Bio-Electric Stimulation in Postpolio: BESTIPP Study Results

This White Paper describes the rationale, design and results of a clinical study that assessed the utility of bio-electric stimulation therapy (BEST), also known as microcurrent electrotherapy (MET), in postpolio (PP) patients.

Glossary

ATP	adenosine triphosphate
BEST	Bio-Electric Stimulation Therapy
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
EMG	electromyography
LOCF	Last Observation Carried Forward
MET	microcurrent electrotherapy
PP	postpolio
PPS	postpolio syndrome / sequelae

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The Problem

Polio is often perceived as a disease on the brink of extinction, yet, in the US and Europe there are over 1 million polio survivors alive today and polio is still the 2nd leading cause of paralysis in the USA, after stroke (Halstead, 2004).

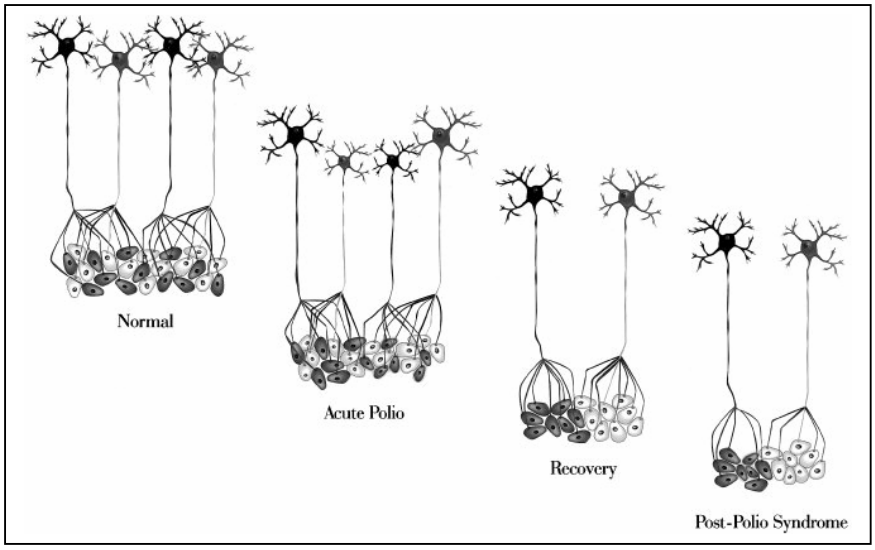
In Europe and the USA there are > 1 million people alive today who survived acute poliomyelitis as children

Historically, polio has been described in three stages : acute illness, recovery period and stable disability. Since the 1980's, however, it became increasingly clear that a fourth stage can be identified – variously described as late effects of polio, or more commonly, postpolio syndrome or sequelae (PPS) (Farbu et al., 2006) .
PPS is characterized by three main symptoms : progressive new weakness, fatigue and pain. No specific diagnostic test exists, hence the diagnosis is not straight forward, and is essentially one of exclusion. PPS represents a huge problem as around 50% of polio survivors are affected by this late deterioration (Halstead, 2004).

PPS is characterized by three main symptoms :

- **Weakness**
- **Fatigue**
- **Pain**

Most authorities now agree that PPS is caused by a late degeneration of the already abnormally enlarged motor units – essentially a progressive neuromuscular decompensation (Muniz, 2005).



Treatment of PPS

- **Individualized approach**
- **No satisfactory therapy**

Treatment of PPS is also a challenge, no specific therapies exist and management programs usually focus on support, rehabilitation such as pacing and resting, and symptomatic treatment of the three main symptoms : fatigue, muscle weakness and pain (Trojan & Cashman, 2005).

Pharmacotherapy has not proven to be of real benefit either, and some medications can even aggravate PPS symptoms – medications to avoid include beta blockers, benzodiazepines, and some antibiotics and anticonvulsants (Trojan et al., 2004).

The Technology

BEST delivers minute amounts of electricity to cells, copying what the body usually does to function and to maintain a physiological balance

BEST is a very specific form of electrotherapy, delivering extremely small amounts of current to the body (less than 1 milliAmpere, 100 times less than a typical TENS machine). It mimics what happens inside our cells, and as such restores the physiological balance.

Some of the relevant documented physiological effects include :

- **an increase in ATP**, the energy molecule used for all cellular activities

BEST has been shown to increase ATP production by up to 500%

Independent studies have shown BEST can increase ATP production by up to 500%. (Cheng et al., 1982; Seegers et al., 2002).

- ATP produced in mitochondria
- ATP formation driven by a proton gradient
- Water exists as an equilibrium
  $H2O = OH^- + H^+$
- LOW current enhances proton (H^+) supply

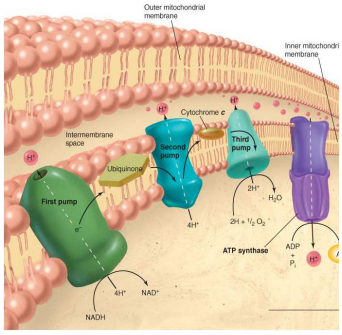


Diagram of mitochondrion, illustrating how a proton gradient between the two membranes drive the production of ATP

- **enhanced transmembrane transport**
  Examples are :

BEST works at the level of the cell, by

- **Boosting energy**
- **Restoring homeostasis (physiological balance)**

- amino acids, the building blocks of all proteins

- proline, a precursor to hydroxyproline, (used to produce collagen, the connective tissue in tendons, ligaments, etc)

- calcium, though the opening of voltage-sensitive calcium channels in membranes. One of the effects of this increase in Ca^{++} is an increase in insulin receptors, needed for both protein and DNA synthesis.
  (Bourguignon & Bourguignon, 1987; Nessler & Mass, 1987)

BEST is very safe, with no known side effects

BEST is a very safe therapy, with no known side effects. For example, the KFH Energy prototypes used in the BESTIPP study, deliver around 20 times less current than the threshold needed to induce skin damage (Becker RO & Selden G, 1985).

In conclusion, there is a strong scientific rationale to evaluate BEST in chronic conditions where fatigue is a major problem.

Study Design

25 patients were recruited, from 4 different countries

This investigator initiated study was coordinated by Prof. Bert Op ' Eijnde, from the University College in Hasselt, Belgium.

25 known postpolio patients were recruited, from 4 countries in Europe. The study made use of Patient Reported Outcomes , a design increasingly used by medical companies and accepted by the FDA, particularly for support of claims.

3 main endpoints were assessed:

- **Fatigue**
- **Endurance**
- **Pain**

Baseline consisted of a run-in period of 2 weeks, then longitudinal follow-up over 12 weeks, plus another 12 weeks extension (where possible). Treatment effects were evaluated through intra-patient comparisons (patient data at various time points compared with their own baseline data).

24 week study period

12 weeks as main part

plus an extension period of 12 weeks

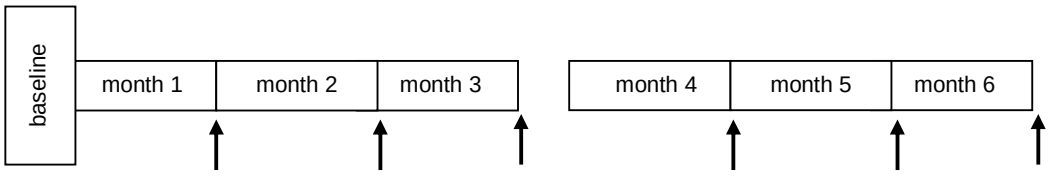
The main study period was for 3 months , with patients treating themselves on a daily basis for 1 hour at a time. An extension phase of another 3 months was optional.

The following Patient Reported Outcomes were recorded, initially weekly and later on a monthly basis:

Fatigue	~ BFI (Brief Fatigue Inventory)
Endurance	~ Borg RPE (Rate of Perceived Exertion)
Pain	~ BFI (Brief Pain Inventory)

These questionnaires are all internationally validated, and have been used in many medical publications. In addition, the Borg scale has been proven to reliably measure effort or exertion in PP patients (Finch 1994).

The study design is shown diagrammatically below :



3 months study extension

Baseline = average of two scores, start and end of a 2 week run-in period, without any BEST therapy

↑ = monthly assessments, as described above

Study Protocol

Title	BESTIPP : Effect of BEST in Post-polio Rehabilitation
Objective	To determine the efficacy of BEST in postpolio patients
Study Population	Twenty five post-polio syndrome patients
Study Endpoints	Fatigue (BFI score) Endurance (Borg RPE scale) Pain relief (BPI score)
Inclusion Criteria	History of previous poliomyelitis
Exclusion Criteria	Contra-indications for BEST (cancer, pregnancy, cardiac pacemakers) Previous BEST
Study Outline	Patients used devices at home, BEST sessions took place daily, from Monday to Friday, (1 hour per day). A User Guide with detailed instructions was provided. The study was performed according to the Ethical Guidelines of the Helsinki Declaration.
Data Analysis	All data analysis was performed by an independent statistical agency. For all three main endpoints, the following statistical test were done; - paired Student's t tests (baseline versus week 12, LOCF and week 24) - analysis of variance for repeated measures (4 time points from baseline to week 12) - analysis of variance for repeated measures (7 time points from baseline to week 24) The threshold for statistical significance was set at $p < 0,05$

Study Results

BEST significantly improved all 3 main endpoints :

- **Fatigue**
- **Endurance**
- **Pain**

Summary

Bio-Electric Stimulation Therapy had a positive, and statistically significant, effect on all 3 endpoints. The average scores for the whole group showed :

- Fatigue 34 % reduction ($p < 0.0001$)
- Endurance 40% improvement ($p < 0.0001$)
- Pain 34 % reduction ($p < 0.0001$)

In addition, these clinical benefits were maintained during the extension phase of the study, again for all 3 main endpoints.

[these results are discussed in more depth on the next few pages]

Gait Analysis on subset of 5 patients

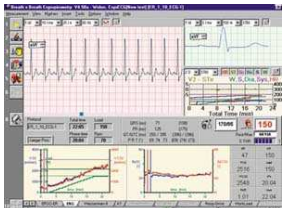
In addition to the design as described above, the 1st 5 patients also underwent a full gait analysis, as a subset of the BESTIPP study. This was done in order to verify our anecdotal observations (backed up by video evidence) of a dramatic improvement in walking in a Dutch lady with PPS.

The analysis took place in a specialized Clinical Motion Analysis Laboratory, under the auspices of Prof. K Desloovere in the University Hospital of Leuven, Belgium.

The aim was to see if a quantifiable effect of BEST on walking pattern and efficiency could be documented over a period of 12 weeks. Apart from the gait analysis, the treatment protocol was exactly the same as for all other BESTIPP participants.

Assessments included

- video plus infrared computerized gait analysis
- muscle strength
- EMG
- energy consumption (O_2 cost)



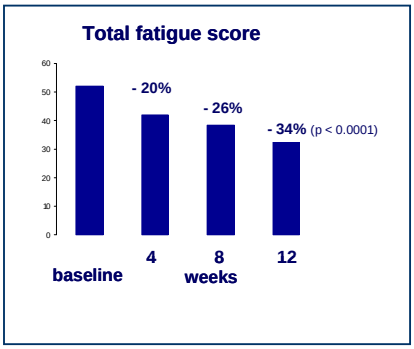
Results

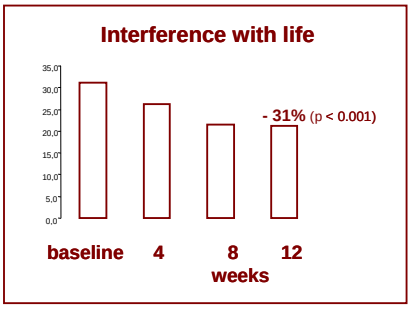
- no real differences in gait patterns could be established
- small increases in walking speed and gait length were documented
- no change in muscle strength or O_2 cost were observed

Conclusion : no obvious effect on gait could be established after 3 months of BEST treatment. This was not unexpected, as all patients had long term fixed gait compensation as well as previous surgeries and walking aids.

Study Results

Note : of the 25 patients who entered the study, 3 dropped out within 4 weeks, and have thus not been included in the analysis below.





Endpoint 1 : Fatigue

For the group as a whole, a consistent and statistically significant reduction of 34% in the total fatigue score was observed.

These results were closely mirrored for the other aspects of fatigue recorded : worst level of fatigue, as well as the level of interference with daily life.

Looking at it slightly differently by comparing categories of response, one can see that 8 out of 10 patients had a positive response:

- 50 % had a major response
  (> 30% improvement, ranging from 32% to 74%)
- 36% had a minor response (10 – 30% improvement)
- 14 % showed no change

Conclusion 1 :

BEST has a consistent and meaningful effect on fatigue

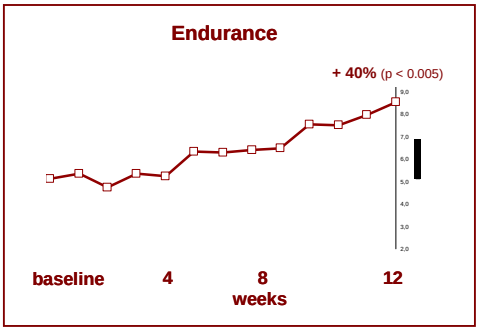
Endpoint 2 : Endurance

Note : 3 patients felt the exertion test would be physically too demanding and hence did not participate in this part of the study.

Here too a consistent and statistically significant benefit was seen: a 40% increase in stamina, as measured by the Borg RPE Scale.

Grouping patients by category of response showed that only about one in 5 patients did not benefit:

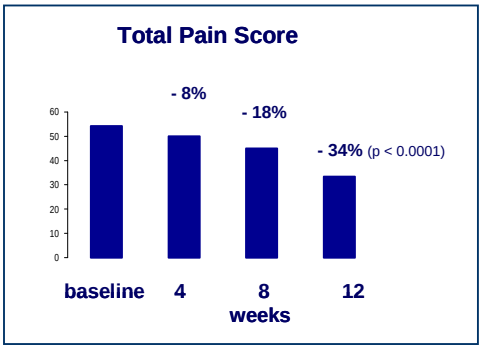
- 53 % had a major response
  (> 40% improvement, ranging from 41% to 88%)
- 26% had a minor response (10 – 40% improvement)
- 21 % showed no change

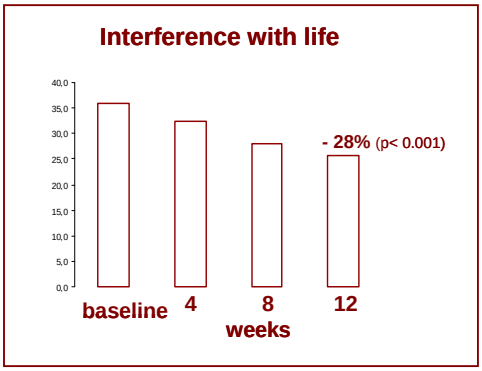


Conclusion 2 :

BEST significantly increases endurance

Study Results





Endpoint 3 : Pain Relief

Note : 4 patients did not have pain, as evidenced by a baseline BPI score < 20, and hence did not participate in this part of the study.

Again, for the group as a whole, a statistically significant reduction of 34% in the total pain score was found.

Around 7 out of 10 patients saw some benefit, although 3 in 10 did not have any pain relief:

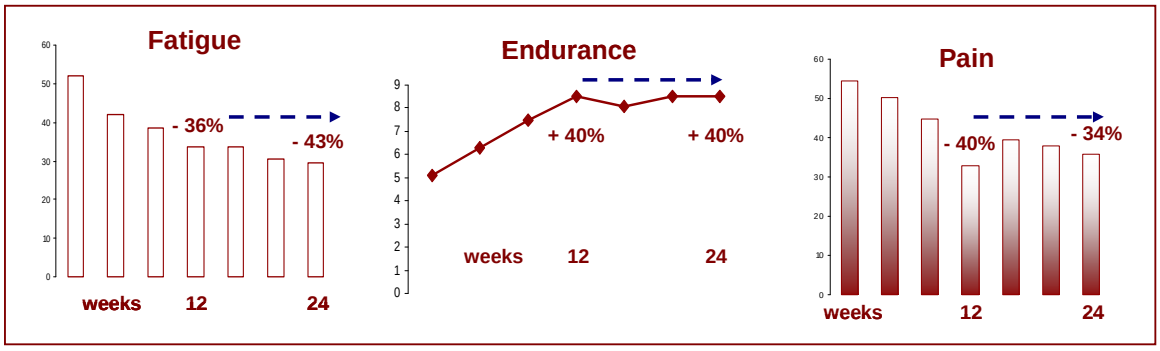
- 50 % had a major response
  (> 30% improvement; ranging from 34% to 93%)
- 22% had a minor response (10 – 30% improvement)
- 28 % showed no change

Conclusion 3 :
BEST can effectively relieve pain

Extension Data

A total of 11 patients completed another 3 months of the study, providing valuable information on the sustainability of the clinical effects observed after 12 weeks of therapy. Most patients treated themselves less frequently; on average twice weekly.

The graphs below clearly demonstrate a maintenance effect on all three main endpoints, with statistical significance maintained at 24 weeks for fatigue, endurance and pain relief (illustrated by dashed blue arrows).



Conclusion 4 :
Clinical benefits are sustained during maintenance therapy

Discussion

Pathophysiology of PP fatigue

85% of PPS patients experience fatigue, usually the peripheral or physical form

Fatigue is a major cause of a lower quality of life in PPS patients – various surveys report that over 85% of PPS patients experience such crippling and unusual tiredness (Agre et al., 1989; Chetwynd et al., 1993; Halstead & Rossi, 1987).

A large study in Norway confirmed that physical , peripheral fatigue was a far greater problem than the central or mental fatigue that some patients may also experience (Schanke & Stanghelle, 2001). Neurophysiological findings corroborated this by showing that the ability to recover from fatiguing exercise was related to local muscle factors (Rodriguez & Agre, 1991).

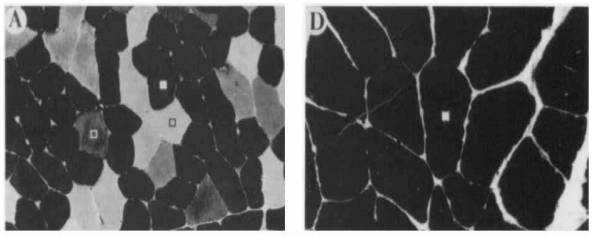
- Over many years, as the body tries to compensate for the damage done by the polio virus, the constant process of denervation and re-innervation eventually takes its toll, and lead to abnormal changes in the muscles of PP patients at three levels:

Muscles of PP patients are abnormal at 3 levels

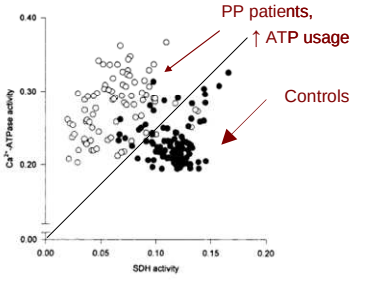
- **Anatomy**
- **Function**
- **Energy metabolism**

- **anatomy**
  muscle fiber composition changes , to become almost exclusively Type I muscle fibers, and these fibers are hypertrophied (much bigger than normal) – as can be seen under the microscope:

muscle biopsy,
cross section Tibialis Anterior



(Grimby et al., 1996)



Enzyme-histochemical properties, showing metabolic ratios (ATP use vs ATP production)
Grimby, 1996

- **function**
  muscle strength is often found to be more or less normal, but they fatigue very quickly, hence endurance is reduced and recovery slower (Agre et al., 1997; Nollet et al., 2001). Furthermore, the fibers work abnormally hard, by contracting in an 'all or nothing' way, as opposed to recruiting only those fibers that are needed for a specific task (Tollback et al., 1992).

- **energy metabolism**
  there is substantial evidence that PP patients have an energy deficit in their muscles. A high energy utilization and low energy resynthesis, i.e. an energy imbalance, has been demonstrated by different groups (Grimby et al., 1996; Sharma et al., 2007). Similarly, lower oxidative enzyme capacity contributes to a lack of energy-related substances (Borg & Henriksson, 1991).

Discussion

The effect of BEST on fatigue and endurance can thus be readily explained, but the pain relief shown in the BESTIPP study is more difficult to understand in terms of mechanism. At the site of microinjury or overuse, ATP supplies can become diminished, offering one explanation for the positive effects of BEST (Bailey S, 1999). Other mechanisms could be via inhibition of inflammatory cytokines (McMakin CR et al., 2004) or the known regenerative and healing effects of BEST on tissues (Gardner et al., 1999).

BEST has been known to relieve pain in other conditions, including post-operative analgesia and more chronic conditions such as spinal cord injury (El-Husseini et al., 2007; Tan et al., 2006).

There were no reports of any side effects

There have been no reports of any side effects, consistent with what is known about BEST. In addition patients quickly learnt how to administer the therapy on a daily basis, and there no were no reported problems in terms of the practical usage of the device.

BEST seems to be a promising therapy to address the key symptoms of PPS

The design of the study did not include a placebo-controlled group, and one should thus be careful when interpreting these results. Nevertheless, the scale and magnitude of patient responses have been staggering, and is corroborated by powerful patient testimonials (for more details see www.kfhealth.com). In addition, Kingfisher Healthcare is planning to do further studies in PP (see below).

In conclusion, the overall picture in PPS is therefore consistent with (over)compensation and overuse over a long period of time, leading to mitochondrial insufficiency. The results of the BESTIPP study provide further support for this theory as BEST addresses the problem by correcting the known energy imbalance in the muscle fibers.

It is too early to draw definitive conclusions

It is too early to draw definitive conclusions, particularly as the BESTIPP study did not have a placebo-controlled arm. Nevertheless, at the very least BEST appears to be a promising therapy to improve the major symptoms of PPS.

Future Research

we are particularly interested in two different aspects, and will pursue further clinical research in these areas :

KFH will pursue further clnical research in PPS

- energy metabolism
  a more detailed evaluation of the effects of BEST, for example with non-invasive magnetic resonance spectroscopy
- responders vs non-responders
  a better understanding of why some patients respond, and others not. For example, identification of clinical biomarkers to improve prognosis and/or monitoring

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