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Study of the effectiveness of hippotherapy on the symptoms of multiple sclerosis – Outline of a randomised controlled multicentre study (MS-HIPPO)

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ABSTRACT

Background: Hippotherapy is a form of therapeutic riding which is used in the treatment of neurological and muscular disorders. Until now there has not been any high-quality randomised study that has proven its effectiveness.
Objective: The aims of this study are to evaluate whether hippotherapy (as add-on to physiotherapy and/or pharmacotherapy) is superior to the standard treatment (physiotherapy and/or pharmacotherapy as prior to the study) in terms of balance function and other patient relevant outcomes in patients with multiple sclerosis.
Methods: The MS-HIPPO study is a prospective, randomised, examiner-blinded, controlled multicentre study. Patients were randomised to one of two groups: 12 weeks of hippotherapy accompanied by physiotherapy and/or pharmacotherapy (intervention) or 12 weeks of physiotherapy and/or pharmacotherapy as prior to the study (control). The primary endpoint is the change in balance function, as measured by the Berg Balance Scale (BBS). The treatment comparison is evaluated using a covariance analysis with baseline BBS, centre, age, gender and EDSS as covariates. Secondary endpoints include fatigue, quality of life, pain intensity and spasticity.
Results and conclusions: The described study is the first randomised study evaluating the benefits of hippotherapy for patients with multiple sclerosis. In 5 national centres ten study physicians will screen potential participants. The expected results will help to improve the knowledge on non-pharmaceutical therapeutic options in this field.

1. Introduction

Hippotherapy, also known as equine therapy, is a form of therapeutic riding. It is a one-on-one physiotherapy treatment with and on the horse for children and adults with neurological and muscular disorders.

Hippotherapy is mainly used in the treatment of neurological movement and muscular disorders. Along with infantile cerebral palsy (ICP), multiple sclerosis (MS) constitutes the main indication for hippotherapy.

Though the term “hippotherapy” is not legally protected in Germany, the concept of hippotherapy may vary depending on the provider of therapeutic riding. Yet, the leading provider of professional qualifications is the German Consortium for Therapeutic Riding (Deutsches Kuratorium für Therapeutisches Reiten e.V., DKThR). The therapy in Germany shall take place in accordance with the guidelines for hippotherapy of the DKThR. They imply that the horse is led on a long rein by a horse leader walking behind the therapy horse. A hippotherapist walks beside the therapy horse and can be supported by an assistant [1].

In Germany, 67 centres with approximately 1.600 qualified hippotherapists offer hippotherapy according to the above

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mentioned guidelines [2]. On average 25 patients per centre can be covered [3].

During hippotherapy, more than 100 three-dimensional vibration pulses per minute are transmitted to the patient when the horse is led at a walking pace with the patient sitting upright on the horse. In addition to this neuromotor approach, the children and adults sense the body of the horse during the therapy session. That induces learning (sensorimotor approach). The horse has a psychomental effect on the patients (psychomotor and sociomotor approach).

The primary goals of hippotherapy are to regulate muscle tone (reduction of spasticity) and breathing, to strengthen the torso muscles, and to improve balance control, coordination and gait as well as symmetry. Furthermore, hippotherapy promotes social communication and joy in life and strengthens self-esteem [4].

Although there have been reports of a possible effectiveness of hippotherapy on symptoms of MS since 1978 [5], until now there has not been any randomised controlled study that has proven the effectiveness of hippotherapy.

This study is based on the results of two prior monocentric pilot studies [6,7] which were carried out by the Zentrum für Therapeutisches Reiten Johannisberg e.V. These two pilot studies indicated that hippotherapy might provide a better outcome with respect to balance, spasticity, quality of life and pain. We therefore decided to choose these four endpoints and, in addition, fatigue.

The aim of this study is to investigate the effects of hippotherapy on symptoms of patients with multiple sclerosis. It thus represents a trial that aims to prove the feasibility and effectiveness of hippotherapy in a real-world setting based on its efficacy.

2. Participants and methods

2.1. Design

The study design (see Fig. 1) presented here is a prospective, randomised, examiner-blinded, multicentre study with two parallel groups.

The underlying study design enables a parallel group comparison after 12 weeks and conclusions about the effectiveness of hippotherapy (as add-on to physiotherapy and/or pharmacotherapy) as compared to the standard treatment (physiotherapy and/or pharmacotherapy as prior to the study).

The patients of the intervention group are to receive hippotherapy once a week over a period of 12 weeks as an add-on therapy to the previous physiotherapy and/or pharmacotherapy; the patients of the control group shall continue their previous physiotherapy and/or pharmacotherapy as well without hippotherapy. As physiotherapy is reimbursed in accordance with uniform regulations within the German statutory health

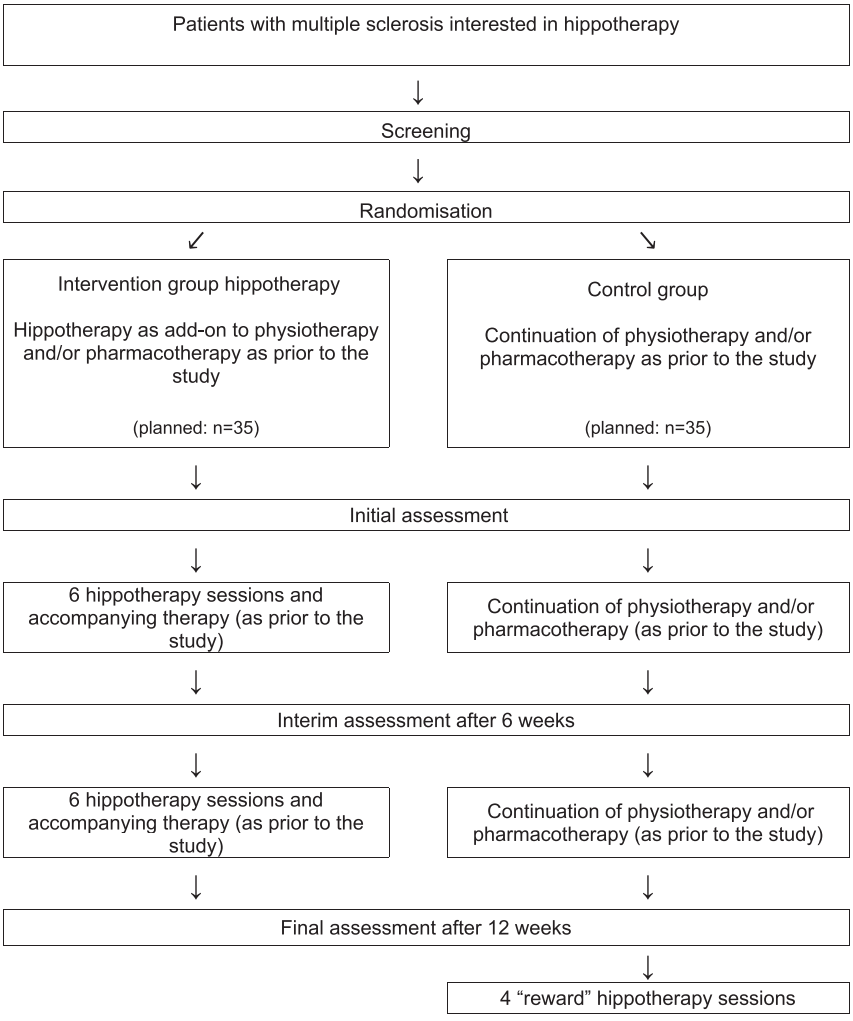

Fig. 1. Study design.

Table 1
Study centres.

	Study centre	Central contact
1	Centre for Therapeutic Riding Johannisberg e.V., Windhagen	Neubauer, Marie-Louise
2	Gut Uettingshof, Bad Mergentheim	Dr. Kaplirz zu Sulewicz, Sabine
3	Centre for Therapeutic Riding, Nuetzen	Kos-Luebben, Maren
4	Carolinenhof, Essen	Braun, Sibylle A.
5	Kastanienhof, Frankfurt-Kalbach	Jaeger, Susanne

Table 2
Requirements for the study centres.

- DKThR-certified facility
- Implementation of hippotherapy according to DKThR guidelines
- Designation of the head hippotherapist and his/her deputy
- Designation of the responsible physiotherapist and his/her deputy
- Separate room for the initial, interim, and final assessments
- At least 2 therapy horses must be available for the therapy
- At least 6 patients must be treated per week
- Comprehensive cooperation with the monitor

insurance scheme holding around 90% of the population we can assume that both groups are similar in terms of the volume of physiotherapy.

The study physician has the task to inform prospective participants about the course and possible risks of the study, to clarify the inclusion and exclusion criteria, and to provide the consent form. In the case of suitability, the signed consent form must be submitted to the relevant study centre. Any tests to assess the status of patients at the beginning and throughout the study (interim and final assessment of patients) are performed by physiotherapists who are blinded. After the initial test the participants of the intervention group shall begin with the first therapy unit.

The participants of the control group shall be offered four “reward” hippotherapy sessions after the end of the 12-week observation period, this is intended as a motivation for the control group to show up and participate in the examinations.

2.2. Study population

All patients, who meet the inclusion and exclusion criteria, are to participate in the study and are to be randomly assigned to the intervention or control group.

2.3. Trial centres

Patients are to be enrolled at five centres in Germany (see Table 1). Ten study physicians will screen potential participants. The participating centres have to meet the following pre-defined requirements: see Table 2.

2.4. Inclusion and exclusion criteria

(see Tables 3 and 4).

Table 3
Inclusion criteria.

- Confirmed multiple sclerosis with spasticity of the lower limbs
- EDSS score between 4 and 6.5
- Written informed consent of the patient
- Approval of the responsible study physician
- Legal competence
- Minimum age of 18 years

Table 4
Exclusion criteria.

- Hippotherapy within the last 12 months
- Parallel participation in other interventional trials
- Persons, who are in a dependent/working relationship with the funder or investigator
- Stay in an institution due to a court or administrative order
- Body weight over 90 kg
- Acute exacerbation during the four-week period before the start of the therapy
- No balance while sitting
- Planned start of treatment with new anti-spastic drugs or with medications that may have an influence on the test parameters (examples: Sativex®; neuraxial administration of baclofen; 4-aminopyridine)
- Seizure disorders not controlled with drugs
- No or insufficient capability to spread the legs so that the patient can sit on the horse
- Known severe osteoporosis
- Known severe osteoarthritis of the hip
- Known severe scoliosis, which could be made worse by hippotherapy
- Severe disorders of blood coagulation, posing the risk of hematoma due to the hippotherapy
- Insufficiently stable secondary diseases in the areas of internal medicine, gynecology and/or surgery
- Insurmountable fear of horses
- Horse hair allergy
- Pregnancy

Table 5
Berg balance scale.

		Score (0–4)
1	Sitting to standing	
2	Standing unsupported	
3	Sitting unsupported	
4	Standing to sitting	
5	Transfers	
6	Standing with eyes closed	
7	Standing with feet together	
8	Reaching forward with outstretched arm	
9	Retrieving object from floor	
10	Turning to look behind	
11	Turning 360°	
12	Placing alternate foot on stool	
13	Standing with one foot in front	
14	Standing on one foot	
Total		

Source: Berg K, Wood-Dauphinee S and Williams JI: The Balance Scale: reliability assessment with elderly residents ans patients with an acute stroke. Scand J Rehabil Med 1995; 27 (1): 27–36.

2.5. Interventions

The patients of the intervention group shall complete one 30-min hippotherapy session once a week for 12 weeks according to the guidelines for hippotherapy of the DKThR [1].

All study participants shall continue their current physiotherapy without any change. The medication shall be kept stable over the study period. In general, during the study no therapies shall be stopped or initiated.

2.6. Outcomes

The primary endpoint of the study is the change in balance function after 12 weeks of therapy (change from baseline). The instrument used is the Berg Balance Scale (BBS) [8], which has been considered the gold standard for the measurement of balance since the 1990s (see Table 5).

Due to its sensitivity to change (responsiveness) and its very good reliability, the BBS is especially suited for measurements over the course of time. The scale is very reliable with repeated measurements by the same examiners (intra-tester reliability), as well as by two different examiners (inter-tester reliability). The implementation of this assessment takes approximately 15–20 min [9].

Secondary outcome measures are as follows: Fatigue is assessed by the Fatigue Severity Scale (FSS), which contains 9 items. By means of this scale, the severity of a fatigue can be shown [10]. It allows a distinction between cognitive, affective and somatic dysfunctions. The FSS is considered to be the gold standard for validating other or new fatigue scales and is recommendable due to its simplicity and rapid implementation [11].

The Multiple Sclerosis Quality of Life-54 (MSQoL-54) instrument is a disease-specific questionnaire for patients with multiple sclerosis which extends the generic SF-36 questionnaire with 18 MS-specific items [12].

The change in the pain and spasticity symptoms is displayed in the Visual Analogue Scale (VAS) [13,14] and/or the Numeric Rating Scale (NRS) [15]. Through these simple and easy-to-use scales, the patient can document his/her symptoms (see Table 6).

2.7. Visits and assessments

After screening by the study physicians, patients will be randomised to one of the two treatment groups. The subsequently initial assessment will take place prior to the first hippotherapy session or first observation week. The interim assessment will be carried out 6th – 7th week, the final assessment 13 weeks after initial assessment (see Table 7). During the assessments the respective primary and all secondary endpoints are to be determined (duration approx. one hour). The assessments shall take place in a separate room at the study centre or in the physiotherapists' own premises. Since blinding of the patients is not possible due to the nature of the intervention, the examining physiotherapists are to be blinded during the entire study phase to ensure an observer-blinded endpoint assessment. Accordingly, they do not know whether the respective patient is in the intervention group or in the control group. In a central training session for the physiotherapists, it shall be explicitly pointed out that any questioning of the patients or the hippotherapists is prohibited. The patients shall

Table 6
Secondary outcome measures.

- Change in fatigue: Fatigue Severity Scale (FSS)
- Change in quality of life: Multiple Sclerosis Quality of Life-54 (MSQoL-54)
- Change in pain intensity: Visual Analogue Scale (VAS)
- Change in Spasticity: Numeric Rating Scale (NRS)

Table 7
Visit schedule.

	Enrolment (Day 0)	Visit 1 (Day 1)	Visit 2 (Week 6–7)	Visit 3 (Week 13)
Enrolment				
Screening for eligibility	X			
Informed consent	X			
Allocation	X			
Interventions				
Hippotherapy		12 sessions within 12 weeks		
Physiotherapy and/or pharmacotherapy		physiotherapy and/or pharmacotherapy as prior to the study within 12 weeks		
Assessment				
Demographic data, medical history	X			
Balance function		X	X	X
Fatigue		X	X	X
Quality of life		X	X	X
Pain intensity		X	X	X
Spasticity		X	X	X
AEs/SAEs		X	X	X
End of treatment/study				X

also be individually instructed that they are obliged to confidentiality.

2.8. Sample size calculation

The sample size calculation is based on the primary endpoint change of the BBS after 12 weeks of therapy (difference between BBS after 12 weeks and initial value of BBS). The assumptions for the expected therapy effect are based on the results of the pre-post pilot studies by Sager et al. (2007; n = 16) [6] with an average improvement of 5.6 points after 12 weeks, as well as the pilot study with the control group by Schneider et al. (2010; n = 12) [7] with an average improvement of 6.5 points after six weeks of hippotherapy. Based on the standard deviations found in the two previous studies (Sager: 8.3; Schneider: control group: 5.6; therapy group: 7.6), we chose a conservative approach and assumed that the standard deviation is 8.3 in both groups. Under these assumptions, at a type I error rate of $\alpha = 5\%$ (2-sided) and a power of 1-$\beta = 80\%$ with a sample size of 64 (2×32), a difference of 6 points can be revealed using the student's t test. It can be assumed that in the covariance analysis, which is described for the evaluation of the primary endpoint, the power is increased compared with the t test. Assuming a drop-out rate of approximately 10%, a total 70 patients (2×35) shall be randomised.

2.9. Screening and randomisation

Patients were consecutively informed and screened by the study physicians, and eligible patients are included in the study. After giving written informed consent, patients are randomly assigned to one of the two treatment groups: the hippotherapy intervention group or the control group. The randomisation of patients will be stratified by centre and disability as measured with the expanded disability status scale (EDSS) [16] (<5 vs. $\geq$ 5) (permuted blocks of varying length) and implemented by sealed opaque envelopes generated on the basis of a computer-generated randomisation list.

2.10. Data management and monitoring

Data management is to be performed using REDCap software [17]. For infrastructural reasons in the study centres, the data shall be collected on paper, not electronically. Inconsistencies and implausibilities shall be clarified in writing by the project manager with the study centres. These queries are to be answered in a timely manner by the study centres. The data shall be entered into the study database by the project manager and another independent person. A third independent person shall compare the data entries and decide in case of discrepancies.

To ensure the quality of the study, a monitoring by the Centre for Clinical Trials Cologne (ZKS) shall be carried out in the study centres. An initial visit shall take place in each study centre, and a regular visit after enrolment of all patients in the respective study centre.

2.11. Statistical analyses

The primary analysis will be performed according to the intention to treat, i.e. all patients randomised are analyzed as assigned.

The primary target variable is the change of the BBS (difference between BBS after 12 weeks and initial value of BBS). The treatment comparison is evaluated using a covariance analysis (ANCOVA) with the baseline BBS, centre, age, gender and EDSS classification as covariates. Missing values shall be imputed through the last observed value (LOCF). The stability of the results when using different imputation methods shall be verified by sensitivity analyses. As further sensitivity analysis, an evaluation of the course data shall be performed by means of complex mixed-effects models (change in BBS over the course of the study). The secondary endpoints are to be analysed mainly descriptively. In addition, a covariance analysis in analogy to the analysis of the primary endpoint will be done. The safety data are to be reported and listed in summary form. Further details are laid out in the statistical analysis plan.

Three study populations will be analysed. The primary evaluation data set is the *modified intention-to-treat* population (*modified* ITT). This data set includes all patients who were enrolled and randomised in the clinical study and from whom at least the initial value of the BBS was collected.

The secondary evaluation data set is the *per-protocol* population, This data set contains all patients who were treated according to the protocol over the entire study period, i.e. for whom no major protocol violations were documented and who, in addition to the initial assessment, completed at least two assessments (interim assessment and/or final assessment). It is considered a major protocol violation – in the case of the intervention group – if less than 9 of the 12 planned hippotherapy sessions were completed. (A comparable definition is not possible for the control group, because only an already ongoing physical therapy is continued individually.) Analyses of primary and secondary endpoints will be done for *modified* ITT and *per-protocol* population. The analysis of the per-protocol population is considered to be a sensitivity analysis.

The tertiary evaluation data set (safety population) includes all patients who received at least one treatment (hippotherapy or physiotherapy). This population will be used for the safety analyses.

2.12. Safety assessment and reporting of adverse events

Prior to each assessment (and prior to a hippotherapy session), the patients shall be asked whether any adverse or serious adverse events have occurred. Adverse events are to be documented both in the respective questionnaire forms as well as on the AE/SAE form. Each adverse event is to be assessed by the head hippotherapist in the centre, and if necessary by the study physician in order to determine whether an association with the hippotherapy can be suspected.

Adverse events will be assessed from the day of randomization until the regular end of trial follow-up or until premature withdrawal of a patient.

Any event with an unfavourable effect for the participant regardless of an association to the intervention is considered an adverse event. A serious adverse event will be defined as an event that results in death, is immediately life-threatening, requires or prolongs hospitalization for any medical reason, or results in persistent or significant disability or incapacity.

Each serious adverse event will immediately be communicated within 24 h to the study centre and to the coordinating investigator, and the relevant ethics commission will be notified.

3. Ethical and legal aspects

The study was designed and shall be conducted according to the principles of Good Clinical Practice (GCP, ICH E6) and data protection laws. The local ethics committees of all participating centres approved the study protocol. The trial was registered in the German Clinical Trial Register under DRKS00005289.

4. Discussion

Recent estimates suggest that 2.5 million people worldwide are suffering from Multiple Sclerosis. Pharmaceutic studies cover a

wide spectrum in this disease, but the alternative treatment options examined are limited. Until now there has not been any high-quality randomised study that has examined the effectiveness of hippotherapy. The results of this randomised clinical trial will be of utmost relevance both to patients as well as their physicians.

However, the MS-HIPPO study design though following Good Clinical Practice has some limitations. As the trial will be performed in a setting and with therapists who are not regularly involved with studies it will be a challenge. Hippotherapists and physiotherapists will accordingly be trained to strengthen compliance with the guidelines and to clarify the obligation of keeping the allocation of all patients confidential.

Due to the nature of the intervention, blinding of patients is not possible. Therefore it is crucial to ensure an observer-blinded endpoint assessment. That is, physiotherapists will be blinded during the entire study. The importance of keeping the allocation of all patients confidential will be conveyed with emphasis to all who are involved with the trial conduction. Physiotherapists were repeatedly instructed not to request information on the therapeutic regimens of the patients. Likewise the participants were informed about the importance of blinding. Furthermore, participants of the intervention arm were instructed to strictly confine their questions about the intervention to the respective hippotherapists. Blinding of the examiners and a strict intention-to-treat analysis will contribute to the quality and credibility of the upcoming study.

In view of the increasing use and relevance of hippotherapy in the treatment of various neurological and muscular disorders, it is of utmost relevance to investigate whether MS-patients benefit from an additional hippotherapy or not. MS-HIPPO is the first randomised controlled trials evaluating the effects of hippotherapy on symptoms of MS and life quality and hence will close a gap in research and serve patients' demands.

5. Conclusion

The trial is the first randomised trial evaluating the benefits of hippotherapy for patients with multiple sclerosis. The expected results will help to improve the evidence base and will allow conclusions on the effectiveness of hippotherapy on the symptoms of multiple sclerosis.

Trial organisation

The coordinating investigator is Dieter Pöhlau, MD, DRK Kamillus Clinic Asbach. The project co-ordination, correspondence with regulatory authorities and data management are performed by Dipl. Ges.Ök. Vanessa Wollenweber, Institute of Health Economics and Clinical Epidemiology (Institut für Gesundheitsökonomie und Klinische Epidemiologie, IGKE), University of Cologne. The head office of the study is represented by Marion Drache, Zentrum für Therapeutisches Reiten Johannisberg e.V. Central monitoring is carried out by the Clinical Trials Centre Cologne (Zentrum für Klinische Studien Köln, ZKS), University of Cologne. Statistical design, randomisation and data analysis are performed by the Institute of Medical Statistics, Informatics and Epidemiology (Institut für Medizinische Statistik, Informatik und Epidemiologie, IMSIE), University of Cologne.

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Conflict of interest statement

Vanessa Wollenweber was an employee at the Zentrum für Therapeutisches Reiten Johannisberg e.V. Her position was financed by the Willi Drache Foundation. Marion Drache is chairwoman of the Willi Drache Foundation. S. Schickendantz, A. Gerber-Grote, P. Schiller, and D. Pöhlau have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2016.02.001.

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