 20.9 Change from baseline: 0.0 ± 8.4 P<0.05 Age category 8 to 18 years	Outcomes assessors / investigators blinded to intervention : unclear because it is not reported who assessed the outcomes, but it is stated that the pharmaceutical company that produces the SynchroMed Infusion System provided some support for data collection and analysis including assisting with statistical analysis Number of participants not completing treatment: 11 of the 44 patients who received pumps were excluded for the following reasons: 2 developed an infection in the pump pocket 1 wanted to become pregnant and withdrew from study 4 had orthopaedic surgery during the study period 3 did not have data on migration % at 12 months and 1 at baseline Number of participants with	**Funding** Medtronic, Inc. (Minneapolis, Minnesota) supplied SynchroMed ™ Implantable Pumps and Lioresal Intrathecal ™ for the duration of the study and provided some support for data collection and analysis , including assisting with statistical analysis **Other information**

	CP 3 (crawling with hands and knees on wheelchair): 6 (12 hips) CP 4 (May commando crawl or roll): 12 (24 hips) CP 5 (Totally dependent for activities of daily living, no independent motor activity): 6 (12 hips)		Number of hips: 34 Baseline: 23.8 ± 20.2 12-month: 25.0 ± 17.2 Change from baseline: 1.2 ± 12.8 P<0.05 <u>Absolute migration percentage by CP classification (%) (mean ± SD):</u> (this outcome includes adult patients) CP 1 and 2 Number of hips: 18 Baseline: 22.7 ± 18.8 12-month: 19.7 ± 10.3 Change from baseline: -3.0 ± 14.9 P<0.05 CP 3 Number of hips: 12 Baseline: 23.6 ± 8.4 12-month: 27.1 ± 13.2 Change from baseline: 3.5 ± 8.9 N.S CP 4 Number of hips: 24 Baseline: 19.9 ± 18.3 12-month: 23.4 ± 16.9 Change from baseline: 3.5 ± 11.6 N.S CP 5 Number of hips: 12	no available outcome data: none Selective outcome reporting: no Sample size: small, no power calculation performed Indirectness Population: 5 adults included Intervention: None Comparison: N.A Outcomes assessed: none	

			Baseline: 34.8 ± 31.3 12-month: 36.3 ± 32.6 Change from baseline: 1.4 ± 7.3 N.S <u>Change of 5% or more in migration percentage by CP classification (number of patients and %)</u> (Worse=increased ≥5%; better= decreased ≤5%; unchanged=changes within 5% of more) (this outcome includes adult patients) CP 1 and 2 Number of hips: 18 Worse: 4 (22.2) Unchanged: 12 (66.7) Better: 2 (11.1) CP 3 Number of hips: 12 Worse: 5 (41.7) Unchanged: 6 (50.0) Better: 1 (8.3) CP 4 Number of hips: 24 Worse: 9 (37.5) Unchanged: 11 (45.8) Better: 4 (16.6) CP 5 Number of hips: 12 Worse: 4 (33.3) Unchanged: 7 (58.3)		
			Better: 1 (8.3)		

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment
Authors Awaad,Y., Tayem,H., Munoz,S., Ham,S., Michon,A.M., Awaad,R. **Year of publication** 2003 **Country of study** USA **Aim of Study** To describe the outcomes of a series of patients with CP who received intrathecal baclofen to reduce spasticity **Ref ID** 58588 **Type of study** Prospective case series	**Inclusion Criteria** Phase 1 (testing) A diagnosis of CP At least 4 years of age Weight more than 30 pounds Have severe spasticity in lower extremities (defined as an average Ashworth Scale score of at least 3) Patients also had to undergo a trial of oral antispasmodic agents for at least 6 months prior to be considered for CITB Phase 2 (CITB) A positive response to testing (defined as a 1-point reduction in the average Ashworth scores in the lower extremities) Agreement from the family to have the pump implanted Patients considered “appropriate” candidates for the therapy (no other details provided) **Exclusion Criteria** Phase 1 (testing) - Severe contractures	**Intervention** Phase 1 (testing) Bolus of intrathecal baclofen 50 µg into the lumbar region (no other details provided) Phase 2 (CITB) CITB delivered via a programmable pump After the pump was implanted the patients received individualised rehabilitation, including physical and occupational therapies, speech therapy and gait training. Patients had on average, 2 to 3 visits per week for rehabilitation **Comparison** Phase 1 (testing) N.A Phase 2 (CITB) N.A **Background treatment** Phase 1 (testing) Unclear Phase 2 (CITB) Rehabilitation programmes based on individual needs, including physical and occupational therapies, speech therapy and gait training. Patients had on average 2 to 3 visits/weeks for rehabilitation	Phase 1 (testing) - Spasticity Measured when: every 2 hours after the injection (unclear how many times) Measured by: physical and occupational therapists Instrument/test: Ashworth scale Unit of measurement: Ashworth scores for seven lower-extremity muscle groups (hip adductors, abductors, and flexors; knee flexors and extensors; and ankle dorsiflexors and plantarflexors) and four upper extremity muscle groups (wrist and elbow flexors and extensors) were averaged for one combined score Results: (n=28, all children) (Mean, SD) Before trial: 3.19 (0.56) After trial: 1.34 (0.50) Change: -1.85 (0.51) P<0.001 Adverse effects were not reported for testing	Phase 1 (testing) Outcomes assessors blinded to intervention : no Number of participants not completing treatment: All patients completed testing but only 39 proceeded to have pumps implanted. The following reasons explain why 10 did not: 3 patients elected to use oral medications 2 had “family issues” 1 child’s body size was too small 1 child died unrelated to the baclofen trial 1 child underwent spinal fusion 1 child had “medical issues” and 1 family decided not to undergo implant at time of study (unclear why) Number of participants with no available outcome data: 6 patients did not have baseline PEDI scores and were not included in the data analysis (and apparently they did not receive a pump) Selective outcome reporting: Adverse effects were not reported for testing, unclear	**Funding** not stated **Other information** Phase 1 (testing) Sample size: small, no power calculation performed Indirectness Population: none, adult patients included but subgroup analysis performed Intervention: None Comparison: N.A Outcomes assessed: Ashworth scores for lower-extremity muscle groups and upper extremity muscle groups were averaged for one combined score which is both methodologically and clinically incorrect and should be reported as score for individual muscles instead Phase 2 (CITB) Sample size: small, no power calculation performed Indirectness Population: none, adult patients included but subgroup analysis performed Intervention: None Comparison: N.A Outcomes assessed: Ashworth scores for lower-extremity

	Phase 2 (CITB) - None stated **Participant characteristics** Phase 1 (testing) Total: 55 patients Sex: 19 females and 36 males Age: between 4 and 32 years (mean age 13.09y, SD 7.49) PEDI functional skills mobility scores: mean 25.39 SD (20.18) Phase 2 (CITB) Total: 39 patients Sex: 12 females and 27 males Age: between 4 and 32 years (mean age 13.69y, SD 7.43) PEDI functional skills mobility scores: mean 25.44 SD (20.41)		Phase 2 (CITB) Spasticity Measured when: 12 months after pump implantation Measured by: physician, nurse and/or physical therapist Instrument/test: Ashworth scale Unit of measurement: Ashworth scores for seven lower-extremity muscle groups (hip adductors, abductors, and flexors; knee flexors and extensors; and ankle dorsiflexors and plantarflexors) and four upper extremity muscle groups (wrist and elbow flexors and extensors) were averaged for one combined score Results: Ashworth score at 12 months and change as compared to baseline (mean, SD) (children only) Ashworth score: 1.76 (0.64) Change: -1.49 (0.69) P<0.001 Adverse effects Measured when: unclear, presumably at postoperative follow-up assessments (1, 6,	whether it is because there were not any Phase 2 (CITB) Outcomes assessors blinded to intervention : no Number of participants not completing treatment: 2 patients had their pump removed, one because of a change of behaviour owing to an increased in seizure activity and another one owing to pocket infection Number of participants with no available outcome data: 10/39 patients lacked follow-up data: 2 were followed at other facilities, 6 did not have follow-up PEDI scores and 2 patients had their pump removed (see above) Selective outcome reporting: no	muscle groups and upper extremity muscle groups were averaged for one combined score which is both methodologically and clinically incorrect and should be reported as score for individual muscles instead 28 of the 39 patients who had the pump implanted were children, but it is unclear what were the ages of the patients who did not have available follow up data to begin with, or the age of those who were lost to follow up at different assessment times, therefore it is not possible to tell exactly how many children were included in the sample whose outcomes are reported here. This is a serious limitation of the study

			12, 18 and 24 months) Measured by: unclear, presumably physician, nurse and/or physical therapist Instrument/test: unclear Results: Total number of adverse effects: 35 Total number of patients involved: unclear Nausea: 4 Constipation: 6 Increased in seizure frequency: 2 (unclear if this includes the patient in which the pump had to be stopped after 5 months because of a change of behaviour owing to an increased in seizure activity) New-onset seizures: 2 Increased oral secretions: 2 Sleepiness: 2 Urinary retention: 2 Total number of patients who required their pump to be explanted: 4 (unclear whether any of these patients were children) Reasons: Meningitis: 1 Infection: 2 (1 was a “pocket infection”, unclear about the other one) Lack of effect-no clinical		

			improvement: 1 (unclear if the latter the same patient in which the pump had to be stopped after 5 months because of a change of behaviour owing to an increased in seizure activity)		

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment

Authors Gilmartin,R., Bruce,D., Storrs,B.B., Abbott,R., Krach,L., Ward,J., Bloom,K., Brooks,W.H., Johnson,D.L., Madsen,J.R., McLaughlin,J.F., Nadell,J. **Year of publication** 2000 **Country of study** USA **Aim of Study** to asses the efficacy of continuous intrathecal infusion of baclofen (CITB) in patients with spastic cerebral palsy (CP) **Ref ID** 58683 **Type of study** Phase 1: Double-blind cross-over RCT (placebo-controlled) Phase 2: Prospective case series	**Inclusion Criteria** Phase 1 (testing): Patients with congenital CP or who had acquired spastic CP before 2 years of age, with moderate to severe spasticity (as indicated by an Ashworth score of 3 or more in the four lower extremity measurements: hip abductors, knee flexors, knee extensors and foot dorsiflexors) and with/without a mild degree of atethosis or dystonia. Patients had to be 3 years or older and with sufficient body mass to accommodate and implantable pump Phase 2 (CITB): a positive response to testing, defined as a reduction in 1 point in the average Ashworth Scale score for all 8 lower-extremity sites maintained over two successive measurements between 1 and 8 hours after the bolus dose (either 50, 75 or 100 µg of intrathecal baclofen) was delivered **Exclusion Criteria** None stated for phase 1 Phase 2: positive response to placebo or no reduction of 1 point in the average Ashworth Scale score in the lower extremities after administering	**Intervention** Phase 1 (testing): 50 µg of Lioresal Intrathecal (baclofen injection), one single dose. If no positive response the patient was given an additional open-label 75-µg bolus injection. If no positive response to the previous a 100 -µg bolus injection was delivered open-label 24 hours later. Patients were assigned to a baclofen-placebo or placebo-baclofen sequence with a 48-hour washout period between injections Baclofen/placebo were delivered by lumbar puncture, percutaneous spinal catheter or implanted port with spinal catheter Phase 2 (CITB): Continuous intrathecal infusion of baclofen (CITB) via the programmable infusion pump Medtronic SynchroMed Infusion System. Two baclofen injection concentrations were available: 500 µg/mL and 2000 µg/mL Maximum refill interval was 90 days. The pump reservoir was refilled every 1 to 3 months as needed **Comparison**	Phase 1 (testing): Spasticity Measured when: 4 hours after the bolus was delivered Measured by: unclear, but the same evaluator throughout the trial for any given patient Instrument/test: Ashworth scale Unit of measurement: Ashworth scores bilaterally assessed in 4 lower-extremity muscle groups ((hip abductors, knee flexors and extensors; and foot dorsiflexors) and also in the upper extremities (unclear which muscles) Results: Lower extremities (at 4 hours and after single dose 50µg) (mean, SD; SE; range) (n=51) Baclofen: 2.14 (0.85); 0.12 (1.00 to 4.75) Placebo: 3.11 (0.69);0.14 (1.75 to 5.00) p<0.001 Lower extremities (after open label dose 75µg) (mean, SD; SE; range) (n=10) Baclofen: 2.04 (0.67); 0.21 (1.37 to 3.50)	Phase 1 (testing): Randomisation and blinding: methods unclear Allocation concealment: unclear Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment: All patients completed treatment with at least one single dose of 50 µg of baclofen but 7 did not proceed to have the pump implanted for the following reasons: 3 patients had a positive response to placebo, 2 did not have a positive response to the 50-µg baclofen dose and withdrew before getting a higher dose (unclear why), 1 patient developed meningitis and 1 patient had an adverse event of nausea, vomiting, elevated blood count, nystagmus and agitation (the investigator noted that this patient had intercurrent	**Funding** supported in part by Medtronic, Inc **Other information** Phase 1 (testing): Sample size: small, no power calculation performed Indirectness Population: adult patients included and no subgroup analysis performed Intervention: None Comparison: placebo not used for testing in UK clinical practice Outcomes assessed: None Ashworth scores for lower-extremity muscle groups and upper extremity muscle groups were averaged in both cases which is both methodologically and clinically incorrect and should be reported as score for individual muscles instead Phase 2 (CITB): Sample size: small, no power calculation performed Indirectness Population: Unclear as specific characteristic of patients included in this phase were not reported Intervention: None

	100 µg of baclofen **Participant characteristics** Phase 1 (testing): Total: 51 patients Sex: 22 females and 29 males Age: between 4 and 31.3 years (mean age 10y 3mo, median 11y 2mo) Cerebral palsy type: 12 spastic diplegia 4 spastic paraplegia 35 spastic quadriplegia Phase 2 (CITB): Total: 44 of the previous patients, specific characteristics not reported	Phase 1 (testing): 50 µg of 0.9% preservative-free sodium chloride injection Phase 2 (CITB): N.A **Background treatment** Phase 1 (testing): Oral baclofen was stopped prior to study participation unless discontinuation presented a hazard to the patient which happened in 2 cases. In these 2 patients the dose was held constant during phase 1 Phase 2 (CITB): 2 patients received oral baclofen after pump implantation; in one the oral baclofen was discontinued 1 month post implantation, and the second patient withdrew from the study after 4 months (unclear whether these were the same patients who also received oral baclofen during phase 1)	Baseline: 3.31 (0.60);0.19 (2.00 to 4.00) p<0.001 Lower extremities (after open label dose 100µg) (mean, SD; SE; range) (n=2) Baclofen: 1.81 (0.62); 0.44 (1.37 to 2.25) Baseline: 3.44 (0.62);0.43 (3.00 to 3.87) Upper extremities (at 4 hours and after single dose 50µg) (mean, SD; range) (n=51) Baclofen: 1.92 (0.80); (1.0 to 4.4) Baseline: 2.21 (0.80); (1.0 to 4.5) p<0.001 Adverse effects Measured when: during the 3-day inpatient procedure Measured by: unclear Instrument/test: unclear Results: Total number of adverse effects: 29 (7 during placebo) Total number of patients affected: 18 (4 during placebo) 1 patient developed meningitis (withdrew from	gastroenteritis) Number of participants with no available outcome data: none Selective outcome reporting: results for placebo not reported for the upper extremities Phase 2 (CITB): Outcomes assessors blinded to intervention : N.A Number of participants not completing treatment: 7 patients withdrew after pump implantation for the following reasons: 2 developed and infection in the pump pocket, 2 had “family issues”, 1 wanted to become pregnant and, 2 died (1 as passenger in a motor vehicle accident and 1 of respiratory failure due to pneumonia) Number of participants with no available outcome data: Lower limbs Ashworth scores: 2 patients at 6 months, 4 patients at 12 months, 11 patients at 24 months Upper limbs Ashworth scores: 3 patients at 6 months, 4 patients at 12 months, 12 patients at 24 months	Comparison: N.A Outcomes assessed: Ashworth scores for lower-extremity muscle groups and upper extremity muscle groups were averaged in both cases which is both methodologically and clinically incorrect and should be reported as score for individual muscles instead

			study) 1 patient developed nausea, vomiting, elevated blood count, nystagmus and agitation. The investigator noted that the child had intercurrent gastroenteritis (withdrew from study) Nausea, vomiting and drowsiness were common effects reported during baclofen, but unclear how many children involved in each of them <u>Phase 2 (CITB-pump):</u> Spasticity (n=44) Measured when: within 2 weeks of implantation, monthly for 6 months and then at 3-month intervals Measured by: unclear Instrument/test: Ashworth scale Unit of measurement: Ashworth scores bilaterally assessed in 4 lower-extremity muscle groups ((hip abductors, knee flexors and extensors; and foot dorsiflexors) and also in the upper extremities (unclear which muscles)	Selective outcome reporting: no	

			Results: Lower extremities (mean, SD; range) -at 24 months after implantation(n=33): 2.21 (0.75); (1.0 to 3.5) -at 12 months after implantation(n=40): 2.15 (0.60); (1.1 to 3.3) -at 6 months after implantation(n=42): 2.33 (0.64); (1.0 to 3.8) -Baseline (n=44): 3.64 (0.57); (3.0 to 5.0) Upper extremities (mean, SD; range) -at 24 months after implantation(n=32): 1.72 (0.69); (1.0 to 3.1) -at 12 months after implantation(n=40): 1.73 (0.66); (1.0 to 4.1) -at 6 months after implantation(n=41): 1.80 (0.72); (1.0 to 3.8) -Baseline (n=44): 2.54 (0.98); (1.0 to 4.5) Adverse effects Measured when: unclear, presumably during the 10 routine visits required by protocol in the first year post-implantation Measured by: unclear		

			Instrument/test: unclear Results: Total number of device related events: 59 Total number of patients involved: 30 39 were procedure related and 20 system related (“procedure” related occurred in the first 60 days after implantation and were not directly attributable to device, and “system” after 60 days and the other way round) Procedure related (number of events): Pocket seroma: 7 Pocket infection: 5 Catheter dislodged: 3 CSF leak: 3 Other: 20 System related: Catheter break: 2 Catheter dislodge: 2 Back pain at catheter site: 2 Other: 14 Total number of baclofen related events: 65 Total number of patients involved: unclear		

			Most common baclofen related events (number of events): Hypotonia: 16 Seizure: 15 Headache: 9 Total number of patients requiring pump explantation: 3 (unclear whether any of these patients were children) Reasons: the 3 because of infections of the pump pocket: 1 had a second pump re-implanted to complete study and the other 2 withdrew from study)		

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Authors Hoving,M.A., van Raak,E.P., Spincemaille,G.H., Palmans,L.J., Sleypen,F.A., Vles,J.S., Dutch Study Group on Child Spasticity. **Year of publication** 2007 **Country of study** The Netherlands **Aim of Study** (1) to select children eligible for CITB treatment (2) to assess the effective ITB bolus dose; and (3) to evaluate effects, side effects, complications, and procedures **Ref ID** 58704 **Type of study** Double-blind cross over RCT (placebo-controlled)	**Inclusion Criteria** 1. Age between 4 and 16 years 2. Spastic diplegia or tetraplegia as part of cerebral palsy 3. Insufficient response to oral spasticity-reducing medication 4. In a mixed cerebral palsy syndrome, spasticity is the most prominent sign 5. Spasticity results in a decrease in the quality of life of the child and/or its caregivers 6. Sufficient motivation for study participation including availability for follow-up 7. Magnetic resonance imaging of the brain rules out progressive diseases 8. Minimal weight of 20kg (valid until 1 January 2004) 9. Wheelchair bound without ability to creep or sit unsupported (valid until 1 January 2004) 10. Child is able to understand and carry out instructions (valid until 1 January 2004) (Note: From January 2002 to December 2003 many children who wished to participate were not included because they did not meet the weight, mobility, and/or cognition criteria. Authors therefore	**Intervention** After admission, the neurosurgeon inserted under general anaesthesia an external lumbar catheter (Perifix 300 Mini Set; B Braun, Melsungen, Germany) Postoperatively and during the test days, the children stayed on the paediatric medium care unit, where vital signs were monitored. The morning after catheter insertion, the first study medication bolus was administered intrathecally via the catheter During the first two test days the bolus randomly contained baclofen 25µg or placebo. On each of the subsequent six test days the bolus contained baclofen 50 µg or placebo, then baclofen 75 µg or placebo, and, finally, baclofen 100 µg or placebo. In a given two-day treatment period, patients received baclofen and placebo in random order. **Comparison** Placebo (unclear what it consisted of) 14 children preventively received one to four doses of cefazoline perioperatively	Spasticity Measured when: every day before bolus administration (baseline) and 2, 4, and 6 hours afterward Measured by: an experienced paediatric physiotherapist. For each child scores were always rated by the same physiotherapist Instrument/test: Ashworth scale Unit of measurement: Ashworth scores bilaterally assessed in seven lower-extremity muscle groups. Before catheter insertion, authors selected the hip, knee, and ankle-related muscle group with highest tone on both sides, in total identifying six muscle groups per child (hip adductors, flexors, and extensors; knee flexors and extensors; and ankle plantarflexors and dorsiflexors) Results: Baclofen (n=17): The Ashworth scores, assessed 2, 4, and 6 hours after administration of the effective ITB dose, significantly decreased in	Randomisation and blinding: An independent statistician generated the randomization lists, permitting a balanced distribution of study medication sequences within the same child as well as between the children. The pharmacist prepared and numbered the study medication in accordance with these randomization lists Allocation concealment: unclear Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment : none Number of participants with no available outcome data: 15 One boy who responded to ITB 20µg had two separate test treatments. During the first day of the first test treatment he experienced apathy and, in an upright position, nausea	**Funding** Main sponsor: the Research Fund of the University Hospital Maastricht. In addition: grant from Medtronic Inc., Heerlen, the Netherlands. Medtronic Inc **Other information** Sample size: small, but the fact that this is a cross over trail increase the power. No calculation was performed based on the outcomes assessed in this report Indirectness Population: None Intervention: None Comparison: placebo not used for testing in UK clinical practice Outcomes assessed: None

	decided to widen the eligibility criteria by omitting inclusion criteria 8, 9, and 10 from January 2004) **Exclusion Criteria** 1. Hypersensitivity to baclofen 2. Contraindications for general anaesthesia 3. Insufficient general health 4. Intractable epileptic seizures 5. Infection of the lumbar skin 6. Systemic infection **Participant characteristics** 38, 23 males and 15 females, were referred as possible candidates for the Dutch national ITB study. The main reasons for referral were 'having pain' and problems with 'ease of care'. Total: 17 children Sex: 9 females and 8 males Age: between 7 and 16 years (mean age 13y 2mo [SD 2y 9mo]) Weight: (range 17 to 84 kg) Cerebral palsy type: 12 spastic, 5 spastic/dyskinetic, 3 diplegia, 14 tetraplegia GMFCS level: III (1), IV (2), V (14) Most children had one or more	On the day that a positive clinical response was observed, the test treatment ended and the study medication code was broken. Only if this positive clinical response was observed on the first test day did the child and caregivers have the opportunity to experience the results of the second test day before the test treatment was ended. We offered this opportunity because the decision on pump implantation should be well based. Having noticed a positive clinical response on the first test day, children and parents might have a need for confirmation by observing a lack of effect on the second test day. If the code break proved that the child had responded to baclofen, they were considered eligible for further treatment with CITB. If after eight test days no positive clinical effect had been observed, the child was not eligible for pump implantation Clinical effect defined as positive only if the following two criteria were met:	comparison with baseline for all muscle groups ($0.001 \leq p \leq 0.040$), except for the left hip flexors 2 hours after ITB administration ($p=0.080$) <u>Placebo (n=17):</u> Did not change significantly in any muscle group at any test moment ($0.083 \leq p \leq 1.000$). In the three children who had two placebo days, the results of the first placebo day were used Ease of care Measured when: Each VAS was rated once before the test treatment started (baseline) and at the end of each test day, reviewing the observations of that day. During VAS rating, the children and parents did not know the Ashworth scores for that day Measured by: Depending on both the ability to understand the test and to draw a vertical line, the VAS was rated by the child or by a parent Instrument/test: Visual Analogue Scale (VAS) for individually formulated problems	and vomiting. His vital signs were normal. The test treatment was broken off because his condition impeded the observation of effects and side effects. During a second admission, authors decided to do an open label test treatment administering ITB 20µg by lumbar puncture. This resulted in a positive clinical response and slight lethargy as a side effect. Authors decided to exclude the test results from statistical analyses because the test treatment had not been carried out double-blinded. 14 of the 17 children were bed-bound because they had symptoms of lowered CSF pressure. Consequently, certain individually formulated problems could not be evaluated during the test treatment Selective outcome reporting: actual results for the Ashworth scores in individual muscles not reported	

	of the following associated problems: speech problem, drooling, constipation, urological problem, sleeping disorder, visual impairment, epilepsy, bronchopulmonary problem and auditory problem	(1) a satisfying improvement in the individual treatment goals as experienced by the child and/or the caregivers; and (2) at least a one-point reduction on the Ashworth scale compared with the baseline score of that specific day, in at least three of the six individually selected muscle groups. This one-point reduction had to last for two successive measurements on the same day. **Background treatment** 7 children still used oral baclofen and they continued this use during the test	Unit of measurement: Straight 10cm horizontal line with anchor points of 'very dissatisfied' (score 0) and 'very satisfied' (score 10) Results: Baclofen (n=14): (mean, SD) Baseline: 2.3 (1.4) After baclofen: 7.4 (2.2) Difference: 5.1 (2.1) P=0.001 Placebo (n=13): (mean, SD) Baseline: 2.4 (1.4) After baclofen: 3.3 (2.0) Difference: 0.9 (1.7) P=0.093 Pain Measured when: Each VAS was rated once before the test treatment started (baseline) and at the end of each test day, reviewing the observations of that day. During VAS rating, the children and parents did not know the Ashworth scores for that day Measured by: Depending on both the ability to understand the test and to draw a vertical line, the VAS was rated by the child or by a parent		

			Instrument/test: Visual Analogue Scale (VAS) for individually formulated problems Unit of measurement: Straight 10cm horizontal line with anchor points of 'no pain' (score 0) and 'unbearable pain' (score 10) Results: Baclofen (n=11): (mean, SD) Baseline: 3.2 (2.0) After baclofen: 6.5 (3.1) Difference: 3.3 (2.9) P=0.010 Placebo (n=10): (mean, SD) Baseline: 3.2 (2.1) After baclofen: 4.3 (2.6) Difference: 1.1 (3.5) P=0.262 Adverse effects Measured when: twice every test day, before bolus administration and at the end of the test day, reviewing the observations of that day Measured by: caregivers Instrument/test: caregivers' notes on		

			standardised forms, which included time of occurrence Results: <u>Baclofen (n=17):</u> Total number of adverse effects: 9 Total number of children affected: 8 7 children became slightly lethargic, including a child who also experienced transient excessive hypotonia One child: excessive perspiration of hands and feet Total number of complications: 19 Total number of children affected: 16 14 children presented one or more symptoms that could fit in with the diagnosis of lowered CSF pressure (included lethargy, decreased appetite, dry mouth, dizziness, perspiration, pallor, nausea, vomiting, and headache). The last four symptoms appeared or increased only in an upright position. None of these symptoms were observed in 3 children in		

			whom the neurosurgeon had tunnelled the catheter subcutaneously for a few centimetres In 3 children, CSF leaked from the catheter connection. In one of these, the catheter connection was defective, so a new catheter had to be inserted; in the other two, reconnection of the cap solved the problem. One child had radicular pain in his right leg postoperatively. The pain was completely resolved by retracting the catheter for 5cm Another child first had abdominal cramps due to constipation, developing gastroenteritis later on. At that time, more children on the ward had gastroenteritis. Overall, none of the children required respiratory support or admission to intensive care. None of the children developed meningitis.		

			<u>Placebo (n=17):</u> None reported Other individually formulated problems In individual cases, improvements were noted concerning transfers, voiding, startle responses, operating the electric wheelchair, and arm function. One boy underwent the test treatment because of deteriorating gait in spite of multilevel treatment with botulinum toxin. He saw his goals fulfilled: with ITB 50µg the pain in his hamstrings disappeared and walking took less energy		

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment
Authors Hoving,M.A., van Raak,E.P., Spincemaille,G.H., Palmans,L.J., Becher,J.G., Vles,J.S., Dutch Study Group on Child Spasticity. **Year of publication** 2009 **Country of study** The Netherlands **Aim of Study** To study the efficacy of continuous infusion of intrathecal baclofen (CITB) in the treatment of children with problems caused by intractable spastic cerebral palsy **Ref ID** 58706 **Type of study** Double-blind before randomisation Open-label after randomisation Parallel RCT	**Inclusion Criteria** 1. Age between 4 and 16 years 2. Spastic diplegia or tetraplegia as part of cerebral palsy 3. Insufficient response to oral spasticity-reducing medication 4. In a mixed cerebral palsy syndrome, spasticity is the most prominent sign 5. Spasticity results in a decrease in the quality of life of the child and/or its caregivers 6. Sufficient motivation for study participation including availability for follow-up 7. Magnetic resonance imaging of the brain rules out progressive diseases 8. Minimal weight of 20kg (valid until 1 January 2004) 9. Wheelchair bound without ability to creep or sit unsupported (valid until 1 January 2004) 10. Child is able to understand and carry out instructions (valid until 1 January 2004) (Note: From January 2002 to December 2003 many children who wished to participate were not included because they did not meet the weight, mobility, and/or cognition criteria. Authors therefore	**Intervention** Programmable Synchromed infusion pump (no other details provided on the specific model) (Medtronic Inc., Minneapolis, MN) after 1 month Children also received "standard treatment" described by the authors as "any physiotherapy, speech therapy and occupational therapy". No other details were provided **Comparison** "Standard treatment" only **Background treatment** 3 children in the CITB group and 4 in the control group used oral baclofen. The children in the CITB group gradually discontinued this use, all during the first 10 post operative days	<u>Primary outcomes</u> Individually formulated problems Measured when: at 6 months after pump implantation/standard treatment initiation Measured by: Depending on both the ability to understand the test and to draw a vertical line, the VAS was rated by the child or by a parent Instrument/test: Visual Analogue Scale (VAS) for individually formulated problems Unit of measurement: average of 3 individually formulated VAS scores per child Results (6-month-change scores) (Mean, SD) CITB group (n=9) 4.0 (1.7) Control group (n=8) -0.2 (1.3) P=0.001 Ease of care Measured when: at 6 months after pump implantation/standard treatment Measured by: Depending on both the ability to understand	Randomisation, blinding and allocation concealment: an independent statistician generated the allocation schedule with an unpredictable sequence of assignments. The investigator who enrolled the children had no entry into this list and was at the time of each enrolment not aware of next assignment in the sequence. For assignment the investigator called the independent statistician who consulted the allocation list Participants blinded to intervention : no Carers blinded to intervention : no Investigators blinded to intervention: yes but only before randomisation. The main investigator was present during all admissions and follow-up visits of the children Number of participants not completing treatment: None Number of participants with no available outcome data: None	**Funding** Grants from the Research Fund of the University Hospital Maastricht. Grant from Medtronic Inc., Heerlen, the Netherlands. **Other information** Sample size: small. Power calculation was based on the results of a study about children with spastic CP who were treated with selective dorsal rhizotomy. In this study caregiver assistance scale scores for PEDI self care domain at baseline and 12-mont follow-up were compared. After 12 months PEDI scores had significantly improved with 4.44 points (SD 1.32). Authors assumed that in this study the children would have not reached maximum improvement after 6 months yet and therefore set the clinically significant difference worth to detect in this study at three points with an estimated SD of 1.82. With a significance level of 0.005 and a power of 90% the number of patients needed per group was 8. allowing for a drop out of 10% a maximum of 18 children would be included.

	decided to widen the eligibility criteria by omitting inclusion criteria 8, 9, and 10 from January 2004) **Exclusion Criteria** 1. Hypersensitivity to baclofen 2. Contraindications for general anaesthesia 3. Insufficient general health 4. Intractable epileptic seizures 5. Infection of the lumbar skin 6. Systemic infection **Participant characteristics** Total: 17 children Sex: 9 females and 8 males Age: between 7 and 16 years (mean age 13y 2mo [SD 2y 8mo]) ITB patients Total: 9 children Sex: 4 females and 5 males Age: mean age 13y 9mo [SD 2y 3mo]) Cerebral palsy type: 7 spastic, 2 spastic/dyskinetic, 1 diplegia, 8 tetraplegia GMFCS level: III (0), IV (1), V (8) Control group (“standard treatment”) Total: 8 children Sex: 5 females and 3 males Age: mean age 12y 4mo [SD 3y 2mo]) Cerebral palsy type: 5 spastic, 3 spastic/dyskinetic, 2 diplegia,		the test and to draw a vertical line, the VAS was rated by the child or by a parent Instrument/test: Visual Analogue Scale (VAS) for individually formulated problems Unit of measurement: VAS scores Results (6-month-change scores) (Mean, SD) CITB group (n=9) 3.9 (2.2) Control group (n=7) 0.1 (1.6) P= 0.008 Pain Measured when: at 6 months after pump implantation/standard treatment Measured by: Depending on both the ability to understand the test and to draw a vertical line, the VAS was rated by the child or by a parent Instrument/test: Visual Analogue Scale (VAS) for individually formulated problems Unit of measurement: VAS scores Straight 10cm	Selective outcome reporting: Yes. Actual scores of the Ashworth scale were not reported because there were “too many data” according to the authors	Baseline characteristics: There were no apparent significant differences between both groups, although figures were not reported Indirectness Population: None Intervention: None Comparison: unclear as not described in detail. Outcomes assessed: None Other limitations: it is unclear whether the standard treatment that both groups received was exactly the same, or even whether there were any variations within groups [STUDY 2009a]

	6 tetraplegia GMFCS level: III (1), IV (1), V (6)		horizontal line with anchor points of 'no pain' (score 0) and 'unbearable pain' (score 10) Results (6-month-change scores) (Mean, SD) CITB group (n=6) 4.2 (2.9) Control group (n=6) -1.3 (2.4) P= 0.016 Movement and function (activities and participation in the ICF-International Classification of Disability and Health) Measured when: at 6 months after pump implantation/standard treatment Measured by: unclear Instrument/test: Dutch version of the Paediatric Evaluation of Disability Inventory (PEDI)-PEDI caregiver assistance scale Unit of measurement: PEDI scores Results (6-month-change scores) (median, range): CITB group (n=9) 0.0 (-11.7 to 4.1) Control group (n=8) 0.0 (-16.0 to 16.0)		

			p=0.720 <u>Secondary outcomes</u> Spasticity Measured when: at 6 months after pump implantation/standard treatment Measured by: an experienced paediatric physiotherapist. For each child scores were always rated by the same physiotherapist Instrument/test: Ashworth scale Unit of measurement: Ashworth scores bilaterally assessed in 7 lower-extremity muscle groups (hip adductors, flexors and extensors; knee flexors and extensors; and ankle plantarflexors and dorsiflexors) and 4 upper extremity muscle groups (elbow and wrist flexors and extensors). Scores of the total 22 muscles separately analysed Results (6-month-change scores): The 6-month-change score between both groups significantly differed in		

			favour of the CITB group for the left hip adductors (p=0.0025), both hip flexors (p=right=0.022; left=0.043) and the right wrist flexors (p=0.038) Movement and function (activities and participation in the ICF-International Classification of Disability and Health)Measured when: at 6 months after pump implantation/standard treatment Measured by: unclear Instrument/test: Dutch version of Gross Motor Function Measure (both the GMFM-66 and the GMFM-88 versions) Dutch version of the Paediatric Evaluation of Disability Inventory (PEDI)-functional skills scale Unit of measurement: scores of previous tests (GMFM-88: 4-point ordinal scale; GMFM-66: interval scaling) Results (6-month-change scores):		

			GMFM-66 overall (Mean, SD) CITB group (n=7) 1.2 (2.3) Control group (n=5) -1.6 (3.0) P=0.028 GMFM-88 lying and rolling (median, range): CITB group (n=7) 3.9 (-12.0 to 10.0) Control group (n=5) 0.0 (-10.0 to 0.0) P=0.512 GMFM-88 sitting (median, range): CITB group (n=7) 3.3 (0.0 to 10.0) Control group (n=5) 0.0 (-7.0 to 7.0) P=0.085 GMFM-88 goal dimensions (median, range): CITB group (n=5) 3.0 (2.0 to 10.0) Control group (n=4) 1.3 (-6.0 to 6.0) p=0.140 PEDI functional skills(median, range): CITB group (n=9) 0.0 (-7.4 to 5.7) Control group (n=8) 0.0(-5.4 to 2.1) P=0.720		

			Quality of Life Measured when: at 6 months after pump implantation/standard treatment Measured by: unclear Instrument/test: Dutch version of the Child-Health Questionnaire-Parent Form (CHQ-PF50) Unit of measurement: scores of CHQ-PF50, each domain is scaled from 0 to 100 with higher scores reflecting a better HRQL. Physical and psychosocial summary scores calculated using normative data from North American children Results (6-month-change scores) (Mean, SD) physical summary CITB group (n=8) 2.1 (10.3) Control group (n=8) -7.5 (6.9) P= 0.074		

			psychosocial summary CITB group (n=8) 3.4 (7.9) Control group (n=8) -5.7 (8.8) P= 0.027 This study did not assess adverse effects		

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment
Authors Motta,F., Stignani,C., Antonello,C.E. **Year of publication** 2008 **Country of study** Italy **Aim of Study** to evaluate, with the use of functional scales, the effect of ITB on generalized dystonia in 19 patients affected by cerebral palsy (CP) and with severe degree of impairments **Ref ID** 58774 **Type of study** Prospective case series	**Inclusion Criteria** Children affected by CP and with severe degree of impairment **Exclusion Criteria** Not stated **Participant characteristics** Total: 19 children Sex: 6 females, 13 males Age at implant: between 2 years 5 months and 16 years 6 months (mean age 8.49 years, SD 3.2) Type of CP: 13 (70%): spastic dystonic tetraplegia with severe generalised dystonia 6 (30%): dystonic tetraplegia All patients suffered form severe limitations to all areas of motor function, even when using aids. They were unable to stay seated or to keep their head steady and the needed assistance with everyday activities. None showed painful retractions before pump implant	**Intervention** Continuous intrathecal baclofen therapy via programmable pump Initially the pump was placed subcutaneously (5 children) whereas from the 3rd year of the study the pump was positioned more deeply in the abdomen between the external oblique muscle and abdominal rectus (14 children) 9 children were implanted the 10-ml SyncroMed pump, 1 with the 18-ml SyncroMed pump and the remaining 10 with the 20-ml SyncroMed pump **Comparison** N.A **Background treatment** None reported	Dystonia Measured when: pre-implant and at 3, 6 and 12 months post-implant Measured by: same team of 2 rehabilitation therapists and same orthopaedic physician Instrument/test: Barry-Albright scale (BAD) and Burke-Fahn-Marsden scale (BFM)-standard video recording was used for assessment Unit of measurement: BAD and BFM scores, both from 0 to 4. A low score equates with less severe dystonias in both scales Results: Overall BAD scores (mean, SD) at 12 months: 17.79 ± 3.3 baseline: 23.84 ± 4.11 P<0.001 (Individual BAD scores not reported for each region, only p values for change) Eyes: <0.05 Mouth: <0.01 Neck: <0.001 Upper limb dx: <0.001 Upper limb sx: <0.001 Trunk: <0.001	Outcomes assessors blinded to intervention: no Number of participants not completing treatment: none Number of participants with no available outcome data : unclear , none apparently Selective outcome reporting: Individual BAD and BFM scores not reported for each body region, only p values for change Dystonia assessed at 3, 6 and 12 months post-implant but outcomes reported only for the 12 month follow up	**Funding** none of the authors received financial support **Other information** Sample size: small, no calculation performed Indirectness Population: 30% may not have had spasticity Intervention: none Comparison: N.A Outcomes assessed: none

			Lower limb dx: <0.01 Lower limb sx: <0.01 <u>Overall BFM scores-movement components (mean, SD)</u> at 12 months: 77.60 ± 20.56 baseline: 98.57 ± 13.07 P<0.001 <u>BFM scores- movement components</u> (actual scores not reported for each region, only p values for change) Eyes: NS Mouth: <0.05 Language-Swallowing: NS Neck: <0.05 Upper limb dx: <0.05 Upper limb sx: <0.05 Trunk: <0.001 Lower limb dx: <0.001 Lower limb sx: <0.001 <u>BFM scores-degree of disability</u> None of the patients showed any change regarding everyday activities Movement and function Measured when: at each follow up (unclear how was analysed) Measured by: patient or caregiver if patient unable to communicate		

			Instrument/test: non-validated questionnaire Results (number of children): Dystonia Improved: 18 Unchanged: 1 Worsened: 0 Hygiene Improved: 12 Unchanged; 6 Worsened: 0 Dressing Improved: 18 Unchanged: 1 Worsened: 0 Feeding Improved: 10 Unchanged: 8 Worsened: 1 Sleeping Improved: 10 Unchanged: 8 Worsened: 1 Pain Improved: 10 Unchanged: 8 Worsened: 1 Acceptability and tolerability Measured when: at each follow up (unclear how was analysed)		

			Measured by: patient or caregiver if patient unable to communicate Instrument/test: non-validated questionnaire Results: Satisfied with the implant: 15 Would do it again: 14 Not totally satisfied: 3 Uncertain whether to do it again: 3 Dissatisfied: 1 Would not do it again: 1 (chose to explant pump 4 years after implant) Adverse effects and complications Measured when: unclear, presumably at 3, 6 and 12 months post-implant Measured by: unclear, presumably same team of 2 rehabilitation therapists and same orthopaedic physician Instrument/test: unclear Results: (only major complications were considered, defined as those that needed medical		

			assistance to be resolved) 1 complication related to catheter breakage and infection, solved by catheter replacement CSF leakage (considered as minor): 4 patients, generally solved spontaneously		

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment
Authors Senaran,H., Shah,S.A., Presedo,A., Dabney,K.W., Glutting,J.W., Miller,F. **Year of publication** 2007 **Country of study** Turkey **Aim of Study** To test the hypothesis that intrathecal baclofen has an effect on the incidence of scoliosis, the rate of curve progression and the magnitude of pelvic obliquity **Ref ID** 58828 **Type of study** Case-control	**Inclusion Criteria** ITB patients: Patients with spastic cerebral palsy who were treated with ITB, had spine radiographs at time of pump implantation and subsequently developed or had progression of scoliosis after ITB which was documented by radiographs at follow-up Controls: Age, gender and GMFCS score-matched patients who did not have ITB **Exclusion Criteria** ITB patients: Having a posterior spinal fusion before or simultaneously with pump implantation developing a sagittal plane deformity whilst on ITB, not having adequate spine radiographs at pump implantation Controls: not stated **Participant characteristics** <u>ITB patients</u> Total number of patients: 2 age at pump implantation (years. Mean, range) 11.8, 5 to 18 sex: 14 female, 12 male GMFCS (number of patients) GMFCS 4: 2, GMFCS 5: 24	**Intervention** Programmable ITB pump (Synchromed EL or II, Medtronic Inc., Minneapolis, MN) **Comparison** No ITB pump, other interventions not reported either **Background treatment** None reported	Rate of curve progression Measured when: - ITB patients: at time of pump implantation and at minimum 2 years follow-up - Controls: at time of diagnosis of scoliosis and at minimum 2 years follow-up Measured by: unclear Instrument/test: standard posteroanterior and lateral radiographs of the spine taken with patient sitting erect, those who could not sit independently were positioned in special adaptative seat with straps to allow them to sit erect, but no attempts to correct the scoliosis were made Unit of measurement: Cobb angle in thoracic, thoracolumbar, lumbar and double major curves Results: (mean, SD) <u>ITB patients (n=26)</u> Curve at follow-up (degrees): 65.19 (24.74) Age at follow-up (years): 14.77 (3.37) Curve at baseline (degrees):	Outcomes assessors blinded to intervention: unclear, possibly not as nothing was reported on the characteristics of the outcomes assessors Number of participants with no available outcome data: no Selective outcome reporting: no Sample size: no calculation performed Baseline characteristics: not statistically compared Other limitations: In case-control studies, data are not available to calculate the incidence rate of the disease being studied. This is the reason why this outcome is not reported here Unclear whether the ITB patients were also quadriplegic Indirectness Population: none Intervention: none Comparison: none Outcomes assessed: none	**Funding** Authors stated that no funds were received in support of this study **Other information**

	follow-up time (years. Mean, range): 2.9, 2 to 7 <u>controls</u> Total number of patients: 25 (all quadriplegic) age at diagnosis of scoliosis (years. Mean, SD, range) 11.6, 3.5, 5 to 18 sex: 10 female, 15 male GMFCS (number of patients) GMFCS 4: 3, GMFCS 5: 22 follow-up time (years. Mean, range): 4.0, 2 to 11		24.08 (15.97) Age at baseline (years): 11.84 (3.66) <u>Controls (n=25)</u> Curve at follow-up (degrees): 73.00 (21.81) Age at follow-up (years): 15.64 (3.75) Curve at baseline (degrees): 28.16 (17.53) Age at baseline (years): 11.60 (3.51) P value comparing both groups: 0.181		

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment
Authors Shilt,J.S., Lai,L.P., Cabrera,M.N., Frino,J., Smith,B.P. **Year of publication** 2008 **Country of study** USA **Aim of Study** To examine the effect of intrathecal baclofen (ITB) treatment on the progression of scoliosis in patients with cerebral palsy (CP) **Ref ID** 58834 **Type of study** Case-control	**Inclusion Criteria** ITB patients: Patients with CP who received ITB treatment in the multidisciplinary paediatric spasticity clinic at the School of Medicine aged between 3 and 18 years diagnosis of spastic CP failed oral spasticity management completed positive ITB bolus study, denoted by a 1 grade improvement in the Ashworth scale and had no prior spinal fusion or a concomitant spinal fusion and ITB pump implantation Controls: Patients with CP, chosen from the multidisciplinary spasticity clinic database, which includes all patients with spasticity at the School of Medicine. For each ITB patient a control patient was matched by age (± 12 months), sex, topographical involvement (i.e. diagnosis of diplegia or quadriplegia) and an initial Cobb angle within 10 degrees. In cases where multiple cases were identified, one was randomly chosen. No matched controls were	**Intervention** ITB programmable infusion pump, technical details not reported One surgeon performed the implantation of ITB pumps and catheter in all patients. The catheter was placed percutaneously through the interspinous ligament in the lumbar spine. The catheter was connected to the pump through a subcutaneous tunnel around the torso. The pump was located anteriorly in a subfacsial pocket created in the potential space under the rectus fascia. **Comparison** No ITB pump, but other interventions not reported either **Background treatment** None reported	Progression of scoliosis Measured when: - ITB patients: initial angle measured before or within the immediate postoperative period after pump insertion and final angle at most recent follow-up - Controls: unclear, but all had serial radiographs, one initial and at least one at follow-up Measured by: unclear Instrument/test: - ITB patients: posteroanterior radiographs of the spine taken with patient in seated position when possible. If unsupported sitting not possible, then a supine radiograph was used. (36/104 films were obtained in the supine position. All but 7 of these were from historically obtained control patients - Controls: chest or spine radiographs taken with patient in supine or prone position Unit of measurement: Cobb angle degrees of the primary curve of scoliosis in the coronal plane Results: Initial Cobb angle (degrees: mean, SD, range)	Outcomes assessors blinded to intervention: unclear, possibly not as nothing was reported on the characteristics of the outcomes assessors Number of participants with no available outcome data: 2 patients for whom a control could not be found were excluded from comparison analysis Selective outcome reporting: none	**Funding** 3 of the authors received financial support by a grant from Medtronic, Inc (Minneapolis, Minn) **Other information** Sample size: the sample size was calculated assuming a type 1 error of 0.005 and a type 2 error of 0.10. the difference before and after ITB pump insertion identified in a previous study was 7.3 degrees per year, was used as the expected difference between patients with an without ITB in this study. The SD was assumed to be twice the median difference (14.6). The sample size needed to identify the expected difference was 42 in each group. To increase power to identify differences between ITB and control groups additional patients were included in the study Baseline characteristics: there were no significant differences in population characteristics (age, sex, type of CP), follow-up time and outcome measures at baseline (Cobb angle) Indirectness:

	matched for more than one ITB patient. Similar to the ITB patients 2 measurements were used among the control patients: 1 initial measurement at the age of match and 1 final measurement at the last follow-up in the database **Exclusion Criteria** None stated **Participant characteristics** ITB patients Total number of patients: 50 Age (years. Mean, SD, range) 9.8 (3.7), 3.6 to 16.7 Age groups (years, % children) 3.1 to 5.0: 8 5.1 to 10.0: 50 10.1 to 15.0: 32 15.1 to 17.0: 10 Sex (female, %): 38 Follow-up time (years. Mean, SD, range) 2.7 (1.4), 0.2 to 6.3 Controls Total number of patients: 50 Age (years. Mean, SD, range) 9.7 (3.9), 3.4 to 16.9 Age groups (years, % children) 3.1 to 5.0: 14 5.1 to 10.0: 40 10.1 to 15.0: 34		ITB patients: 15 (13), 0 to 76 Controls: 13 (13), 0 to 67 P=0.06 Final Cobb angle (degrees: mean, SD, range) ITB patients: 28 (20), 0 to 87 Controls: 27 (21), 2 to 91 P=0.38 Progression of scoliosis (%) >5 degrees: ITB patients: 62 Controls: 70 P=0.40 >10 degrees: ITB patients:44 Controls: 36 P= 0.41 >50 degrees: ITB patients:4 Controls:4 P=1.00 Mean annual progression in Cobb angle, degrees per year (mean, SD, range) ITB patients: 6.6 (11.3), -4.9 to 63.7 Controls: 5.0 (6.1), -4.1 to 27.7 P=0.39 Results from multiple linear regression showed that adjusting for age, sex,		Population: none Intervention: none Comparison: none Outcomes assessed: none

	15.1 to 17.0: 12 Sex (female, %): 38 Follow-up time (years. Mean, SD, range) 3.0 (1.6), 0.3 to 6.9		topographic involvement and initial Cobb angle the mean progression of Cobb angle was 0.9 degrees per year greater in the ITB group compared with controls, however this result was not statistically significant		

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment
Authors Hoving,M.A., van Raak,E.P., Spincemaille,G.H., van Kranen-Mastenbroek,V.H., van,Kleef M., Gorter,J.W., Vles,J.S., Dutch Study Group on Child Spasticity. **Year of publication** 2009 **Country of study** The Netherlands **Aim of Study** To study the efficacy at 12 months and safety up to 24 months after start of continuous infusion of intrathecal baclofen (CITB) in children with intractable spastic cerebral palsy **Ref ID** 64321 **Type of study** Prospective case series (follow-up of previous study)	**Inclusion Criteria** As described in Hoving 2007 and in addition having had a successful response to the testing (as previously defined by the authors) **Exclusion Criteria** As described in Hoving 2007 **Participant characteristics** Total: 17 children Sex: 9 females and 8 males Age at time of pump implantation: between 7 and 17 years Weight: range 17 to 84 kg Cerebral palsy type: 12 spastic, 5 spastic/dyskinetic, 3 diplegia, 14 tetraplegia GMFCS level: III (1), IV (2), V (14)	**Intervention** Programmable Synchromed infusion pump (no other details provided on the specific model) (Medtronic Inc., Minneapolis, MN) after 1 month Position pump in abdominal wall (n patients): Left subcutaneously: 7 Right subcutaneously: 2 Left subfascially: 3 Right subfascially: 4 Right subfascially/ subcutaneously: 1 SynchroMed (Medtronic Inc) pump model (n patients): EL 8627-18: 2 EL 8627-10: 1 EL 8627L-18: 1 EL 8626L-10: 2 II 8637-20: 11 Catheter model(n patients): 8709: 5 8731: 12 **Comparison** None **Background treatment** “Standard treatment” including any physiotherapy, speech therapy and occupational therapy. No other details provided 7 children took oral baclofen at	<u>Primary outcomes</u> Individually formulated problems Measured when: at 6 and at 12 months after CITB started Measured by: Depending on both the ability to understand the test and to draw a vertical line, the VAS was rated by the child or by a parent Instrument/test: Visual Analogue Scale (VAS) for individually formulated problems Unit of measurement: average of 3 individually formulated VAS scores per child Results at 6 months (change from baseline) (Mean, SD) (n=17) 4.1 (2.1) p=0.000 Results at 12 months (change from baseline) (Mean, SD) (n=17) 4.7 (2.0) p=0.000 Ease of care Measured when: at 6 and at 12 months after CITB started Measured by: Depending on both the ability to understand the test and to draw a vertical line, the VAS was rated by the	Outcomes assessors blinded to intervention: No Number of participants not completing treatment: None Number of participants with no available outcome data: None Selective outcome reporting: Yes. The outcomes of the Ashworth scale for individual muscles were not reported because there were “too many data” according to the authors. Ashworth scores at 6 months were not reported either	**Funding** Grants from the Research Fund of the University Hospital Maastricht. Grant from Medtronic Inc., Heerlen, the Netherlands. **Other information** Sample size: small for a case series Indirectness Population: None Intervention: None Comparison: None Outcomes assessed: None [STUDY 2009b]

		the time of pump implantation. 6 children gradually discontinued this use during the first 10 post operative days. In one child the dose was largely reduced	child or by a parent Instrument/test: Visual Analogue Scale (VAS) for individually formulated problems Unit of measurement: VAS scores Results change from baseline at 6 months (Mean, SD) (n=16) 4.4 (2.1) p=0.000 change from baseline at 12 months (Mean, SD) (n=16) 5.2 (2.1) p=0.000 Pain Measured when: at 6 and at 12 months after CITB started Measured by: Depending on both the ability to understand the test and to draw a vertical line, the VAS was rated by the child or by a parent Instrument/test: Visual Analogue Scale (VAS) for individually formulated problems Unit of measurement: VAS scores Straight 10cm horizontal line with anchor		

			points of 'no pain' (score 0) and 'unbearable pain' (score 10) Results change from baseline at 6 months (Mean, SD) (n=12) 4.5 (2.6) p=0.002 change from baseline at 12 months (Mean, SD) (n=12) 5.4 (2.7) p=0.002 Movement and function (activities and participation in the ICF-International Classification of Disability and Health) Measured when: at 6 and at 12 months after CITB started Measured by: unclear Instrument/test: Dutch version of the Paediatric Evaluation of Disability Inventory (PEDI)-PEDI caregiver assistance scale Unit of measurement: PEDI scores Results change from baseline at 6 months (median, range) (n=17) 0.0 (-16.6 to 32.7) p=0.893		

			change from baseline at 12 months (median, range) (n=17) 0.0 (-16.6 to 26.3) p=0.917 <u>Secondary outcomes</u> Spasticity Measured when: at 12 months after CITB started Measured by: an experienced paediatric physiotherapist. For each child scores were always rated by the same physiotherapist Instrument/test: Ashworth scale Unit of measurement: Ashworth scores bilaterally assessed in 7 lower-extremity muscle groups (hip adductors, flexors and extensors; knee flexors and extensors; and ankle plantarflexors and dorsiflexors) and 4 upper extremity muscle groups (elbow and wrist flexors and extensors). Scores of the total 22 muscles separately analysed Results (12-month-change scores): The Ashworth score decrease significantly in 5/8 upper extremity		

			muscle groups (0.008 ≤ p ≤ 0.046) and 9/14 lower-extremity muscle groups Movement and function (activities and participation in the ICF-International Classification of Disability and Health) Measured when: at 12 months after CITB started Measured by: unclear Instrument/test: Dutch version of Gross Motor Function Measure (both the GMFM-66 and the GMFM-88 versions) Dutch version of the Paediatric Evaluation of Disability Inventory (PEDI)-functional skills scale Unit of measurement: scores of previous tests (GMFM-88: 4-point ordinal scale; GMFM-66: interval scaling) Results change from baseline at 6 months		

			GMFM-66 overall (Mean, SD) (n=12) 1.4 (2.2) p=0.034 GMFM-88 lying and rolling (median, range) (n=12) 0.0 (-20.0 to 10.0) p=0.357 GMFM-88 sitting (median, range) (n=12) 3.3 (-15.0 to 15.0) p=0.045 GMFM-88 goal dimension (median, range) (n=9) 0.0 (2.0 to 10.0) p=0.041 PEDI functional skills (median, range) (n=17) 0.0 (-11.0 to 13.8) P=0.615 change from baseline at 12 months GMFM-66 overall (Mean, SD) (n=12) 1.6 (3.1) p=0.110 GMFM-88 lying and rolling (median, range) (n=12) -1.0 (-25.0 to 11.0) p=0.448 GMFM-88 sitting (median, range) (n=12) 3.3 (-4.0 to 22.0) p=0.022 GMFM-88 goal dimension (median, range) (n=9) 4.0 (0.0 to 26.0) p=0.007 PEDI functional skills		

			(median, range) (n=17) 0.0 (-15.0 to 15.8) P=0.158 Quality of Life Measured when: at 6 and at 12 months after CITB started Measured by: unclear Instrument/test: Dutch version of the Child-Health Questionnaire-Parent Form (CHQ-PF50) Unit of measurement: scores of CHQ-PF50, each domain is scaled from 0 to 100 with higher scores reflecting a better HRQL. Physical and psychosocial summary scores calculated using normative data from North American children Results change from baseline at 6 months (Mean, SD) physical summary (n=16) 3.8 (9.6) p=0.134 psychosocial summary (n=16) 6.2 (8.3) p=0.023		

			change from baseline at 12 months (Mean, SD) physical summary (n=16) 4.6 (10.7) p=0.163 psychosocial summary (n=16) 5.4 (9.0) p=0.088 Adverse events Measured when: from operation until 24 months after CITB started Measured by: unclear Instrument/test: standardised forms Definition of adverse events any undesirable experience occurring to a participant during the study whether or not related to CITB-included aggravation of symptoms or signs which were present before CITB started Serious adverse event: untoward medical occurrence or effect that: resulted in death, was life		

			threatening, required hospitalisation or prolongation of existing hospitalisation or resulted in persistent or significant disability or incapacity Results Total number of non-procedure or device related events: 51 during a follow-up of 312 patients-months (24 different events) Total number of children involved: 14 The most common non-procedure or device related events were (n events): temporary lethargy (8), excessive hypotonia (4, 3 of them enduring), temporary pressure sores (4), drooling (4, 2 of them enduing) 5 non-procedure or device related events were considered serious because they resulted in significant disability:		

			difficulty swallowing (1), dysarthria (1), excessive hypotonia (2) and epileptic seizure (1) Total number of procedure or device related events: 26 during a follow-up of 312 patients-months (24 different events) Total number of children involved: 11 3 procedure or device related events were considered serious and required children to undergo a second operation resulting in a prolonged hospital stay: 1 incomplete operation 1 abrupt lack of ITB effect 4 hours postoperatively 1 postoperative pain at pump site Procedure or device related events considered non		

			serious were (n events) Swelling at pump site: 7 Lumbar swelling: 3 Pruritus at pump site: 3 Moving pump: 3 Beeping pump: 2 Possible CSF leakage: 2 Wound leakage: 1 Pruritus at lumbar scar site: 1 Cystitis: 1 Acceptability and tolerability Measured when: at last follow-up visit Measured by: unclear Instrument/test: children and/or their parents were asked in they would participate in the test treatment and implantation procedures again Unit of measurement: children's and/or their parents' views on treatment		

			Results 15/17 children and/or their parents stated that they would participate in all procedures again. Two parents were not sure in spite of the achieved individual treatment goal for their children. The doubts in one case were based on both the new onset seizures and the girl's stress during pump refills and in another case were based on a worsened trunk and head balance		

Bibliographic details	Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality Assessment	Reviewer comment
Authors Ramstad,K., Jahnsen,R., Lofterod,B., Skjeldal,O.H. **Year of publication** 2010 **Country of study** Norway **Aim of Study** To explore the timing of effects of intrathecal baclofen therapy in children with cerebral palsy **Ref ID** 133153 **Type of study** Prospective case series	**Inclusion Criteria** 1. Child with cerebral palsy 2. Started continuous intrathecal baclofen therapy (CITB) during the inclusion period (September 2002 to September 2005) **Exclusion Criteria** Not reported **Participant characteristics** N = 38 (However, 3 children discontinued treatment, and data is only reported for the 35 who completed treatment) Age / months (median (range)): 103 (30 - 186) Sex: 25 M / 10 F Gross Motor Function Classification System level (n): III: 2 IV: 13 V: 20 Cerebral palsy diagnosis and classifications were made according to a 2006 consensus report. All children were bilaterally affected. In 26 patients, spasticity was the dominating motor impairment, and in 9 patients dyskinesia dominated over the spasticity	**Intervention** All children underwent a successful test treatment with intrathecal baclofen before they received a programmable Synchromed infusion pump. The catheter tip was placed at the thoracic level. Treatment was given as continuous intrathecal baclofen infusions, as either: - the same infusion rate throughout the day (simple mode) - varying infusion rate (complex mode) The dosage for each patient was based on individual needs, and the median dose was 132 micrograms per day (range 65 - 199) at six months, and 157 micrograms per day (range 86 - 576) at eighteen months. **Comparison** N/A **Background treatment** 14 children received anti-epileptic drugs daily. No children started with anti-epileptic drugs or underwent major surgery during the observation period. Standard treatments such as physiotherapy, occupational therapy and speech therapy were continued.	Assessments were made on the day before pump implantation (T0), and at 6 months (T1) and 18 months (T2) of CITB. <u>Sleep disturbances</u> Measured when: baseline, 6 months and 18 months Measured by: parental interview, but unclear who conducted interview and how Instrument/test: parental interview Unit of measurement: frequency of awakenings during the night on average in the last 4 weeks Results: <u>Number of awakenings (median (range))</u> T0: 1.0 (0 - 25) [n = 32] T1: 0.0 (0 - 10) [n = 29] T2: 0.0 (0 - 10) [n = 30] p-values for change: T0 - T1: 0.005 T0 - T2: 0.006 T1 - T2: 0.731 <u>Pain (frequency and severity</u> Measured when: baseline, 6	Outcome assessors blinded to intervention: unclear Number of participants not completing treatment: Three - one patient discontinued CITB after 3 months because the family suspected intolerable side effects (agitation). In two patients, the pump had to be removed because of infection, and the families did not want another pump Number of patients with no available outcome data: The 3 participants who stopped treatment have no data reported. Various outcomes have missing data for some out of the 35 participants who completed treatment; however it is not clear why this data is missing. Selective outcome reporting: no Other limitations: small sample size (N=35); exclusion criteria and any exclusions are not reported	**Funding** Source of funding not reported **Other information** Surgical revision of the drug delivery system was performed in 6 patients. In these cases, the assessment (T1) was postponed until 6 months after the problem had been resolved, and the assessment at T2 until twelve months after T1. <u>Statistical analysis</u> Due to the small sample size and skewed data, the authors used the Wilcoxon test to compare changes in outcome measures between baseline and T1 and T2. Medians and ranges are reported.

	that was also present.		months and 18 months Measured by: parental interview, but unclear who conducted interview and how Instrument/test: parental interview Unit of measurement: frequency of pain episodes when not sleeping on average in the last 4 weeks, and severity of pain on a 0 - 4 scale Results: <u>a. Pain: frequency (median (range))</u> T0: 2.0 (0 - 3) [n = 35] T1: 1.0 (0 - 3) [n = 31] T2: 1.0 (0 - 3) [n = 31] p-values for change in pain frequency T0 - T1: 0.000 T0 - T2: 0.005 T1 - T2: 0.019 <u>b. Pain: severity (median (range))</u> T0: 2.0 (0 - 3) [n = 35] T1: 1.0 (0 - 3) [n = 31] T2: 1.0 (0 - 3) [n = 31] p-values for change in pain severity T0 - T1: 0.005 T0 - T2: 0.011 T1 - T2: 0.550		

			Spasticity Measured when: baseline, 6 months and 18 months Measured by: experienced physiotherapists Instrument/test: Modified Ashworth Scale Unit of measurement: knee flexors right and left were measured using Modified Ashworth Scale Results: a. Spasticity: right knee flexors (median (range)) T0: 4.0 (2 - 6) [n = 27] T1: 4.0 (2 - 6) [n = 25] T2: 3.0 (1 - 6) [n = 26] p-values for change in spasticity of right knee flexors T0 - T1: 0.627 T2 - T0: 0.022 T1 - T2: 0.062 b. Spasticity: left knee flexors (median (range)) T0: 4.0 (2 - 6) [n = 27] T1: 3.5 (2 - 6) [n = 26] T2: 3.0 (1 - 6) [n = 28] p-values for change in spasticity of left knee flexors T0 - T1: 0.353 T2 - T0: 0.022		

			T1 - T2: 0.062 <u>Movement and function</u> Measured when: baseline, 6 months and 18 months Measured by: experienced physiotherapists (GMFM-66) and parental interview (PEDI) Instrument/test: Gross Motor Function Measure (GMFM-66); Paediatric Evaluation of Disability Inventory (PEDI) Functioning Skills Scale and Caregiver Assistance Scale Unit of measurement: GMFM-66 total score; PEDI scaled scores Results: <u>a. GMFM-66 total score (median (range))</u> T0: 22.7 (0.0 - 48.3) [n = 35] T1: 22.0 (0.0 - 45.9) [n = 32] T2: 24.0 (0.0 - 47.1) [n = 31] p-values for change in GMFM-66 total score T0 - T1: 0.032 T0 - T2: 0.005 T1 - T2: 0.064		

			b. PEDI Functional Skills Scaled Scores (median (range)) - Self-care T0: 33.6 (0.0 - 58.6) [n = 32] T1: 33.0 (0.0 - 61.8) [n = 28] T2: 36.0 (0.0 - 73.6) [n = 27] p-values for change in PEDI Functional skills self-care score T0 - T1: 0.246 T0 - T2: 0.027 T1 - T2: 0.124 - Mobility T0: 23.2 (0.0 - 53.1) [n = 32] T1: 20.9 (0.0 - 48.8) [n = 27] T2: 35.9 (0 - 54.8) [n = 27] p-values for change in PEDI Functional skills mobility score T0 - T1: 0.285 T0 - T2: 0.017 T1 - T2: 0.012 - Social Function T0: 57.9 (0.0 - 96.3) [n = 31] T1: 59.2 (0.0 - 96.3) [n = 27] T2: 64.1 (0.0 - 100.0) [n =		

			27] p-values for change in PEDI Functional skills social function score T0 - T1: 0.041 T0 - T2: 0.002 T1 - T2: 0.035 c. PEDI Caregiver Assistance Scaled Scores (median (range)) - Self-care T0: 15.9 (0.0 - 57.9) [n = 32] T1: 11.6 (0.0 - 63.4) [n = 28] T2: 11.6 (0.0 - 76.7) [n = 27] p-values for change in PEDI Caregiver assistance self-care score T0 - T1: 1.000 T0 - T2: 0.272 T1 - T2: 0.678 - Mobility T0: 11.7 (0.0 - 70.5) [n = 32] T1: 29.0 (0.0 - 58.8) [n = 28] T2: 36.9 (0.0 - 72.7) [n = 27] p-values for change in PEDI Caregiver		

			assistance mobility score T0 - T1: 0.066 T0 - T2: 0.008 T1 - T2: 0.034 - Social Function T0: 58.3 (0.0 - 100.0) [n = 30] T1: 66.9 (0.0 - 100.0) [n = 28] T2: 65.9 (0.0 - 100.0) [n = 26] p-values for change in PEDI Caregiver assistance social function score T0 - T1: 0.035 T0 - T2: 0.004 T1 - T2: 0.025		