Intrathecal baclofen for dystonia of complex regional pain syndrome

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ABSTRACT

Dystonia in complex regional pain syndrome (CRPS) responds poorly to treatment. Intrathecal baclofen (ITB) may improve this type of dystonia, but information on its efficacy and safety is limited. A single-blind, placebo-run-in, dose-escalation study was carried out in 42 CRPS patients to evaluate whether dystonia responds to ITB. Thirty-six of the 38 patients, who met the responder criteria received a pump for continuous ITB administration, and were followed up for 12 months to assess long-term efficacy and safety (open-label study). Primary outcome measures were global dystonia severity (both studies) and dystonia-related functional limitations (open-label study). The dose-escalation study showed a dose-effect of baclofen on dystonia severity in 31 patients in doses up to 450 µg/day. One patient did not respond to treatment in the dose-escalation study and three patients dropped out. Thirty-six patients entered the open-label study. Intention-to-treat analysis revealed a substantial improvement in patient and assessor-rated dystonia scores, pain, disability and quality-of-life (Qol) at 12 months. The response in the dose-escalation study did not predict the response to ITB in the open-label study. Eighty-nine adverse events occurred in 26 patients and were related to baclofen ($n = 19$), pump/catheter system defects ($n = 52$), or could not be specified ($n = 18$). The pump was explanted in six patients during the follow-up phase. Dystonia, pain, disability and Qol all improved on ITB and remained efficacious over a period of one year. However, ITB is associated with a high complication rate in this patient group, and methods to improve patient selection and catheter-pump integrity are warranted.

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1. Introduction

Complex regional pain syndrome (CRPS) is a poorly understood disorder that predominantly affects women, and is usually preceded by an injury or surgery [28,38]. Early clinical features of CRPS include persistent pain, swelling, increased sweating, and changes in skin color and temperature, and may reflect an aberrant inflammatory response to trauma [21,38]. Various studies have reported the involvement of perturbed functions of both C and A delta fibers of sensory nerves (neurogenic inflammation) and also a perturbed function of the local immune system in the skin [6,14,15,18]. Several other studies have reported axonal degenera-tion in small distal nerve fibers of patients with CRPS [3,24,32]. Aberrant processing of spinal and supraspinal sensorimotor neural networks is held responsible for the development of chronic pain, allodynia, hyperalgesia, and movement disorders [17,35]. Approx-imately, 20% of patients with CRPS develop dystonia [13,29,38], which is defined as abnormal involuntary muscle contractions that cause twisting or repetitive movements or sustained postures [11]. Dystonia in CRPS is predominantly characterized by fixed flexion postures, frequently has a delayed onset and may spread to other extremities [29,36,37]. Dystonia in CRPS is generally refractory to treatment [5] and therefore adds considerably to the disease bur-den, leaving some patients severely disabled.

Knowledge of the mechanism that underlies dystonia in CRPS is a prerequisite for the development of a treatment. In 2000, we re-ported on the beneficial effects of continuous administration of intrathecal baclofen (ITB) in six CRPS patients with multifocal or generalized dystonia [34]. Baclofen stimulates the presynaptic gamma-aminobutyric-acid B ($GABA_b$) receptor, which inhibits sen-sory input to spinal neurons [20], but may also act post-synaptic-ally [25]. The aim of the current study was (1) to further

elucidate the efficacy of ITB in a dose-escalation study of a large group of patients with CRPS-related dystonia and (2) to evaluate whether ITB is effective and safe in this population over a 12-month period.

2. Methods

2.1. Patients

All the patients who visited our clinic with a diagnosis of CRPS-1 and dystonia in at least one extremity and who fulfilled the CRPS criteria of the International Association for the Study of Pain (IASP) [21] were considered for inclusion in the study. The IASP criteria include a combination of (1) the presence of an initiating noxious event or a cause of immobilization, (2) continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to any inciting event, (3) evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain and (4) absence of a condition that would otherwise account for the degree of pain and dysfunction. Criteria 2–4 are necessary for a diagnosis of CRPS [21]. We increased the homogeneity of the population by only including CRPS patients, in whom a noxious event triggered the onset of the syndrome in the first affected extremity. Patients were only eligible if they experienced no benefit of oral baclofen up to a minimum daily dose of 60 mg or if this treatment caused dose-limiting side effects. Exclusion criteria were other causes of dystonia (birth injury, head trauma, neuroleptic treatments), other medical or psychiatric concomitant disorders that could affect the surgical risk or completion of the trial, pregnancy and spinal deformities that could interfere with the implantation of the pump/catheter system. Physicians throughout the Netherlands referred patients to our department. Patient consent was obtained in accordance with the Declaration of Helsinki and the local Ethics Committee approved the study.

2.2. Dose-escalation study

A single-blind, placebo-run-in, dose-escalation study with a continuous infusion of baclofen was conducted. This design was chosen for the following reasons. Firstly, our increasing experience of ITB in CRPS patients with dystonia indicates that bolus injections may result in effects lasting for several days. These prolonged effects suggest that the previously used cross-over design [34] with baclofen and placebo on alternate days is inappropriate. We therefore chose to administer placebo before baclofen. Patients were blind as to which days they received placebo. Secondly, bolus injections with ITB are less effective than continuous infusions with ITB [4].

Baclofen or placebo was administered via a percutaneous catheter that was introduced into the subarachnoid space (L3–4) and advanced to the lower thoracic region. The other end of the catheter was tunneled subcutaneously to the flank and connected to an external micro-infusion pump. Two days of placebo infusion were followed by the start of ITB infusion on the third day at a rate of 200 µg per day, which was increased daily according to a fixed schedule (200–250–300–375–450–525–600–700–800 µg) until the responder criteria (see below) were reached. If a baclofen-related side effect occurred, the dose was decreased or maintained, depending on the severity of the side effect.

2.3. Open-label study

A programmable pump (SynchroMed Infusion system, Medtronic Inc., Minneapolis, MN) for ITB administration was implanted subcutaneously in the lower abdominal wall in patients who met the responder criteria. The catheter was introduced in the subarachnoid space (L2–L3) under X-ray guidance with the placement of the distal tip of the catheter in the midthoracic region. The catheter was placed in the same position in all the patients, irrespective of upper or lower extremity involvement of dystonia. The catheter was then tunneled subcutaneously and connected to the pump.

ITB was started at a rate of 150 µg per day and increased in 10–20% steps until (1) patients experienced a satisfactory reduction of dystonia, (2) a maximum daily dose of 1300 µg was reached, or (3) dose-limiting side effects occurred. Pump-catheter system integrity was verified postoperatively in all patients and again in patients who showed no effect when a minimum daily dose of 1000 µg was reached or who deteriorated after an initial positive response.

2.4. Outcome

Patients completed global dystonia severity (GDS) and dystonia-related functional limitations (DFL) ratings at hourly intervals at home for five consecutive days and also for the duration of the dose-escalation study. GDS was assessed using a numeric rating scale (NRS) ranging from 0 (absent) to 10 (most severe). DFLs involved four items (transfers, general mobility, left/right arm functions) with four response options, ranging from 0 (no limitations) to 3 (severe limitations).

Patients participating in the open-label study were evaluated at baseline, and 3, 6, 9, and 12 months after surgery. Primary outcome measures included the GDS and DFL scores. All other outcome measures were considered secondary. Dystonia severity was rated using the Burke–Fahn–Marsden (BFM) dystonia rating scale [9], which is the sum of the scores of the individual body regions. Pain severity was evaluated using a numeric rating scale, ranging from 0 (no pain) to 10 (worst possible pain). The Rivermead Mobility Index (RMI) was used to assess mobility and includes 15 questions addressing a wide range of activities, from turning over in bed to running. The items are scored dichotomously (0–1) and summated, with a higher score reflecting better mobility (0–15) [10]. Activities of daily living were scored using the Barthel index (range 0–20) [19], while the Rankin Scale was used to determine global disability (0: no symptoms to 4: severe disability) [26]. Health-related quality-of-life was assessed with the EuroQol-5D [1]. The Euro-Qol-5D includes five items with three response options, from which a health state value (EQ-Tariff) is calculated, which ranges from 0 (death) to 1 (perfect health), although negative values for health states considered worse than death are possible. It also includes a visual analog scale for general health (ranging from 0; worst imaginable to 100; best imaginable). Higher scores in the RMI, the Barthel index and the EuroQol-5D correspond to better mobility, ADL and quality-of-life, respectively. Higher scores in all other measures indicate symptoms with a higher degree of severity or poorer function.

Safety was evaluated by recording the frequency and severity of adverse events, which included any new symptom or worsening of a pre-existing symptom.

2.5. Statistical analysis

2.5.1. Dose-escalation study

The scores of six hourly intervals from the home evaluation (11:00–16:00) were summed (range 0–60) for each of the 5 days. The selection of these six time points was based on the fact that these were the hours that patients were active and able to record their evaluations. Sleeping, bathing and other activities often caused a larger number of missing values in the earlier and later parts of the day. The mean of these 5 days was used as the baseline score. A mean sum score was similarly calculated for the two pla-

cebo days and each baclofen day. Missing values in the diary were replaced with the value of the previous hour if this concerned two scores or less per day. A day was excluded from analysis if three or more values were missing. The placebo and baclofen responses were expressed as the percentage change from baseline (i.e., home evaluation). The GDS score was used as the primary outcome. The responder criteria were set at $a \geqslant 25\%$ difference between the $GDS_{baclofen}$ and $GDS_{placebo}$ responses on two consecutive baclofen days.

2.5.2. Open-label study

The primary outcome measures were the changes in the GDS and DFL from baseline to 12 months. Missing data in the primary outcome measures were handled in the same way as in the dose-escalation study. Secondary outcome was defined as the changes from baseline on all other scales. Data from any particular patient's scale were excluded from statistical analyses if 25% or more of the data were missing from the scale. The results were analyzed both on an "intention-to-treat" and on an "on-treatment" basis. Score differences between baseline and 12 months were compared using the paired-samples t-test or Wilcoxon-signed-rank test. The relationship between the results from the various scales was assessed using a Spearman's rho test. A logistic regression analysis was performed to evaluate which patient characteristics or screening parameters predicted responsiveness to treatment in the open-label study, where $a \geqslant 25\%$ reduction in patient-reported dystonia was considered a positive response. Statistical analyses were performed using SPSS (version 14.0). A 95% confidence interval (CI) excluding 0 indicated a significant difference at an alpha level of 0.05 (two-sided). No adjustments were made for multiple testing.

3. Results

3.1. Dose-escalation study

Fifty-seven CRPS patients were assessed for eligibility between January 2002 and January 2007, of which 42 patients (40 women) with a mean disease duration of 10.3 (standard deviation 6.1) years participated in the study (Tables 1 and 2). Nineteen percent of study patients had CRPS in two extremities, another 19% in three extremities and 62% had symptoms in four extremities. Three percent of patients suffered from dystonia in one extremity while two,

Table 1
Demographic and clinical characteristics of patients ($n = 42$).

Characteristic	Value
Age – mean (SD), years	35.7 (12.8)
Sex – male/female, no.	2/40
Disease duration – mean (SD), years	10.3 (6.1)
Trauma preceding first affected extremity – no. (%)	
Soft tissue injury	23 (55)
Fracture	11 (26)
Surgery	8 (19)
Extremities affected by CRPS – no. (%)	
2	8 (19)
3	8 (19)
4	26 (62)
Extremities affected by dystonia – no. (%)	
1	1 (3)
2	13 (31)
3	9 (21)
4	19 (45)
Dystonia in upper and lower extremities – no. (%)	
Only upper	3 (7)
Only lower	1 (2)
Upper and lower	38 (91)

Table 2
Signs and symptoms of CRPS in affected extremities.

Variable	Affected extremity			
	1st ($n = 42$)	2nd ($n = 42$)	3rd ($n = 34$)	4th ($n = 26$)
Pain Present/absent/unknown, no.	42/0/0	42/0/0	34/0/0	26/0/0
Hypoalgesia Present/absent/unknown, no.	38/4/0	32/9/1	26/8/0	19/5/2
Hyperalgesia/allodynia Present/absent/unknown, no.	28/14/0	22/20/0	17/17/0	11/15/0
Edema Present/absent/unknown, no.	39/3/0	29/13/0	17/17/0	12/14/0
Temperature changes Present/absent/unknown, no.	40/2/0	36/4/2	25/8/1	18/6/2
Color changes Present/absent/unknown, no.	40/1/1	38/3/1	24/10/0	19/6/1
Hyper/hypohidrosis Present/absent/unknown, no.	31/10/1	25/15/2	19/14/1	13/11/2
Hair and nail growth changes Present/absent/unknown, no.	35/6/1	32/8/2	23/8/3	15/9/2

Variables were deemed to be present if a symptom, a sign or both were reported or observed.

three and four extremities were affected by dystonia in 31%, 21% and 45% of patients, respectively. Demographic and dystonia characteristics of the 15 excluded patients did not differ significantly from the included patients (Fig. 1, supplementary material online).

Three patients dropped out due to intolerable side effects ($n = 1$), CSF leakage ($n = 1$) and because the study was considered too demanding ($n = 1$). The number of the missing data from the primary outcome never exceeded two scores per day. Thirty-seven patients followed the fixed-dose schedule; side effects required adjustment of the schedule for five patients. Blinding in the dose-escalation study was generally successful until patients perceived an improvement in their dystonia, after which blinding could not be maintained successfully.

The mean $GDS_{placebo}$ response was 7% (95% CI: 3–12). One patient did not respond to ITB. A dose-effect of baclofen on dystonia severity was observed in doses up to 450 µg. Thirty-one patients reached the responder criteria at this dose (Fig. 2). A total of 38 patients showed $a \geqslant 25\%$ difference between the baclofen and placebo responses on two subsequent baclofen days. The mean difference between placebo and baclofen response was 38% (95% CI: 34–43) in favor of baclofen for responders on the first response day and 41% (95% CI: 36–46) on the second response day. The responder criteria were reached at a mean baclofen dose of 415 µg/day (SD 139, range 200–800). The total $DFL_{placebo}$ response score showed a worsening of 2% (95% CI: −3 to 7%). The mean difference between $DFL_{placebo}$ and $DFL_{baclofen}$ response was 25% in favor of baclofen (95% CI: 17–33) on the first response day and 25% (95% CI: 17–31) on the second response day.

3.2. Open-label study

Thirty-six of the 38 patients who met the responder criteria participated in the open-label study. Two patients declined to pro-
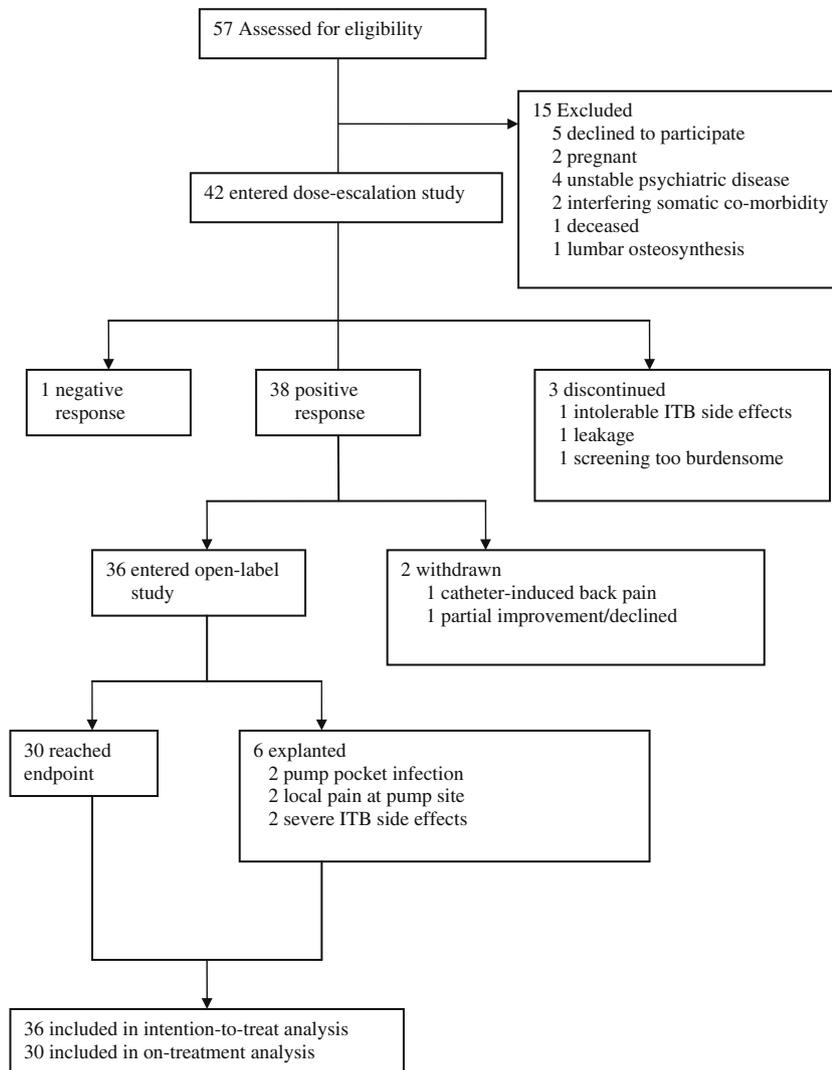
Fig. 1. Enrollment of patients in dose-escalation and open-label studies.

ceed to implantation, due to catheter-induced back pain and persistent partial improvement of dystonia after the dose-escalation study. Missing data never exceeded the predefined criteria. All dystonia scores had improved significantly between baseline and 12 months (Table 3). GDS improved by a mean of 2.9 (SD 3.0) points (40%). The BFM-score showed a similar improvement of 18.8 (27.1) points (38%). BFM subscores for the upper extremities improved by 45%, while dystonia in the lower extremities improved by 33%. GDS and BFM scores decreased during the first six months and remained stable thereafter (Fig. 3A and B). Pain severity measured by the NRS decreased from 7.7 to 5.7 (26%) and there was a correlation between the reduction of pain and the improvement in the GDS score (Spearman's rho 0.50). The DFL total, mobility, transfers, and left/right arm function scores improved by 31%, 19%, 38%, 35% and 33%, respectively. The Rivermead Mobility Index improved by 44%. Of six patients who were completely confined to bed, four changed to using a wheelchair (two of which were able to walk short distances with or without walking aids) and one patient became fully ambulatory. One explanted patient remained confined to bed. Three of four patients who were partially bed-bound changed to full-time wheelchair use. Of the 14 patients who were wheelchair-bound, 10 remained unchanged, two still needed a wheelchair but were able to walk short distances, and two became

fully ambulatory. All four patients with part-time wheelchair use remained unchanged. Of five patients who needed walking aids, four improved to walking without aids. One of three ambulatory patients became part-time wheelchair-dependent due to worsening of CRPS symptoms. The other two patients remained ambulatory. The Barthel index improved by 26%. Distribution of the Rankin Scale improved; 26 patients had moderate to severe disability at baseline, compared to 15 patients during follow-up. The EuroQol-index improved from 0.21 to 0.45 while the health state improved from 42 to 54.

The pump was explanted in six patients before the endpoint was reached (Fig. 1, Supplementary material on line, mean duration of ITB administration = 6 months, range 2–11). Results of the intention-to-treat analysis (n = 36) did not differ from the on-treatment analysis (n = 30). Apart from a slight improvement in GDS score, none of the outcome measures in the off-treatment group changed significantly. Seventy percent of patients on treatment improved by ⩾25% on the primary outcome, whereas 47% of the patients improved by ⩾50%, and 20% improved by ⩾75%.

None of the variables tested in the logistic regression analysis (including patient characteristics and screening characteristics, such as time to response and dose at which the patient met the responder criteria in the screening phase) predicted the response to
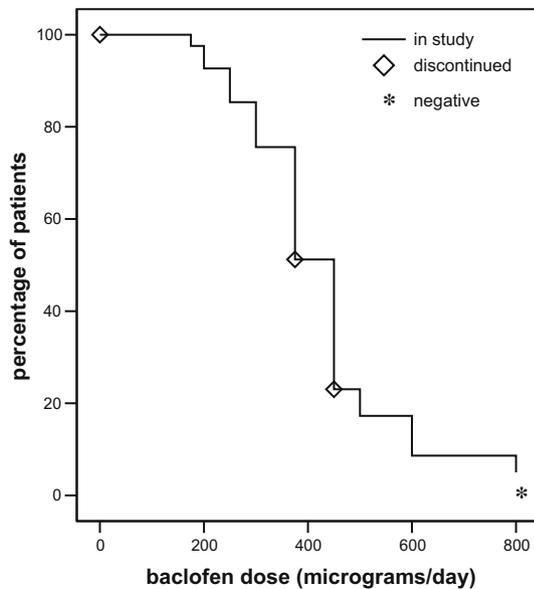
Fig. 2. Dose-escalation study: baclofen dose at which the responder criteria were reached. Kaplan–Meier curve of 42 patients showing the baclofen dose at which patients reached the responder criteria. ◇ denotes three patients that dropped out because of intolerable side effects, CSF leakage and the fact that the study was too burdensome. *One patient who did not respond to ITB.

Fig. 3. Dystonia severity during open-label study. Mean (SD) scores of global dystonia severity (GDS, A) and the Burke–Fahn–Marsden scale (BFM scale, B) before and after 3, 6, 9, 12 months of ITB infusion in the on-treatment group ($n = 30$). *Significant difference compared to baseline values ($p < 0.001$).

ITB in the open-label study. The median ITB dose in the follow-up study increased from 450 µg/day (range 150–1250) after 3 months to 615 µg/d (range 150–1500) after one year.

3.3. Adverse events

Nineteen ITB-related adverse events were reported in 14 patients (Table 4). Most frequent ITB-related adverse events were nausea, vomiting, headache, and short-term urinary retention at the start 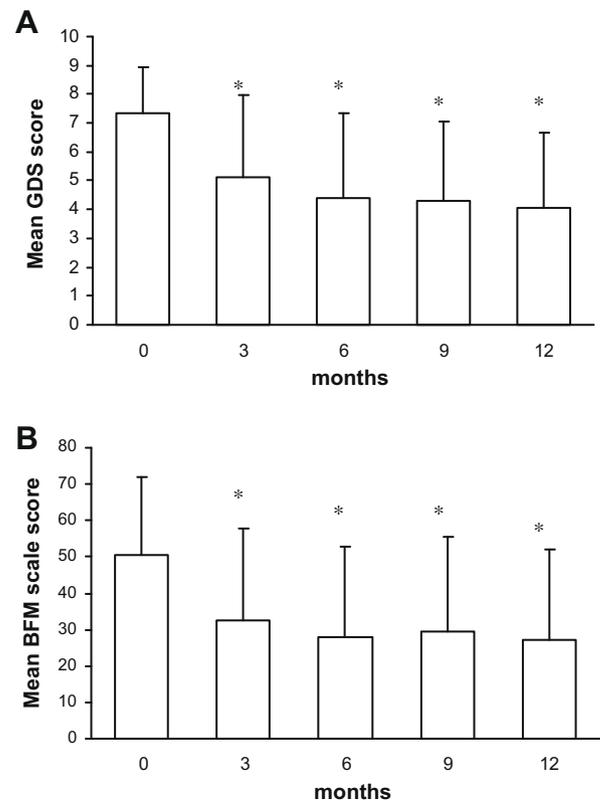of the treatment. Three patients developed baclofen intoxication with somnolence, nausea and vomiting, which required temporary discontinuation of baclofen. Persistent baclofen-related headache and vomiting, which cleared after lowering ITB dose to a minimum rate, led to pump explantation in one pa-

Table 3
Open-label study: primary and secondary outcomes at baseline and 12 months follow-up.

	Intention-to-treat ($n = 36$)				On-treatment ($n = 30$)				Off-treatment ($n = 6$)				
	0 Mo	12 Mo	Change from baseline	95% CI	0 Mo	12 Mo	Change from baseline	95% CI	0 Mo	12 Mo	Change from baseline	95% CI
Outcome (range)												
Global dystonia severity (0–10)	7.3	4.4	−2.9	−3.9 to −1.9	7.3	4.1	−3.2	−4.4 to −2.1	7.1	6.1	−1.0	−1.8 to −0.2
Burke–Fahn–Marsden Scale (0–120)	48.9	30.1	−18.8	−28.0 to −9.6	50.5	27.2	−23.3	−33.3 to −13.3	40.8	44.8	3.9	−12.0 to 20.4
Pain – numeric rating scale (0–10)	7.7	5.7	−2.0	−3.0 to −1.0	7.7	5.4	−2.3	−3.4 to −1.2	7.4	7.4	0	−1.5 to 1.5
Dystonia-related functional limitations												
Total score (0–12)	8.5	5.9	−2.6	−3.8 to −1.5	8.6	5.3	−3.3	−4.5 to −2.1	8.2	8.8	0.6	−1.1 to 2.3
Mobility (0–3)	2.1	1.7	−0.4	−0.6 to −0.1	2.1	1.6	−0.5	−0.8 to −0.2	2.1	2.4	0.3	−0.2 to 0.8
Transfers (0–3)	2.1	1.3	−0.8	−1.1 to −0.4	2.1	1.2	−0.9	−1.3 to −0.5	2.0	2.1	0.1	−0.5 to 0.7
Right hand function[a] (0–3)	2.3	1.5	−0.8	−1.2 to −0.4	2.3	1.3	−1.0	−1.4 to −0.6	2.3	2.3	0	−0.6 to 0.7
Left hand function[a] (0–3)	2.1	1.4	−0.7	−1.1 to −0.4	2.1	1.2	−0.9	−1.3 to −0.5	1.8	2.0	0.2	−0.3 to 0.7
Rivermead Mobility Index (0–15)	5.5	7.9	2.4	0.5 to 4.4	5.7	8.3	2.7	0.4 to 4.9	4.6	5.6	1.0	−1.8 to 3.8
Barthel index (0–20)	11.8	14.9	3.1	1.3 to 5.0	11.6	15.3	3.7	1.7 to 5.8	13.0	13.0	0	−4.4 to 4.4
EuroQol-5D												
Index (EQ-Tariff) (0–1)	0.21	0.45	0.24	0.12 to 0.36	0.24	0.50	0.26	0.13 to 0.41	0.04	0.10	0.06	−0.03 to 0.14
Health state (0–100)	42.2	53.8	11.6	4.4 to 18.7	43.5	54.5	11.0	3.1 to 18.8	34.6	49.8	15.2	−10.9 to 41.3

[a] Right and left hand functions were only assessed in affected hands. Absolute values are given in means. 95% CI denotes 95% confidence interval. Differences in global dystonia severity were tested with the paired-samples *t*-test. For all other outcome parameters, the paired Wilcoxon-signed-rank test was used.

Table 4
Adverse events in open-label study.

Adverse events	Type of event	N
ITB-related (N = 19)	Urinary retention	3
	Somnolence	3
	Psychiatric[a]	3
	Nausea, vomiting	2
	Headache	2
	Fatigue	1
	Dysesthesia	1
	Hypotension, bradycardia	1
	Other[b]	3
Device-related, catheter (N = 43)	Post-dural puncture headache	31
	Dislodgment	5
	Subcutaneous fluid collection/CSF leak	3
	Occlusion/kink	2
	Compression spinal cord or root	2
Device-related, pump (N = 9)	Pump pocket infection	4
	Pain at pump site	2
	Migration of pump	2
	Ulcerations at pump site during pregnancy	1
Other (N = 18)	Worsening CRPS symptoms	3
	Psychiatric[c]	4
	Excessive weight loss	2
	Gastro-intestinal problems (unrelated to ITB)	3
	Infections (unrelated to device)	3
	Internal complications[d]	3

[a] Psychosis: n = 2, depression and anxiety disorders: n = 1.
[b] Diplopia, dizziness, anorgasmia.
[c] Confusional state: n = 2, reactive depression: n = 1, reactive psychosis: n = 1.
[d] Anemia, elevated liver enzymes, electrolyte changes.

tient. Three patients had psychiatric adverse events (two with psychosis and one with depression), which were probably caused by ITB, as symptoms cleared after lowering or stopping ITB. This led to explantation in one of these patients.

Device-related complications were common: 43 catheter-related complications occurred in 33 patients, with post-dural puncture headache (n = 31) as the most frequent complication.

Five patients, who initially responded to ITB, experienced a gradual worsening of dystonia over a period of 1–2 weeks. Catheter dysfunction was found in these patients and dystonia improved after a variable delay of days to months after catheter revision.

Nine pump-related adverse events occurred in eight patients. Two patients experienced refractory pain at the site of the pump pocket, which led to explantation in one of these patients. The pump was explanted in three of four patients who developed a pocket infection. The pump was not re-implanted in two of these patients due to a questionable effect of ITB. The third patient improved to her former level after re-implantation.

4. Discussion

Dystonia is characterized by impaired inhibition of sensorimotor circuitry at multiple levels of the central nervous system [2,7,23]. Findings on dystonia in CRPS are in line with this and showed a loss of spinal and cortical inhibition [23,30,31]. The dose-escalation study showed that ITB reduces dystonia in patients with CRPS. The fact that baclofen is infused around the spinal cord where it is known to stimulate presynaptic $GABA_b$ and possibly postsynaptic receptors [20,25], may indicate that the loss of spinal GABAergic inhibition is an important mechanism in this type of dystonia. However, since baclofen may diffuse more rostrally, we cannot rule out that part of the effect is mediated at a supraspinal level.

The open-label study showed marked improvement of patient and assessor-rated dystonia after one year. The largest improvement in dystonia was seen after 3 months, with a smaller further improvement after 6 months after which dystonia remained stable (Fig. 2). A similar response pattern was observed in deep brain stimulation (DBS) in patients with primary generalized dystonia [39] and contrasts with the more rapid response to DBS of other movement disorders, possibly indicating a typical response characteristic of dystonia. A direct antinociceptive effect of baclofen cannot be ruled out since pain reduction was only partly explained by a decrease in dystonia severity [20]. The median baclofen dose of 615 μg/d after one year of follow-up was similar to doses used in other types of dystonia [4,40], but higher than those reported for spasticity (mean 290 μg/d) [12,16], possibly due to the differences in the pathophysiology of both disorders.

We found improvement in arm function (DFL, 35/33%), transfers (DFL, 38%), and mobility (DFL 19%, Rivermead Mobility Index 44%) on the disability level. The largest changes in mobility were observed in patients confined to bed. The improvements in the impairment and disability levels paralleled those in the quality-of-life. The efficacy of ITB in CRPS-related dystonia is emphasized by the observation that, contrary to the on-treatment group, the off-treatment group failed to change significantly in all measures but the GDS. However, the small change in GDS was not paralleled by a change in the BFM dystonia rating scale.

One may postulate that the benefits reported by the patients on ITB reflect placebo effects, but we consider this unlikely for the following reasons. Firstly, all patients had long-term, progressive dystonia despite numerous interventions, including rehabilitation programs and invasive procedures (e.g. spinal cord stimulation). Secondly, only a small placebo response (7%) was found in the dose-escalation study, which was similar in magnitude to our earlier study [34]. Thirdly, catheter dysfunction led to obvious worsening of dystonia in initial responders when these patients were unaware of the immediate cause. This worsening of dystonia also highlights that ITB acts on a symptomatic level.

All patients had met the 25% responder criteria in the dose-escalation study, but only 70% of the on-treatment patients experienced $a \geqslant 25\%$ reduction in dystonia, which was not anticipated. Malfunctioning of the pump-catheter system or a subtherapeutic dose of ITB could not explain this failure to respond. Pump-catheter system integrity was verified postoperatively in all patients and again in non-responders when a minimal dose of 1000 microgram per day was reached. The cause of the discrepancy between both our studies therefore remains uncertain. A possible explanation is the difference in ITB flow rates between both studies since the flow rate during the dose-escalation study was almost six times higher than the rate in the open-label study. Flow-rate dependent effects of intrathecal administration may influence the drug's distribution along the spinal canal [8] and are currently being evaluated in a new study. We encountered a high percentage of adverse events during the follow-up period, which were related to the surgical procedure, drug delivery system and to baclofen. Particularly, post-dural puncture headache (PDPH) occurred more frequently (86%) than commonly reported for pump implantation in other disorders (up to 42%, [22]). A previous study reported high frequency of CSF leakage in patients with dystonia [4]. CSF leakage related to PDPH was evident in three of our implanted patients, but we cannot rule out CSF leakage at a subclinical level in those patients lacking clear signs of CSF leakage. Migration of the pump leading to the failure of drug delivery occurred in two patients with a body mass index of over 30. ITB likely caused psychosis in two patients and depression in one, since lowering the dose resulted in symptoms clearing. The higher number of device-related adverse events compared to ITB-treated patients with spasticity, can possibly be ex-

plained by the greater mobility in patients with CRPS-related dystonia.

Although the female to male ratio of CRPS is 3–4 in most studies, our patient group included a very high percentage (95%) of female patients. This finding is in line with other studies in patients with CRPS-related dystonia where the percentage of females are much higher (84–86%) [29,33,37]. To date, no satisfactory explanation has been provided for this female predominance.

There is an ongoing controversy over whether dystonia related to peripheral trauma with or without CRPS is caused by organic or psychogenic factors. Seventy-four percent of patients in our study also participated in a case-control study, in which their psychological characteristics were compared with those of patients with affective and conversion disorders [27]. In line with other case-control studies [33,36], this study found no evidence to support a distinct psychological profile in patients with CRPS-related dystonia.

In conclusion, this placebo-controlled dose-escalation study showed that ITB reduces dystonia in CRPS and lends further support to the role of GABAergic mechanisms in this cause of dystonia. ITB also improved disability and Qol and remained efficacious over a period of one year. However, ITB is associated with a high complication rate, and therefore methods to improve patient selection and catheter-pump integrity are warranted to enhance its therapeutic potential.

Acknowledgements

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