Title: Selection, trial, and aftercare for intrathecal baclofen in patients' own community

Short title: intrathecal baclofen out of hospital

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Professor 3

Word count (excl. abstract and references): 2999

Keywords: Ambulatory care, intrathecal baclofen, screening, trial, aftercare

Corresponding author:

Author, Nurse Practitioner, PhD candidate

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Abstract

Background

Intrathecal baclofen (ITB) is used for the treatment of intractable spasticity. The burden of traveling for ITB screening and aftercare is problematic for severely handicapped patients living in nursing homes (NHs). The aim of this study is to report seven years' experience of selection, trial, and aftercare during 3- and 12-month follow-ups, for ITB treatment in their own community of adult patients with intractable spasticity. This study contributed to the analysis of the feasibility and safety of the method.

Methods

We analyzed routinely collected observational data from April 2011 to January 2019. We screened patients based on history and a physical examination before selecting them to undergo an ITB trial on location. The trial consisted of a single ITB dose via a lumbar puncture. To assess its effectiveness on spasticity we used the modified Ashworth scale (MAS), spasm frequency, and severity scale. After a positive trial, patients were referred for pump implantation.

Results

Eighty-nine patients met the inclusion criteria for an ITB trial. Eighty-one were suitable for a trial. Sixty-nine underwent a trial in the patient's own community. Two patients experienced a mild post-spinal headache after the trial. In 93%, a single intrathecal dose caused a significant decrease in spasms. Fifty-six received an implant. During the post-implantation follow-up, the most profound decrease in spasticity was in the initial three months.

Conclusions

Intrathecal baclofen selection, trial, and aftercare in the patients' own community is a feasible and safe tool in severely spastic patients.

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Introduction

Spasticity is a common symptom in central nervous disorders such as stroke (28%–40%),[1–3] traumatic brain injuries (13%),[1] spinal cord injuries (70%),[4–6] cerebral palsy (CP) (90%),[7,8] and multiple sclerosis (MS) (41–80%).[1,7,8] Among residents with mentioned pathologies in NHs, the prevalence of spasticity is 73%.[9] Symptoms vary from subtle neurological symptoms to a gross increase in muscle tone causing immobility of joints,[10, 11] contractures, involuntary movements, and pain. Severe spasticity can have a detrimental effect on the activities of daily living, such as care dependency, nursing, sleep pattern, and quality of life.[29]

The cornerstone of pharmacological treatment of spasticity has been treatment with oral spasmolytics.[12–14] Oral baclofen is the most well-known and widely used option, but its effectiveness is limited due to side effects such as nausea, concentration and memory deficits, hallucinations, drowsiness, sedation, ataxia, confusion, and increased weakness and fatigue, particularly when used at higher dosages.[13–15] Immediate administration of baclofen into the cerebrospinal fluid is characterized by a significant reduction in these side effects. Studies have shown the efficacy of long-term ITB administration for reducing intractable spasticity.[16–26] For patients who do not receive enough benefit from oral spasmolytics and/or for whom the side effects have become intolerable, ITB can be considered.[26]

Although ITB is available worldwide, it seems that there is considerable undertreatment and late deployment of therapy is not uncommon.[8] Erwin used the expression "too little, too late" when he concluded that, in patients with MS, ITB options were underutilized due to a focus on disease-modifying therapies rather than symptom control, as well as concerns about costs and safety of ITB therapy, and an underestimation of the impact of spasticity on quality of life.[27] In the Netherlands, where long-term ITB for intractable spasticity has been an accepted treatment for many years, the decision for its application seems to be strongly physician-dependent. Especially in NH residents, spasticity may often be undertreated.[9] Another factor in the undertreatment of severely handicapped

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patients seems to be the burden of traveling to different hospital visits for referral, selection, testing, preoperative anesthesiology assessment, implantation, and aftercare. For this reason, an ambulatory care clinic (ACC) was founded in 2011.[29] The Ministry of Health granted official recognition as a home-based ACC in patients' own surroundings.[29]

Healthcare providers performed the ITB procedures on location where the patient was living. The results were discussed on a multidisciplinary basis in the NH or disability community (care institution where people live with severe physical and mental disabilities, allowing intensive support), and a final decision was made in our university neuromodulation center.

The aim of this study is to report seven years' experience of selection, trial, and aftercare during a 3- and 12-month follow-up for ITB in adult patients with intractable spasticity living in their own community.

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Methods

The local medical ethical committee approved the study (no. 2018-1221) and, due to the retrospective character of the study, waived the requirement to obtain informed consent. We used clinically collected data in patients with intractable spasticity referred to the ACC between April 2011 and January 2019.

An NH physician or rehabilitation physician consulted the ACC for potential ITB treatment. We enrolled adult residents of different NHs or disability communities suffering from severe disabling spasticity deriving from a variety of etiologies. At baseline, patients were not achieving enough spasticity relief with their previous or current more conservative treatment. Table 1 shows the inclusion and exclusion criteria for patients.[28,30]

After referral to the ACC, a specified written patient history regarding earlier spasticity treatment was requested. An anesthesiologist or pain physician specializing in ITB reviewed the information received, and a patient evaluation was performed on location. We provided extensive information to patients (as far as possible), family, and caregivers about the advantages and disadvantages of ITB treatment.

We held a multidisciplinary meeting with the NH physician and rehabilitation physician, discussing the case and treatment goals. If necessary, we involved other members of the multidisciplinary ITB team, e.g., neurologist, neurosurgeon, neuroradiologist, psychologist, and physiotherapist. This care chain is a collaboration among several healthcare providers, clearly reflecting a multidisciplinary approach to treatment.[31]

If we identified the patient as a potential candidate and we obtained a witnessed or written informed consent, we included the patient in the ITB therapy trial. Candidates had at least one week for prior reflection. An anesthesiologist or pain physician and a nurse practitioner (NP) performed the ITB trial in the NH or disability community. During the ITB trial period, the ITB team stayed in the NH for three hours after the treatment. Since the NH physician, physiotherapist, and nurse (of the NH) were part of the multidisciplinary team and present from the beginning, they clinically observed the patient

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throughout the day. Nurses observed the transfer from bed to wheelchair, sitting in the wheelchair, and assistance with dressing and undressing and described these activities in the patient's nursing file. If a (serious) adverse effect ([S]AE) were to occur, the patient would be transferred to our neuromodulation center.

We defined an AE is as any unfavorable medical occurrence were monitored. We defined a minor event as an occurrence causing discomfort that was self-limiting or that could easily be treated. In a moderate or severe event, hospital admission was indicated. Serious adverse effects (SAE) were those that were life-threatening.[32]

To assess a patient's response to ITB, we administered a single bolus injection (50 micrograms [mcg]) via a lumbar puncture (LP).[33] If needed, we prolonged the ITB trial period by one or two days for a second and third injection, with a maximum ITB of 100 mcg. During the trial, we made no change in the oral spasmolytic medication. In cases where patients were receiving anticoagulant or antiplatelet therapy, we followed the neuraxis guidance of the Dutch Association of Anesthesiology for discontinuance.[34]

Before and two hours after intrathecal injection of baclofen, we assessed the severity of spasticity for all the four extremities using the MAS,[35] spasm frequency scale, and clonus scale.[36] In the upper extremities (wrist and elbow flexors and extensors) and lower extremities (ankle dorsiflexion and plantar flexion, knee flexion and extension, and hip adduction and abduction).[20] When using the MAS,[35] 0 is no increase in tone and 4 is a rigid extremity. The spasm scale measures the frequency of spasm with scores from 0 to 4 (0 = no spasm, 1 = mild spasm induced by stimulation, 2 = infrequent spasm < once per hour, 3 = spasm > once per hour, and 4 = spasm occurring > 10 per hour).[21] The clonus scale is a derivation of the Tardieu scale. A score of 1 is fatigable clonus (< 10sec) and 2 is indefatigable clonus (> 10 sec).[36] We observed patients' vital signs for two hours.

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When the ITB trial resulted in at least a two-point reduction in the total scores of the MAS, spasm, and clonus scales, and the patient and the patient's family and treatment team also clinically confirmed the reduction of spasticity, we regarded the patient as a suitable candidate for ITB. We offered patients or their legal representative one week of reflection before they made a decision for a permanent therapy. On confirmation, we referred patients to our neuromodulation center for implantation of a drug delivery system (SynchroMed II®, Medtronic Inc., Minneapolis, MN, USA).

When performing the ITB trial, the ACC brought all the necessary equipment, trial medication, monitoring equipment, and an emergency kit containing material to intravenously administer atropine, clemastine, and ephedrine. We left behind a detailed written consultation letter after each visit, including emergency contact information.

In the neuromodulation center, a multidisciplinary team discussed the patient (after receiving a referral letter), placed the patient on a waiting-list for implantation of the drug delivery device, if eligible, and performed a preliminary preoperative assessment for anesthesia. After implantation, patients stayed one night in the hospital before being discharged to their NH or disability community.

The ITB pump was programmed for a perioperative non-therapeutic minimum delivery rate. The NP performed wound inspections twice weekly. If no sign of complication was apparent at two weeks, we initiated the actual intrathecal treatment. Usually, the initial daily dose would be double the single bolus dose required to attain a recognizable spasmolytic effect. We performed dose titration twice a week with a maximum daily dose increment of 10%. After we observed a decrease of spasticity, we tapered and terminated the oral medication. Following the initial dose titration phase, we included patients in the chronic aftercare program of the ACC, in which NPs performed dose adjustments, programming of the pump, and refill procedures on location.[29]

Statistical Analysis

We used descriptive statistics to determine the frequencies of sample characteristics and of outcome parameters, i.e., the severity of spasticity, spasm frequency, and clonus scale. In addition, we described

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measures of central tendency and of variability, dependent on the shape of each distribution. We used the Shapiro-Wilk test to analyze whether parameters were normally distributed. All the outcome parameters exhibited a skewed distribution. We analyzed differences between baseline and after-trial levels using Wilcoxon signed-rank tests. We analyzed differences in the levels of outcome parameters over the four moments of measurement using the related-samples Friedman's two-way analysis of variance by ranks. For all statistics, we set the alpha at the traditional 0.05 level. We performed analyses using IBM SPSS Statistics 26.

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Results

In the evaluation period (April 2011 to January 2019), 100 patients were referred to our ACC, living in 33 different care institutions (72 in NHs and 28 in disability communities). The mean distance between a NH and a neuromodulation center was 52.3 kilometers (6–158 km). Figure I shows the flow diagram of patients suitable for the ITB trial and, after a positive result, the referral for implantation and aftercare.

Of the 100 patients originally referred, 89 met the inclusion criteria for an ITB trial. Table II shows the demographic and baseline characteristics of the candidate ITB population. Of the 89 patients in the study, we considered 81 suitable for an ITB trial on location. We observed widespread spasticity (upper and lower extremities plus trunk) (table III).

All 81 study participants had passive goals such as improved positioning and wheelchair tolerance, improved daily care (decreased caregiver burden and time), improved quality of sleep, and minimized or terminated oral spasmolytic medication.

Of the 69 screened patients, 64 showed a relevant improvement in their spasm scores and were identified as eligible for implantation of a drug delivery system. Spasticity decreased from a median MAS score of 3.25 (IQR 2) post-trial to 1 (3) on ITB, which was significant (table III). Not all patients showed intentional or spontaneous spasms and/or clonus before treatment. If present, the measured clonus scale score decreased significantly. The spasm scale did not show a significant decrease during the screening test. Figure II shows the median and IQR of MAS by moment of measurement.

During the test, five patients did not respond to the maximum dose of baclofen (100 mcg). For these five, we considered the test to be unsuccessful. Ultimately, 53 patients received a permanent device implant (Figure I).

We could make the decision for permanent implantation after one bolus with 50 mcg baclofen in 41 patients, after two injections (75 mcg total) in 19 patients, and after three injections (100 mcg total) in 5 patients.

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In the MS group (N = 29) who underwent JTB trial treatment, all patients had a positive trial outcome. Nevertheless, in two cases we decided not to implant the pump, as these patients did not want to proceed. Within the MS sub-group, 21 were screened positive with one bolus injection (50 mcg), and in 8 cases the second test with a dose of 75 mcg was positive (Table IV). In stroke cases, 6 out of 13 required a second injection (75 mcg), and 1 patient needed a third injection (100 mcg) (table IV).

Follow-up

Most of the patients used oral antispasmodics in the pre-surgical treatment phase; baclofen in 38/53, tizanidine in 14/53, dantrolene in 4/53, clonazepam in 4/53, and tolpermyo in 1/53 patients. After three months, six patients still used (a lower dose) oral baclofen. One patient used tizanidine. None of the patients used clonazepam or tolpermyo by the end. At the one-year follow-up, two patients were still using oral baclofen and one patient was using tizanidine, due to reduced effectiveness of ITB on the upper extremities.

The start dose of baclofen in a simple continuous infusion modus in 49 cases was 100 mcg/day, in two cases, it was 125 mcg/day, and in two other cases, it was 150 mcg/day. In ten cases, patients received aftercare in the NH (patients with MS) by a geriatrician who was familiar with ITB treatment.

The MAS scores from 3 to 12 months, although significant, decreased further but not as markedly as in the first 3 months post implantation. This could be explained by the fact that patients enter a stable phase after the titration of the baclofen or because of a natural progression of the disease course. We did not compare the dosage increases during the follow-up.

Until now, activities of daily living or quality of life have not been measured on a regular basis via questionnaires in the clinical situation. Using a retrograde database has resulted in this information unfortunately not being available for this study.

Throughout the study, we recorded all (S)AEs (table V) at each visit and discussed them at a multidisciplinary team progress meeting every six weeks.

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To be eligible for ITB therapy, patients had to have an estimated life expectancy of at least one year. Still, eight ITB-implanted patients died within one year. All of them suffered from progressive diseases and were considered frail, but the life expectancy of these patients at the start of the therapy fulfilled the minimal predefined estimated life expectancy. They died sooner than expected due to unexpected disease progression and comorbidity. There is no indication in the patient files that this was related to the ITB therapy itself.

Feasibility

In the first five years of this study, no regular financial reimbursement was available for the provision of specialized medical care on location. In that period, the Ministry of Health accepted the ACC's neuromodulation activities as an innovation project. Since 2016, ITB aftercare performed by an ACC has been regarded as a standard type of care in the Netherlands, with an associated reimbursement structure.

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Discussion

This study summarizes seven years' experience with the home-based ITB-selection concept in a cohort of 100 patients. Applying this concept prevents the burden of frequent hospital visits for intake, selection, preoperative anesthesiology assessment, and aftercare and hospitalization for ITB trial.

Undertreatment of disabling spasticity is a worldwide phenomenon and is especially prevalent in NHs, where ITB is rarely offered.[9] This lack of availability could be explained by the complexity of the set-up required to deliver the therapy and the need for interaction between several medical specialists (including neurosurgery, pain medicine, and neurorehabilitation, all of which may not be present in the same hospital).[41]

We believe that it is not only patients who are functionally disabled by generalized spasticity who should be treated with ITB.[29, 38–40] This is what Erwin et al. stated in their study; the decision to offer ITB therapy to patients should be based on different goals because patients also experience greater comfort from a better sitting position, wheelchair stability, better sleep, and pain reduction.[20, 29, 42] Therefore, ITB treatment should also be available for patients for whom improvement in comfort and in daily care can be achieved.

A multidisciplinary team defined goals and performed a physical examination, and the ITB team stayed in the NH for three hours after administering the treatment. The team assessed spasticity before treatment and at two hours after treatment. The most recently published guideline on best practices for ITB therapy advises to extend this observation period to four hours, as some patients could be late responders. Extending the observation period may have changed the selection of some patients. However, there is always the risk of an inadvertent extradural injection or aberrant spread of the medication. Therefore, we repeated all negative tests with an increased dose up to 100 mcg, which, in our opinion, limits the number of falsely denied suitable candidates.

In retrospect, considering the severe level of suffering in those affected, we were surprised by the high refusal rate of either the family or patients for this likely effective therapeutic option. This may have

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been related to unfamiliarity. Although not part of the study, it seems that when the therapy was better known in a particular NH, more patients were referred.

We realize there are limitations in this study. First, we collected the data retrospectively, the data were sometimes incomplete, and the data were based on a small study group. Second, since the mentioned passive goals and effect on daily care were written in the patients' electronic files but not systematically and unambiguously described, we were not able to analyze these data. Third, there were no other ACC data to compare with the ITB treatment data, and we did not compare the data with the selection and trial of other neuromodulation centers. Finally, the Netherlands is a relatively small country, and we realize that the home-based ITB-selection concept might be more challenging to organize in countries with larger travel distances. Therefore, further investigation will be necessary.

Conclusion

In the Netherlands, ITB administration is a certified and reimbursed therapy for generalized intractable spasticity. We did not question the therapy itself, but the study summarizes seven years' experience in developing a system of care that provides necessary ITB therapy for patients in remote facilities where spasticity limits their care. The results of this study indicate that selection, trial, and aftercare for ITB on location is a safe and powerful tool to reduce the burden of traveling in severely handicapped patients and can be successfully accomplished with an ACC in cooperation with a neuromodulation center. This could potentially be a crucial step in reducing ITB undertreatment in this patient category.

Acknowledgment

We would like to thank Dr Elmar M. Dallas for his contribution in reviewing the manuscript.

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Legend section

Inclusion criteria	Exclusion criteria

- Disabling spasticity
- Severe generalized spasticity
- Ashworth score ≥ 3/most affected extremity
- Spasm scale ≥ 1/most affected extremity (if applicable)
- Clonus scale ≥ 1/most affected extremity (if applicable)
- Refractory to oral baclofen (≤ 100 mg) or unacceptable side effects
- Age ≥ 16 years
- Life expectancy > 1 year
- Compliance of the patient or the caregivers
- Response during screening reduction:
  ○ Ashworth scale ≥ 2
  ○ Spasm scale ≥ 1
  ○ Clonus scale ≥ 1
	- Impaired renal function
	- Immunocompromised
	- Allergic to baclofen
	- Infection

Table I Patient Eligibility Criteria

	MS	Stroke	Acquired brain injury	SCL	CP	Metabolic disease	Others	Total
N	31	13	14	5	14	3	9	89
Age (mean)	52.2	67.1	43.3	57.6	46.7	44.6	49.6	
Age (range)	31–73	52–80	18–72	46–65	28–68	27–57	34–67	

Table II Demographic and baseline characteristics of the candidate ITB population (N = 89)

MS = Multiple scleroses

SCL = Spinal cord lesion

CP = Cerebral palsy

	Baseline	After trial		3-month follow-up	1-year follow-up	
	Median (IQR)	Median (IQR)	P*	Median (IQR)	Median (IQR)	P**
MAS	3.25 (2)	1 (3)	< 0.002	1 (2)	0.75 (1)	< 0.001
Clonus	0 (2)	0 (0)	< 0.001	0 (0)	0 (0)	0.001
Spasm	0 (0.5)	0 (0.5)	1	0 (1)	0 (0)	0.135

Table III Outcome parameters by moment of measurement

P: values < 0.05 are considered significant

P*: the probability of no difference between baseline and after trial

P**: the probability of no difference between all four moments of measurements

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	MS	Stroke	Brain injury	SCL	CP	Metabolic disease	Others	Total
N	29	13	12	2	7	2	4	69
50 mcg	21	6	3	2	4	2	3	41
75 mcg	8	6	2	0	3	0	0	19
100 mcg	0	1	4	0	0	0	0	5
negative test	0	0	3	0	0	0	1	4

Table IV LP test on location N = 69

Phase	(S)AE	Treatment
Trial	Post-spinal headache (N = 2)	None (disappeared spontaneously after a couple of days)
Post-operative	Deviant wound edges (N = 2)	Adjustment of wound dressing
	Dizziness and drowsiness (N = 2)	Oral baclofen interrupted Dose reduction of the ITB
3-month follow-up	Infection of the pump-pocket (N = 1)	Complete pump removal; re-initiated with oral spasmolytic medication
1-year follow-up	Low-grade infection (Staphylococcus aureus) (N = 1)	Complete pump removal; re-implanted after 3 months
	Catheter dislocation (N = 1)	Surgical replacement
	Empty pump reservoir (N = 1)	Pump refilled; dose reduced
	Epilepsy (N = 1)	Not able to determine whether this was a side effect of baclofen (underlying disease CP)[37]

Table V (S) AE

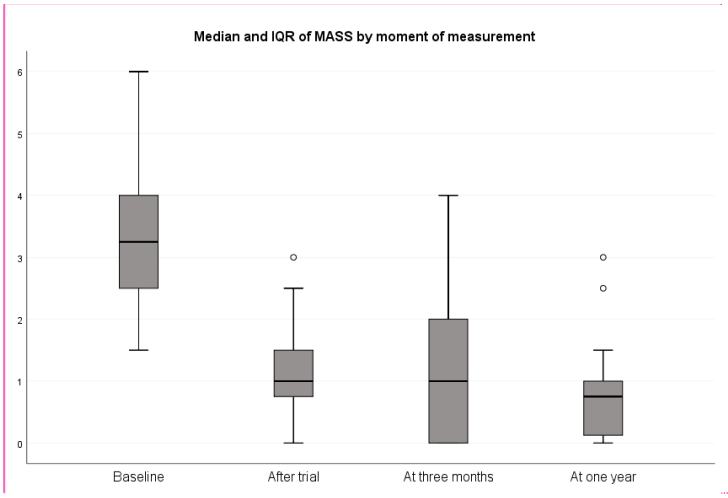

Figure II Median and IQR of MAS by moment of measurement

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