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Transcranial pulse stimulation (TPS) with focused extracorporeal shock waves. A new promising non invasive symptomatic treatment of Parkinson's disease. Casuistics and feasibility study.

Lohse-Busch, Henning, Rheintalklinik, D-79189 Bad Krozingen

Abstract
Focused low energy extracorporeal shockwaves have been used for the treatment of neurological disorders since 1990, starting with different forms of spasticity. Later, the treatment of spinal cord injuries and unresponsive wakefulness and finally Alzheimer's disease followed. In parallel one patient with Parkinson's disease was treated and observed over 8 years and 3 patients were observed over 40 months. All patients received initially during two weeks 6 sessions of TPS with 6000 focused shock waves each on the regions of interest of the brain with an energy flux density of 0,20 mJ/mm² (Duolith, later Neurolith Storz Medical AG). After this, all patients received a monthly maintenance treatment with one TPS session over the following years. Furthermore, after every twelve months a booster of 6 sessions with TPS during 2 weeks was applicated.
After the initial treatment block the disease symptoms improved by over 50% (Unified Parkinson Rating Scale) in all patients. The symptomatic improvements remained stable with this protocol to date in one patient during the follow-up time for 8 years and in the 3 other patients for over 40 years.

Key words: brain, extracorporeal shock waves, transcranial puls stimulation, Parkinson

Introduction

Shockwaves have been used in medicine for over 40 years. Meanwhile, low-intensity shockwaves proved to be effective for the treatment of an increasing number of indications in, for instants, tendon and muscle pain, non-unions, heart insufficiency, erectile dysfunction chronic wounds and other indications from aesthetics to finally neurological rehabilitation.

The treatment with focused low energy extracorporeal shock waves (ESWT) of neurological indications started very early in the 1990s with the treatment of the spasticity of children with cerebral palsy [1]. In 2005 the first treatments of spinal cord injury [2,3] and of the brain of patients with unresponsive wakefulness [4] 2005 were put into practice.

The ESWT working principle is the mechanical stimulation of biological processes called "mechanotransduction" resulting in the following effects:

- Release of nitric oxide (eNO)[5]
- Increased cell wall permeability , blood brain barrier opening [6]
- Increased cell metabolism [7]
- Release of growth factors like VEGF, BMP, TGF-β, GABA, GDNF and BDNF resulting in angiogenesis [22] and neurogenesis [5, 7]

- nerve regeneration in the rat [7,8]
- Anti-inflammatory effect [5]
- Vasodilatation [5]
- Stimulation of stem cells (proliferation, migration and differentiation) [9,10]

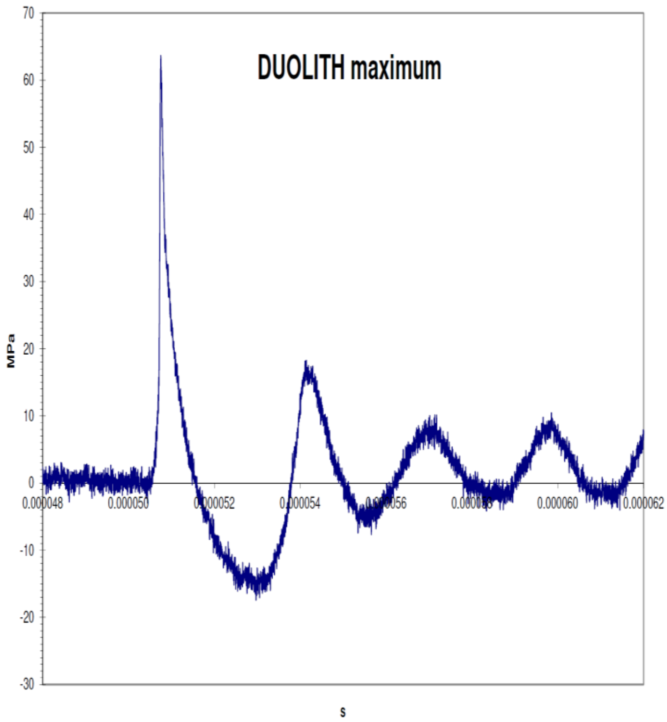
Despite the diversity of the various systemic influences, it is astonishing that no undesirable effects have been reported so far.

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. Typical symptoms are tremor, muscular rigidity, slowness of movement and difficulty walking. The symptoms of the disease are the result of a dopamine deficit due to the death of cells mainly in the substantia Nigra, the major source of dopamine.

After 2005, experimental transcranial extracorporeal shock wave therapies of patients with minimal consciousness (17) were very successful. Nowadays experimental transcranial extracorporeal shock wave therapy is called "Transcranial Puls Stimulation" (TPS).
Based on the promising results of the minimal consciousness patients, the trials were expanded to also treat patients with Alzheimer's and Parkinson's disease. At the beginning, the patients were treated with varying treatment rhythms and varying dosage of shock waves in order to find out a feasible treatment protocol. In 2011 this treatment protocol was determined with encouraging results for both Alzheimer's and Parkinson's disease. Then the official study with the TPS of Alzheimer's disease [11] followed.

Method and Material

The TPS uses focused shockwave pulses for the stimulation of the brain tissue. Focused shockwaves are different from focused ultrasound signals **(Fig. 1)**. Ultrasound is a continuous train of pulses with a high frequency of typically 1-5 MHz. High intensity focused ultrasound can heat up the tissue. Conversely, shockwaves are very short, approximately 1 µs pulses with a very steep leading edge (in the range of 10 ns) and a high amplitude of up to 150 MPa. In spite of the high-pressure amplitude, the average power density is only 0.1 W/cm^2 due to the relatively low pulse repetition rate of 5-10 Hz. Thus, there is no heating effect and no micro lesions result.



a

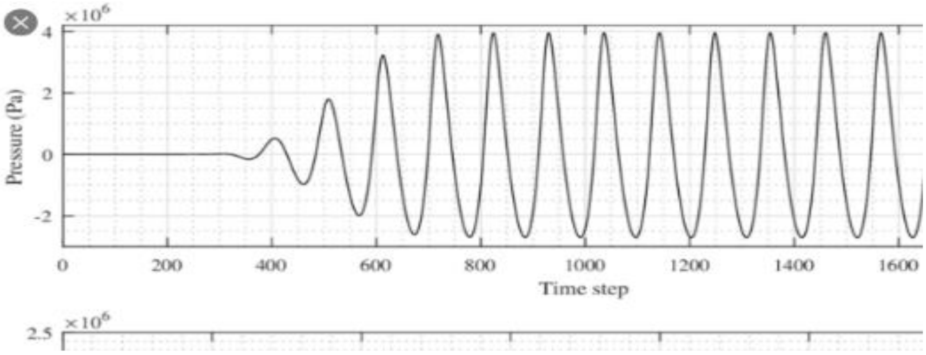


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Fig. 1: Shockwave pulse (a) and ultrasound signal (b)

Safety evaluation

For the intracranial application of the shockwaves, the attenuation of the shockwaves due the propagation through the skull was investigated in a cadaver trial with and without brain tissue. The shockwave pressure amplitude is reduced down to 35% (a) and the energy flux density is reduced down to 15% (b). **(Fig.2)**.

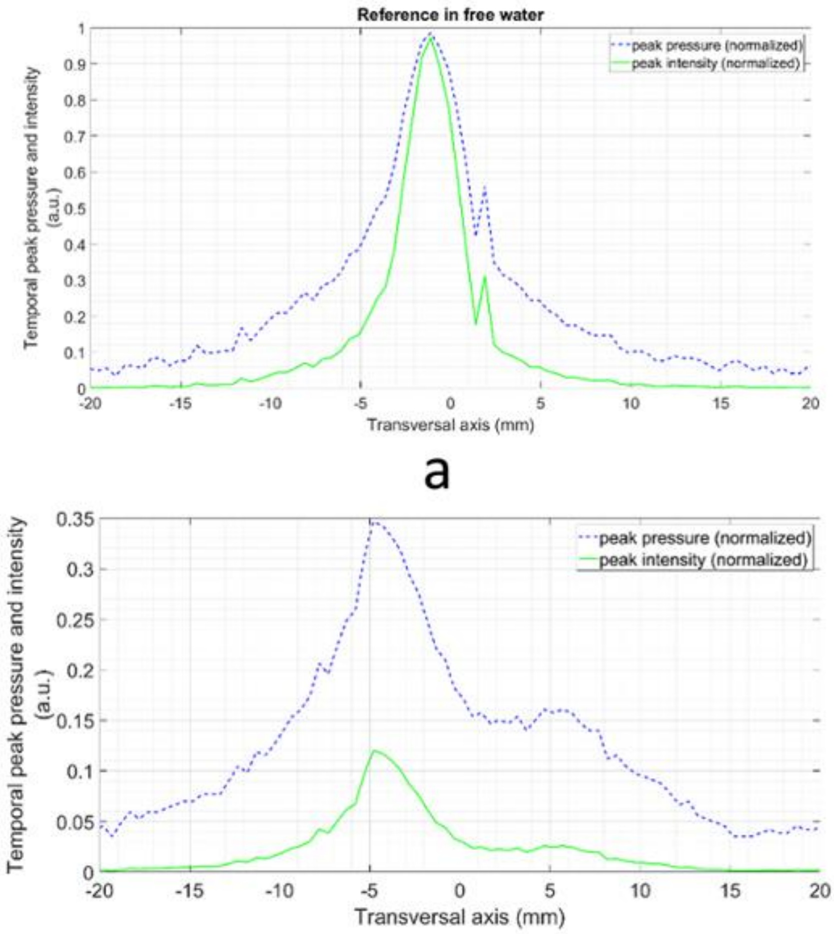

Fig. 2: Shockwave pulse attenuation by human skull. The pressure amplitude is reduced down to 35% (a), the energy flux density is reduced down to 15% (b).

Treatment procedure

Four patients with Parkinson’s disease have been treated with TPS in an experimental long-term feasibility study. The treatment was performed with the device Duolith and later on Neurolith (Storz Medical AG) and consisted of six sessions over two weeks. During each session, 6000 pulses with energy flux density of 0.20 mJ/mm^2 at 5Hz were applied homogeneously over the treatment-relevant brain area, i.e. the frontobasal region, cerebellum and brain stem, especially nucleus Niger, pallidum, striatum and hippocampus.

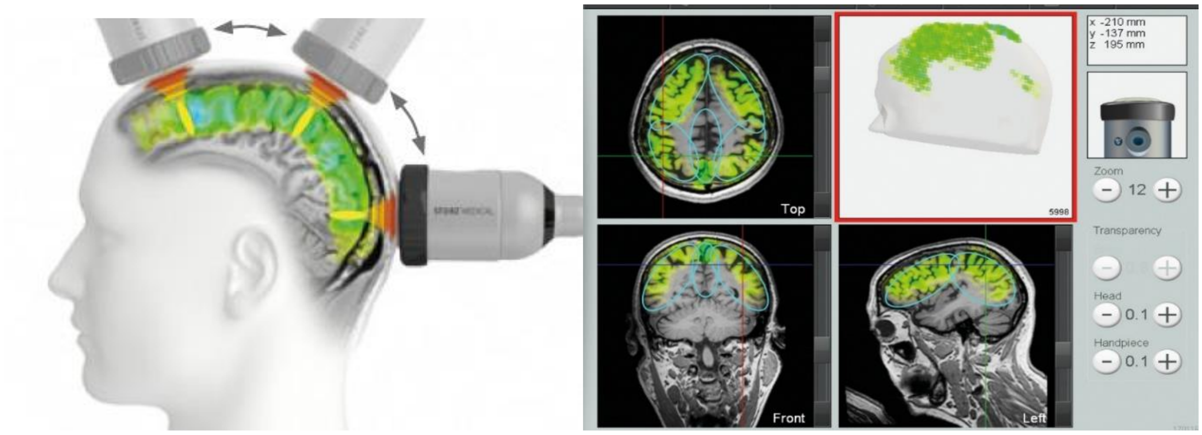

Fig. 3: TPS Treatment setup with BodyTrack System (Neurolith, Storz Medical). for navigation and documentation of the TPS treatment. Personal MRI/CT data is used for the visualization of the shockwave energy delivered to the treated brain areas. The overlay color (yellow-green-blue) shows in real time the distribution of the energy delivered. The treatment handpiece is homogeneously moved over the treated brain areas. Nevertheless, energy is also delivered to deeper brain structures due to the bell-shaped energy profile.

During the TPS-session the application handpiece is smoothly moved over the head **(Fig. 3)** in order to avoid an inappropriate energy cumulation. Coupling ultrasound gel needs to be applied generously over the treated areas for optimal shockwave transmission through the scalp hair. It is not necessary to shave the patient's head. The attenuation due to the gelled hair remains under 10% at most. The focus depth is approximately 40 mm for the maximum of energy flux density. Still, the therapeutical depth stretches even deeper into the brain due to the bell-shaped decrease in shockwave intensity with respect to the focal point.

After the 2 weeks of initial treatment, all patients received a monthly maintenance treatment with one TPS session over the following years. Furthermore, after every twelve months a booster of 6 sessions with TPS was administered.

Results

The patient, who has been in treatment for 8 years, is currently 74 years old. His Parkinson's disease progress was assessed with the Parkinson Disease Questionnaire (PDQ 39) using all items. The initially achieved improvement of about 60% has been maintained by regular re-treatments and yearly booster remained relatively steady over 8 years **(Fig. 4)**. The medication intake could be reduced after 2 years. In the following years, no increase in dosage was necessary.

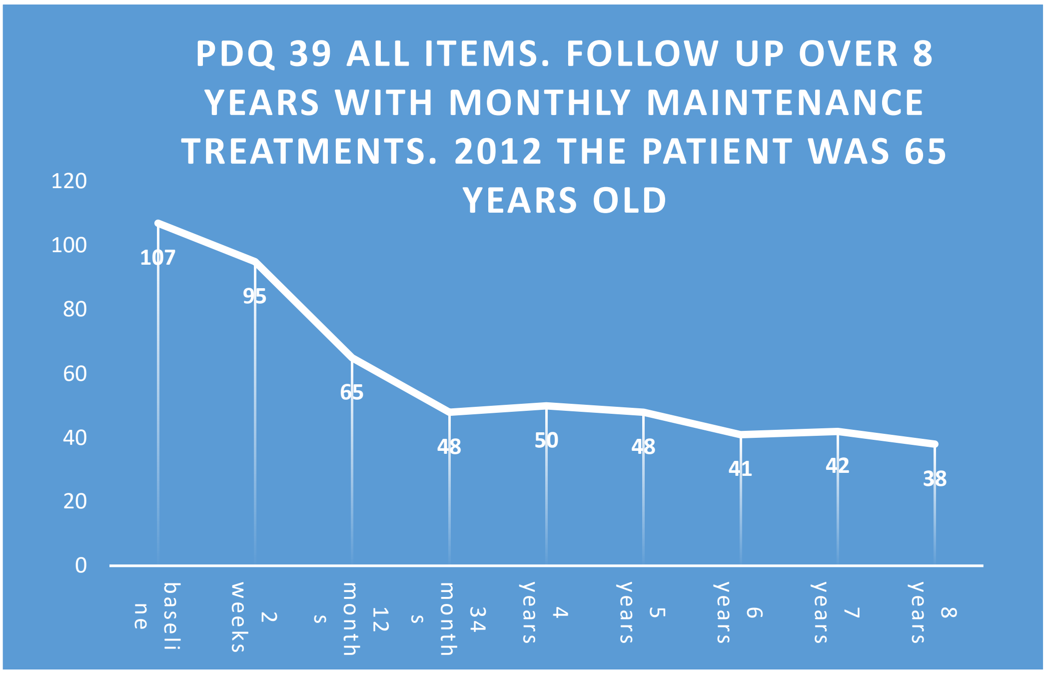

Fig.4: Patient treated for 8 years with TPS. The Parkinson's disease progress was assessed with the Parkinson Disease Questionnaire (PDQ 39), all items. The initially achieved improvement of about 60% was maintained by the regular re-treatments and remained relatively steady symptomatic over the 8 years.

The other 3 patients were tested with the Unified Parkinson Rating Scale (UPDRS). All 3 items of the UPDRS decreased by more than 50% within the treatment period and during a 3-month follow-up. **(Fig. 5)**

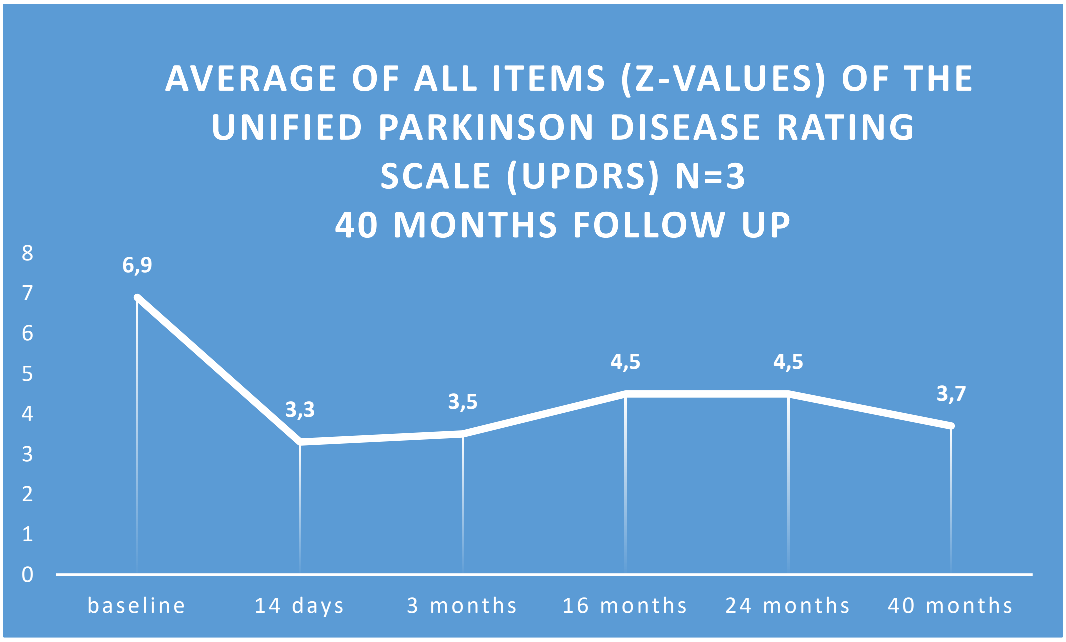

Fig. 5: Three patients have been treated successfully for over 3 years. The Parkinson's disease status has been evaluated with the Unified Parkinson Rating Scale (UPDRS). The motoric part, UPDRS, all 3 items decreased by more than 50% over the treatment period. The improvement has been maintained by regular re-treatments.

During this period, these patients did not need to increase the dosage of their medications. Subsequently, the uniform improvement between roughly 35% and 45% was maintained with regular re-treatments and yearly boosters over a period of over more than 40 months. The TPS treatment was very well tolerated by all patients No negative side effects were observed.

Discussion

Parkinson's disease is not curable, but the symptoms can be reduced. A treatment with different pharmaceuticals exists. Following the progressive development of the disease, the pharmaceutical intake needs to be increased. Further options are the deep Brain Stimulation (DBS) [12] with surgically placed microelectrodes (pacemaker). Another possibility is the coagulation of the tremor initiating cells in the brain stem. Both methods are very invasive. Nowadays there is also the non-invasively treatment by focused ultrasound with MRI navigation [13].

Compared to these partly very invasive treatment methods, TPS is a completely non-invasive and non-destructive treatment method. It mechanically stimulates larger brain areas resulting in a broad scope of biological effects (see introduction). Thus, the progress of the disease seems to be partly reversed and temporarily stopped.

Today we can see a very positive development concerning the brain treatment with TPS. In the beginning of the brain treatment with shockwaves a precise treatment required very advanced tropographical anatomic skills. For such a treatment nowadays, a newly developed navigation system (BodyTrack, Storz Medical AG) is used (Fig. 3). It has been integrated in the mentioned shockwave generator Duolith and is named Neurolith (Storz Medical AG). It has been approved since 2018 (CE-mark) for the treatment of the central nervous system of patients with Alzheimer's disease. The system can trace the patient's head and the handpiece movement in real time and generate a 3D overlay image for the patient's MRI or CT data, showing and documenting the location and intensity (color-coded) of the applied shockwave (TPS). With this device Parkinson patients also can be treated anatomical precisely.

The casuistics presented here are limited to TPS as a form of treatment for the central nervous system only. In order to better assess the effectiveness of the treatment, the number of influencing variables was kept as small as possible. Therefor only the brains of the patients were treated. However, it should be pointed out that the treatment results are significantly better if the very densely innervated soles and the interosseous and lumbrical muscles of the feet are also included in the treatment. Experience showed that the treatment of the soles with ESWT from plantar with 1500 impulses and an energy flux density between 0.10 to a maximum of 0.15 mJ/mm^2 has proven effective. It gives the patients a better sole-ground contact and helps remarkably against the muscular stiffness of the lower limbs.

In any case, as it is with every medical treatment, the patient's individual pain threshold must be taken into account when selecting the energy flux density.

Our patients were only mildly to moderately affected by the disease. Further research is needed to observe possible effects of the TPS in severely affected patients.

Conclusions

The Parkinson's disease treatment with TPS is safe and effective. Nevertheless, regular maintenance treatment is necessary in order to maintain the symptomatic improvement after the initial treatment series of two weeks. Then the progress of the disease seems at least to be decelerated or even stable for years. The broad scope of the shockwave-stimulated effects in the brain seems to be an interesting and promising extension to the traditional treatment.

Outpatient treatment

Significant reduction of the symptoms for years

- Free of pain, no side effects
- Not necessary to shave patient's head
- Very well tolerated by the patients

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