The usefulness of qualitative and quantitative tests in measuring the effect of a continuous ITB test-infusion in ambulatory patients with spasticity

Submitted
ABSTRACT

Objective: The aim of this pilot study is to determine which qualitative and quantitative tests are clinically useful in measuring the effect of a continuous intrathecal baclofen (ITB) test-infusion in ambulatory patients with spasticity.

Design: A prospective pilot study, evaluating dose-effect data of various qualitative and quantitative tests.

Setting: University Medical Center Groningen.

Participants: Ten ambulatory patients with severe spasticity of diverse etiology.

Interventions: All patients were admitted for a continuous ITB test-infusion.

Main Outcome Measures: The outcome measures were scored in 3 domains; each domain including one qualitative and one quantitative test. Spasticity was measured using the Modified Ashworth rating Scale (MAS) and the Hoffmann-reflex. Strength was evaluated using the MRC-rating scale and dynamometry. Ambulatory function was measured using the Timed Up and Go (TUG) and knee flexion measurements. Furthermore, patients rated their own functioning using the Patient Global Impression of Change (PGIC).

Results: The MAS ($r_s -0.46$) and H-reflex ($r_s -0.54$) showed a significant dose-effect association during the ITB test-infusion, while overall the tests measuring strength and ambulatory function did not. Eight out of ten patients scored their condition as improved on the PGIC, but this did not show a dose-effect association.

Conclusions: Only the tests measuring spasticity, MAS and H-reflex, showed a comparable significant dose-effect association, which was not the case for the tests rating strength, ambulatory function and PGIC.
INTRODUCTION

Intrathecal baclofen (ITB) therapy is considered as an effective and safe treatment for patients with severe spasticity, who cannot be treated optimally with oral spasmyotics. ITB-therapy is also suitable to improve walking capabilities in ambulatory patients with spasticity. Candidates for ITB therapy are offered an ITB test-infusion, to test its effect. If the ITB test-infusion proved successful, a permanent ITB pump is implanted.

During continuous infusion of ITB, steady-state concentration is reached after 24 hours. This offers patients a stable effect of ITB, in contrast to the peak-concentration of ITB caused by an ITB bolus trial. The dose of ITB is slowly up-titrated. The effect of an ITB test-infusion is evaluated based on the patient’s own opinion, combined with the effect of ITB on spasticity using the Modified Ashworth Scale (MAS). However, ITB also affects various other domains, besides spasticity, such as muscle strength and ambulatory function.

The aim of this pilot study is therefore to determine which qualitative and quantitative tests on the domains of spasticity, strength, ambulatory function, and the patient’s personal impression are useful in measuring the effect of a continuous ITB test-infusion in ambulatory patients with spastic gait.

METHODS

This study was approved by the Ethical Review Board of the University Medical Center Groningen. Written informed consent was obtained from each patient.

Patients

Inclusion criteria for the study were: spasticity not sufficiently responsive to -, and/or side-effects from, oral spasmyotics and age between 18–75 years old. Exclusion criteria were not being able to walk, a baseline strength of knee extensors below Medical Research Council (MRC) scale grade 4, and the presence of contra-indications for permanent ITB pump implantation, like pressure ulcers or (skin) infections.

ITB test-infusion

The ITB test-infusion was started while the oral spasmyotics were continued, in order to reduce the burden of tapering off the oral spasmyotics for just a few days. All patients received an intrathecal catheter with the catheter tip at the level of vertebra Th10. The catheter was connected to an extracorporeal infusion pump (Chrono Five infusion pump; Cane Medical Technology, Turin, Italy).
ITB infusion (50 µg/ml) was started at a low continuous dose of 36 µg/day. Dose changes took place after at least 24 hours of a particular infusion rate, to guarantee a steady state concentration of baclofen in the cerebrospinal fluid, in order to make an adequate clinical assessment (based on the intrathecal half-life of 1-5 hours). The ITB dose was up titrated every day with steps ranging from 6 – 36 µg / day, based on the physician’s clinical opinion and the patient’s personal impression. When a patient experienced negative effects (e.g. side-effects, muscle weakness), the ITB dose was lowered. The ITB infusion was stopped when the patient was satisfied with the effect (e.g. good spasmolysis, better functional abilities, less pain) and the physician did not expect further dose changes to contribute to the effect, or when the patient didn’t experience any positive effects after three different doses. No doses higher than 144 µg / day were administered, to prevent side-effects.

**Qualitative and quantitative tests**

The effect of ITB was monitored by one qualitative and one quantitative test in three clinical domains, consisting of severity of spasticity, muscle strength and ambulatory function. Furthermore, the patient’s personal impression was measured using the Patient Global Impression of Change (PGIC). Baseline scores for all tests were determined before starting the ITB test-infusion. Tests were repeated 24 hours after every change of dose. The results for right- and left extremities were averaged for all tests.

Severity of spasticity was rated using the qualitative Modified Ashworth Scale (MAS). The cumulative score for hip-, knee-, and ankle flexors and -extensors, as well as hip abductors and -adductors was used (range 0 – 40). (N.B.: for analysis purposes, the 1+ score was converted to 2 and scores >2 were increased by 1 point, which means that the MAS scores ranged from 0 to 5). The Hoffmann’s reflex (H-reflex) of the soleus muscle after stimulation of the tibial posterior nerve was used as a quantitative measure for spasticity. More specifically, the ratio between maximum H-reflex amplitude and the amplitude of the maximal direct muscle response ($H_{max}/M_{max}$ ratio) was used as final outcome parameter.

Muscle strength was graded using the MRC-scale qualitatively during physical examination, focusing on the cumulative score of hip-flexors, knee- extensors and -flexors and ankle-flexors and -extensors (range 0–25). The maximal isometric strength of the knee-flexors (at 45° knee flexion) and knee-extensors (at 90° knee flexion) was tested quantitatively using a dynamometer (Biodex Medical Systems, Shirley, New York) in sitting position, whereas the maximum result of three consecutive trials was used. Results were corrected for gravity and normalized for weight (Nm/kg).
Ambulatory function was assessed qualitatively using the Timed Up and Go (TUG) test, measuring the time standing up from a chair, walking 3 meters back and forth until sitting down. The patient was allowed to use his or her preferred assistive device (see table 1). To assess ambulatory function quantitatively, knee flexion was measured during two phases of the gait cycle: 1) initial contact (IC) and 2) mid-stance (MSt). These phases are easy to identify in the sagittal plane. Knee flexion at MSt was measured at the moment when the contralateral knee passed the ipsilateral knee. The knee flexion measurements were performed using video recordings (Everio Z-MG30; JVC, Yokohama, Japan) in the sagittal plane, while the patient was walking at his/her preferred walking speed. The final outcome was the average knee flexion of three consecutive measurements.

Finally the patient’s own impression was rated 24 hours after each dose change, using the 7-point Patient Global Impression of Change (PGIC) scale, on which the patient is asked to rate the overall change in condition as compared to baseline. The PGIC scale ranges from 1 / 2 / 3 (very much improved / much improved / minimally improved), 4 (no change) to 5 / 6 / 7 (minimally worse / much worse / very much worse).

**Data analysis**

Individual dose-effect curves were plotted for each test. The association between dose and effect was calculated using the non-parametric Spearman’s rank correlation ($r_s$). Although our design was based on repeated measures and the observations were thus dependent within patients, we could not take intra-individual dependency into account in our analysis because of the low number of patients. This implies that the calculated correlations are indications of the dose-effect association and should be interpreted with caution.

**RESULTS**

A total of 10 patients were included in this study. The patient characteristics are summarized in table 1.

**ITB test-infusion**

Most patients received 3 (range 2 – 4) different ITB doses, administered using continuous infusion. ITB doses ranged from 36 – 108 µg/day. There were no serious adverse effects. However, four patients complained about (mild) post-punctional headache, which was treated adequately with acetaminophen. The post-punctional headache was the reason that one patient (#5) could not perform dynamometry and TUG testing during the final dose. The post-punctional headache was resolved at the end of the test-infusion in all
patients, following the removal of the intrathecal catheter. One patient (#6) reported an unpleasant, unsteady sensation in both legs, during the entire test procedure, independent of the dose.

**Dose-effect measurements**

Figure 1 shows the dose-effect curves for the qualitative and quantitative tests in the three domains. Note that in some patients ITB dose was decreased once or twice, causing the dose-effect curve to run backwards on the horizontal axis. The corresponding Spearman correlation coefficient ($r_s$) can be found above each graph.

The data of the dynamometry of the knee flexors and the knee flexion at MSt are not shown, because of their similarity with dynamometry of the knee extensors, and the knee flexion at IC, respectively.

**Severity of spasticity**

Both the MAS and H-reflex scores showed a significant dose-effect association ($r_s$ –0.46 and $r_s$ –0.54 respectively). All patients showed a decrease in spasticity as measured by the MAS and the H-reflex (figure 1A and 1B). Both tests, however, showed large inter-individual variations at baseline. The H-reflex could not be measured in two patients. The $H_{max}/M_{max}$ ratio was already < 0.1 at baseline in three other patients, due to a low $H_{max}$ at baseline, which may be caused by afferent nerve damage. Therefore, these 5 patients were left out of the analysis.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Etiology</th>
<th>Assistive devices</th>
<th>Oral baclofen (mg)</th>
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<td>1</td>
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<td>m</td>
<td>75</td>
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<td>walker</td>
<td>100</td>
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<tr>
<td>2</td>
<td>48</td>
<td>f</td>
<td>70</td>
<td>HSP</td>
<td>walker</td>
<td>75</td>
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<tr>
<td>3</td>
<td>56</td>
<td>f</td>
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<td>SCI (Th8 / Th9)</td>
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<td>80</td>
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<td>cerebral palsy</td>
<td>walker</td>
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</table>

Abbreviations: HSP, hereditary spastic paraplegia; PLS, primary lateral sclerosis; SCI, spinal cord injury.
**Figure 1.** Dose–effect curves and correlation coefficients ($r$) for: (A) Modified Ashworth Scale (MAS), (B) $H_{\text{max}}/M_{\text{max}}$ ratio of the Hoffman's reflex (H-reflex), (C) Medical Research Council (MRC) scale, (D) Dynamometry of the knee extensors, (E) Timed Up & Go test, (F) Knee flexion at initial contact (IC).

* correlation is significant ($p < 0.05$)

**Muscle strength**

MRC and dynamometry overall did not show a dose–effect relationship. (figure 1C and 1D). The dynamometry of the knee flexors showed great similarity with the dynamometry of the knee extensors. Scores on both tests did not change after increasing the ITB dose in the majority of patients. However, two patients (#1 and #4) showed a decrease of strength, as measured by the MRC and dynamometry of the knee extensors, after increasing the ITB
dose from 36 to 72 µg/day, represented by the two curves at the bottom of both graphs. The dynamometry showed much larger interindividual differences as compared to the MRC. Patient #10 could not perform the strength tests.

**Ambulatory Function**

The TUG showed large interindividual differences (range from 10 – 120 seconds at baseline) (figure 1E). In individual patients the TUG showed both positive and negative dose-effect relationships. When analyzing the individual scores, the group can be divided in 6 “quick” patients, who scored <32 seconds at baseline, and 4 “slow” patients, who scored > 60 seconds (3 of whom > 100 seconds) at baseline. The “quick” patients showed an improved TUG score in 5 out of 6 patients ($r_s = -0.43, p = 0.05$). The ‘slow’ patients all performed worse on the TUG ($r_s = 0.57, p = 0.07$). Knee flexion did not show significant changes related to ITB dose increase (figure 1F). Knee flexion at IC and MST were largely similar.

**Personal Global Impression of Change (PGIC)**

The best individual PGIC scores were reached at variable dosages, ranging from 36 – 108 µg/day, whereas no dose-effect association was found ($r_s = 0.29$). At these optimal dosages 8 out of 10 patients rated their condition as “improved” (minimally (N=1), much (N=4), very much (N=3)). Two patients rated their condition as “not changed”. No patients worsened on their PGIC scores.

**DISCUSSION**

Both spasticity tests showed a moderate dose-effect association (MAS: $r_s = -0.54$, H-reflex: $r_s = -0.46$) (figure 1A, 1B). However, the H-reflex could only be measured reliably in half of the patients, possibly as a result of peripheral nerve damage, making it less useful as a general screening instrument. The MAS is less time consuming and doesn’t require any specialized equipment. Therefore, in our opinion the MAS is the preferred test to measure the clinical effect of ITB on spasticity during a continuous ITB test-infusion. This outcome seems to contradict previous data, stating that the MAS should not be used anymore to assess spasticity. However, that study had a cross-sectional design, looking at construct-validity and inter-rater variability. The study actually showed a moderate association with muscle activity and muscle resistance, but a significant rater influence on the MAS scores, which does not rule out the MAS as a reliable follow-up tool, if applied by the same rater, as was the case in our study. The positive dose-effect relationship of both spasticity tests in our study has been confirmed in previous publications.
The MRC score and dynamometry did not show a dose-effect relationship (figure 1C, 1D), but this seems to depend on the baseline strength, especially if there is weakness of the knee-extensors at baseline. The two patients with the lowest baseline strength of the knee-extensors showed a decreased strength after the start of ITB infusion. Therefore, monitoring strength may be clinically useful in patients with a reduced strength at baseline. However, our sample size is too small to draw definite conclusions about this topic. It is clear that the MRC is easier to use, as compared to dynamometry, but dynamometry allows to determine smaller differences in muscle strength in patients who scored maximal on the MRC. Therefore, dynamometry could offer advantages if a more precise assessment of muscle strength is needed. In the literature conflicting results are reported about the value of tools measuring strength, especially the strength of the upper leg muscles. Bowden et. al reported a significant negative dose-effect relationship between ITB and the MRC on the short term. However, this appeared to be different from long-term data, showing an improved strength on the MRC after one year of ITB infusion. At present, it is not clear whether short-term effect of ITB on strength is useful to predict long-term effects.

The third domain which was investigated focused on ambulatory function after ITB infusion. The ambulatory function tests overall did not show a dose-effect relationship (figure 1E, 1F). However, the TUG dose-effect curves of this study can be divided in two subgroups. Most patients with a baseline TUG score of < 32 seconds showed improvement with ITB, while patients scoring a TUG of > 60 seconds at baseline seemed to perform worse with ITB. A previous study reported similar findings, showing that the baseline walking velocity significantly correlated with the increase in velocity after an ITB test-bolus in patients with acquired brain injury. Unfortunately, our group is too small to prove the value of the TUG in monitoring low performance patients after ITB infusion. However, the TUG might be a relevant item for further study, especially since other gait analyzing tests, like 3D gait analysis, have failed to discriminate in this context. Knee flexion did not show a dose-effect relationship in our study, although a recent study from Pruszczynski et. al. reported a significant reduction in knee flexion at IC with continuous ITB therapy. The difference might be explained by the fact that this study included pediatric patients, who also received additional interventions like orthopedic surgery.

Eight out of ten patients scored their condition as improved using the PGIC. However, no dose-effect relationship was found. The PGIC scores were also compared to the changes of all tests included in this study. However, positive test-scores (lower spasticity, higher muscle strength, increased ambulatory function) did not correlate with PGIC scores representing improvement. A striking example consisted of a patient who deteriorated on the TUG, but rated his overall condition on the PGIC as improved. Consequently, the overall personal impression does not correlate with the individual qualitative and quantitative test results,
neither with the dose of ITB. This might be related to the difficulty of scoring ambulatory patients with spasticity. In non-ambulatory patients, the subjective impression of change might largely be related to the level of spasmolysis. However, in ambulatory patients the overall subjective impression of change will be likely based on various domains, including strength, spasticity and ambulatory function, but also on expectations and needs, related to the expectation of an improved walking capability. Therefore, patients use subjective definitions of improvement, also influenced by the heterogeneous nature of their spasticity (table 1).

**Study Limitations**

The main limitation of this pilot study is the small sample size (10 patients), combined with the heterogeneous population, which resulted in large inter-individual differences in baseline scores. The low number of patients also limited the use of statistics, for example the intra-individual dependency could not be taken into account in the correlation analysis. However, this also represents the heterogeneity of the spastic population.

During this study oral baclofen, if already present before study-entry, was continued during the test-infusion, which might have influenced the effect measurements. However, the effect of oral baclofen in this population is considered very limited, because otherwise they would not have been selected for intrathecal baclofen therapy. This is reflected by the low intrathecal baclofen concentrations after oral baclofen administration (<30 µg/l) as compared to intrathecal administration (100-1000 µg/l).\(^{19}\) Furthermore one of the inclusion criteria for the ITB test-infusion was an insufficient response and/or intolerable side-effects on oral spasmolytics.

**Conclusions**

This pilot study showed that both the MAS and H-reflex have significant dose-effect associations during continuous ITB test-infusion in ambulatory patients with spasticity. However, the MAS is our preferred spasticity test because of its ease of use. Strength was not influenced by ITB in most patients, and therefore no overall dose-effect relationship could be established. However, MRC and dynamometry did show an effect on the strength of the knee-extensors after ITB in patients with a reduced strength at baseline. So, this effect should be explored in future studies. Also the TUG might be a valuable tool in patients with a low baseline TUG-score, which also has to be confirmed in larger studies. Finally, the PGIC is a simple tool for patients to judge themselves, but does not correlate with the medical assessments and/or ITB dosages in our ambulatory patients with spasticity. So overall, our
study has shown some promising data with respect to appropriate testing in ITB infusion, but the question which test has the highest predictive value for a successful continuous ITB test-infusion cannot be answered by our dataset, because of the small sample size.

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CHAPTER 7

REFERENCES


