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Hippotherapy for patients with multiple sclerosis: A multicenter randomized controlled trial (MS-HIPPO)

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Abstract

Background: Evidence-based complementary treatment options for multiple sclerosis (MS) are limited.
Objective: To investigate the effect of hippotherapy plus standard care versus standard care alone in MS patients.
Methods: A total of 70 adults with MS were recruited in five German centers and randomly allocated to the intervention group (12 weeks of hippotherapy) or the control group. Primary outcome was the change in the Berg Balance Scale (BBS) after 12 weeks, and further outcome measures included fatigue, pain, quality of life, and spasticity.
Results: Covariance analysis of the primary endpoint resulted in a mean difference in BBS change of 2.33 (95% confidence interval (CI): 0.03–4.63, $p=0.047$) between intervention ($n=32$) and control ($n=38$) groups. Benefit on BBS was largest for the subgroup with an Expanded Disability Status Scale (EDSS) $\geqslant 5$ (5.1, $p=0.001$). Fatigue (−6.8, $p=0.02$) and spasticity (−0.9, $p=0.03$) improved in the intervention group. The mean difference in change between groups was 12.0 ($p<0.001$) in physical health score and 14.4 ($p<0.001$) in mental health score of Multiple Sclerosis Quality of Life-54 (MSQoL-54).
Conclusion: Hippotherapy plus standard care, while below the threshold of a minimal clinically important difference, significantly improved balance and also fatigue, spasticity, and quality of life in MS patients.

Keywords: Berg balance scale, hippotherapy, equine-assisted therapy, multiple sclerosis, spasticity, quality of life

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Introduction

Despite the benefits of pharmacological and non-pharmacological treatments of symptoms in patients with multiple sclerosis (MS), there is a need for better control of these symptoms.

Hippotherapy as a complementary treatment can be defined as one-patient-one-horse physiotherapy treatment with and on the horse. The primary goals of hippotherapy are regulating muscle tone (reduction in spasticity) and breathing, strengthening the torso muscles, improving balance control and coordination, as well as gait. In addition, hippotherapy promotes social communication in the patients' lives and strengthens their self-esteem.[1]

There have been reports on a beneficial effect of hippotherapy on symptoms of MS since 1978.[2] Until now, only one randomized controlled study with 18 MS patients indicated evidence of the effectiveness of hippotherapy. Frevel and Mäurer[3] compared an Internet-based home training program with hippotherapy for 12 weeks. While there was no difference in static and dynamic balance between groups after the intervention, pre–post improvement was statistically significant in both groups. A marked improvement in fatigue and quality of life was also shown in the group receiving hippotherapy.

The hippotherapy for patients with multiple sclerosis (MS-HIPPO) trial is primarily based on the results of

two monocentric pilot studies[4,5] carried out by the Zentrum für Therapeutisches Reiten Johannisberg e.V., in cooperation with partners in the current trial consortium. Patients in the pilot study by Sager et al. (one-arm trial, 16 patients) showed an average improvement of 5.6 points on the Berg Balance Scale (BBS) by week 12. The pilot study by Schneider et al. (randomized crossover trial, 12 patients) showed an average improvement of 6.5 points on BBS after 6 weeks of hippotherapy.

A randomized controlled trial is presented to evaluate whether hippotherapy plus standard care is superior to standard care alone in terms of balance function and further relevant outcomes in patients with MS.

Patients and methods

Trial design

MS-HIPPO was a prospective, randomized, examiner-blinded, multicenter, comparative trial with an allocation of 1:1 to the two groups: hippotherapy plus standard care compared to standard care alone (as prior to the study). The intervention lasted for 12 weeks. A study outline, including details on randomization, inclusion and exclusion criteria, interventional and control treatment, data management, statistical analysis, and sample size calculation, was provided in the MS-HIPPO study protocol.[6] Information required by the CONSORT (Consolidated Standards of Reporting Trials) guideline[7] can be also found in the online appendix. The study was conducted at five sites in Germany, all of which have hippotherapy experience as stipulated by the rules of the German Consortium for Therapeutic Riding.[8] The principles of good clinical practice (GCP, ICH E6) and data protection laws were applied. The study was approved by the respective ethical committees of the participating sites and registered with the German Trial Registry (DRKS00005289).

Patients

MS patients older than 18 years who had a confirmed MS with spasticity of the lower limbs and an Expanded Disability Status Scale (EDSS)[9] score between 4 and 6.5 were eligible for inclusion. Patients who had received hippotherapy within the last 12 months, a body weight over 90 kg, no balance while sitting, and acute exacerbation during the 4-week period before start of the therapy were excluded. A planned start of treatment with new antispastic drugs or other medications that may have an influence on the assessed outcomes also resulted in exclusion. Prior to randomization, written informed consent was obtained from each patient.

Procedures

Eligible patients were randomized to one of the two groups using sealed opaque envelopes on the basis of a computer-generated randomization list. Allocation concealment was assured using permuted blocks of varying length.

Patients of the intervention group received hippotherapy (as defined by the regulations for hippotherapy of the Deutsches Kuratorium für Therapeutisches Reiten e.V. (DKThR))[8] once a week for 12 weeks as an add-on therapy to their standard care, which remained unchanged. Patients in the control group continued their previous therapy. Over the study period, symptomatic drug treatment, immunotherapy, and physiotherapy were kept unchanged in both groups.

Examinations and questionnaires were completed prior to the first hippotherapy session (baseline), after 6–7 weeks (interim assessment) and after 12 weeks (final assessment). Physiotherapists who assessed the endpoints in a separate room were blinded and explicitly trained not to question patients or hippotherapists. Patients were individually instructed to keep confidentiality of their allocation group.

Adverse events (AEs) were documented in the respective questionnaire forms as well as on the AE/serious adverse event (SAE) form by each center's head hippotherapist, physiotherapist, or the study physician. SAEs were immediately communicated according to GCP. In the study centers, monitoring was undertaken by the Clinical Trials Centre Cologne (CTCC).

Outcomes

The primary endpoint was the change in the BBS[10–13] (difference from BBS baseline to week 12). Secondary endpoints were changes from baseline in fatigue (Fatigue Severity Scale (FSS)),[14,15] health-related quality of life (Multiple Sclerosis Quality of Life-54 (MSQoL-54)),[16] pain (Visual Analogue Scale (VAS)),[17,18] and spasticity (Numeric Rating Scale (NRS)).[19]

Sample size

In line with previous studies, it was decided that the smallest difference needed was an improvement of 6 points in the BBS at 12 weeks. Calculations indicated that to demonstrate a BBS improvement of this size, a

sample size of 64 (2 × 32) would be required (α = 5%, power = 80%). Assuming a dropout rate of 10%, a total of 70 patients (2 × 35) needed to be randomized. For simplicity reasons, the calculation was based on Student's *t* test (standard deviation (SD): 8.3, Student's *t* test, type 1 error rate: 5%, two-sided; assumptions based on results of two pilot studies[4,5] as described in the trial protocol by Wollenweber et al.[6]).

Statistical analysis

Analyses were based on the modified intention-to-treat set (modified ITT). This set encompasses all randomized patients with valid baseline assessment. The primary endpoint change of BBS from baseline to 12 weeks was calculated using an analysis of covariance (ANCOVA) with the fixed effects group, center, age, gender, EDSS classification, and baseline BBS (type 2 sums of squares). Missing values were imputed through the last observation carried forward (LOCF) value. Moreover, a mixed-model repeated-measures (MMRM) analysis was done using non-imputed data with the fixed effects group, center, time, group by time, age, gender, EDSS classification, and baseline BBS (type 3 sums of squares, ARH1 covariance structure on time). For both approaches the focus of statistical inference was on the difference in marginal means for the change from baseline to 12 weeks. In a sensitivity analysis, the per-protocol (PP) set including all the patients who were treated according to the protocol over the entire study period (i.e. for whom no major protocol deviations were documented) was used.

Analysis of secondary endpoints was descriptive. In addition, an ANCOVA analogous to the primary endpoint analysis was performed. Safety data, that is, AEs, were summarized by type, seriousness, intensity, and relatedness. Preplanned subgroup analyses with respect to age and EDSS were carried out.[6] These analyses are essentially explorative, thus no correction for multiple testing was done. Calculations were performed with the software SPSS Statistics 22 (IBM Corp., Armonk, NY, USA).

Results

Between September 2013 and March 2014, 70 patients with stable MS (57 females, 13 males, median age: 51 years) were randomly assigned to intervention (32 patients) and control (38 patients). The interval between baseline and final examination was similar in both groups (median (interquartile range (IQR)); intervention: 12.6 (11.9–14.0); control: 13.1 (12.2–14.2)). Information on the flow of patients and the numbers of analyses sets, including reasons of exclusion, is summarized in Figure 1.

Demographic and baseline characteristics were balanced (Table 1). In both groups, two-thirds of patients had an EDSS score of 5 or higher. Median duration of MS was 16.5 years (intervention) or 17.6 (control). About 96% of the patients received physiotherapy at the beginning of the study.

Primary endpoint: balance

Under study conditions and within 12 weeks, BBS improved in both groups. In the intervention group, the change in BBS from baseline to week 12 was 6.00 points (95% CI: 4.2–7.8) versus 2.9 in the control group (95% CI: 1.5–4.4, derived from MMRM) (Table 2 and supplementary figure e-1). The mean difference in change between groups after 12 weeks was 3.07 points (95% CI: 1.00–5.14, $p = 0.004$ (Table 2, MMRM)). Results of the preplanned ANCOVA were 2.33 points (95% CI: 0.03–4.63, $p = 0.047$ (Table 2, LOCF ANCOVA)). The sensitivity analysis of the PP set revealed a difference in change between groups of 4.61 (95% CI: 0.74–7.47, $p = 0.002$ (MMRM)).

Secondary endpoints: fatigue, spasticity, pain, and quality of life

In the intervention group, fatigue (FSS) and spasticity (NRS) improved from baseline to week 12 (FSS: −9.2, SD: 10.3; NRS: −1.7, SD: 2.2; supplementary table e-1), and in the control group, they hardly changed (FSS: −0.9, SD: 8.4; NRS: −0.6, SD: 1.8). The mean difference in change between groups was −6.8 (95% CI: −11.0 to −2.6, $p = 0.002$) for FSS and −0.9 (95% CI: −1.9 to −0.1, $p = 0.031$) for NRS. From baseline to week 12, individual pain perception, as measured via VAS, improved in both groups (intervention: −7.4, SD: 16.8; control: −1.3, SD: 28.0; mean difference in change between groups: −3.1 (−13.4 to 7.3), $p = 0.555$; it should be noted that the values were highly variable at the beginning and over the "study period", supplementary table e-1).

The 54 MSQoL-54 items were summarized in the two subscales: mental health and physical health score. After 12 weeks, a significant effect in favor of the intervention group could be seen in both subscales. The mean difference in change between groups was 12.0 (95% CI: 6.2–17.7, $p < 0.001$) in the physical health scale and 14.4 (95% CI: 7.5–21.3, $p < 0.001$) in the mental health scale (supplementary table e-1).

Subgroup analyses

Within 12 weeks, patients with EDSS < 5 at baseline experienced a similar change in BBS in both groups. In patients with an EDSS ⩾ 5 who received

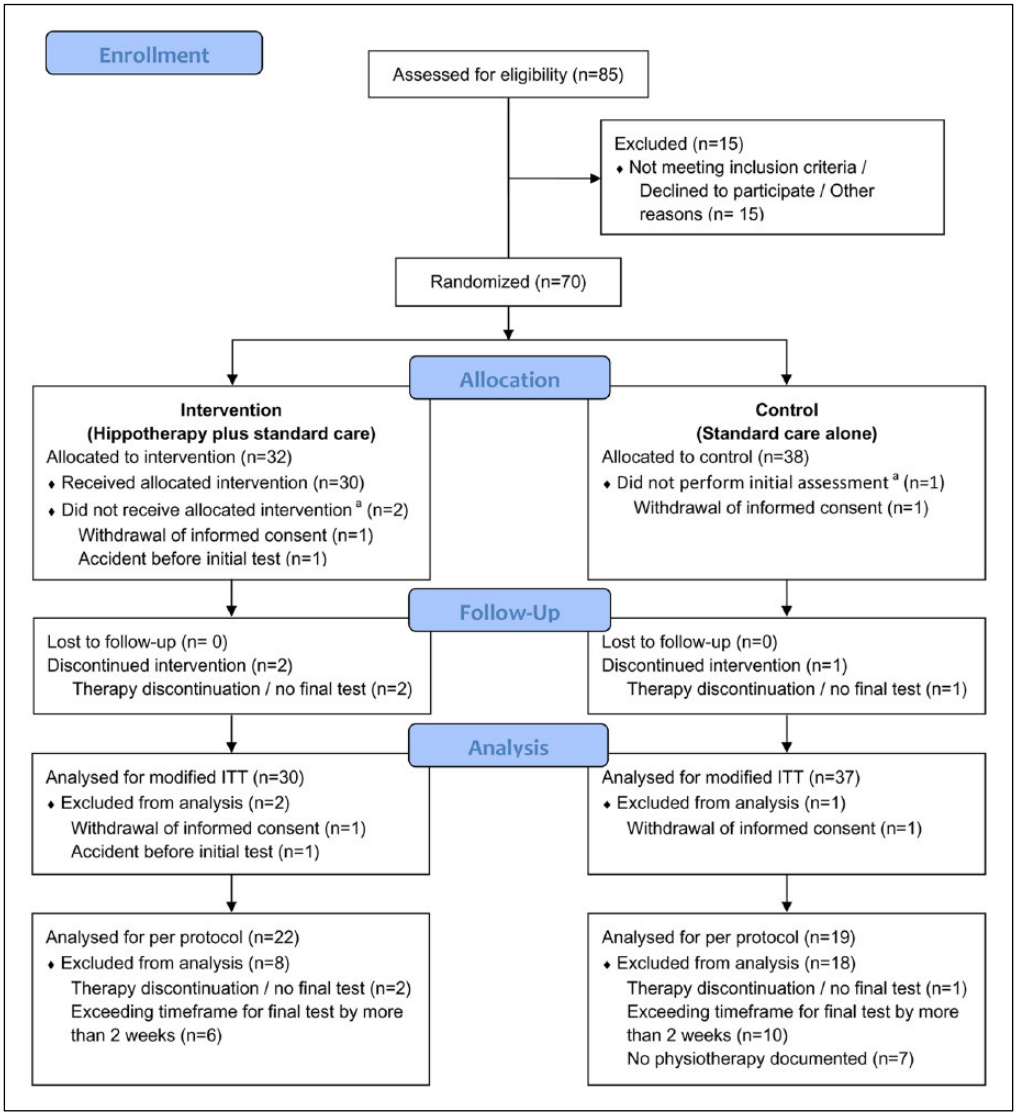

Figure 1. Trial profile.
[a]Events occurred after randomization, but before initial test; discovered after randomization.

hippotherapy, the BBS increased more markedly than in the control group (mean difference in change between groups: 5.1 points, 95% CI: 2.3–7.9, $p = 0.001$; Figure 2). In terms of secondary endpoints (with the exception of VAS), the subgroup of patients with EDSS $\geqslant 5$ who received the intervention also showed a marked improvement as compared to the control group (supplementary figures e-2 and e-3).

Safety

In 28 patients, a total of 49 AEs occurred over 12 weeks (intervention: 22 AEs in 13 patients, control: 27 AEs in 15 patients, supplementary table e-2, separated by subgroups in supplementary table e-3). In the intervention group, one patient fell off the therapy horse but was able to continue therapy. Three further AEs could have been related to the participation in the study: In the control group, one patient had a fractured leg, while in the intervention group, two patients experienced the beginning of an MS relapse accompanied by painful muscle contractions.

In all, 3 of the 49 AEs were classified as being SAEs due to the necessary hospitalization (intervention: 1 SAE (MS relapse), control: 2 SAEs (MS relapse and infection)).

There was no discernible relationship between the hospitalization and participation in the study.

Table 1. Baseline characteristics by assigned treatment.[a]

	Intervention (hippotherapy, $n=30$)	Control ($n=37$)	Total ($n=67$)
Median age (IQR) (years)	50 (45–53)	51 (47–56)	51 (46–55)
Sex			
Female	27 (90%)	27 (73%)	54 (81%)
Male	3 (10%)	10 (27%)	13 (19%)
EDSS at inclusion	5.4 (1.0)	5.3 (0.9)	5.4 (0.9)
<5	10 (33%)	11 (30%)	21 (31%)
⩾5	20 (67%)	26 (70%)	46 (69%)
Weight (kg)	67 (10.3)	70.6 (9.9)	69.0 (10.2)
Median time from onset of MS to inclusion (IQR) (years)	16.5 (11–20)	17.6 (11–27)	17.3 (11–23)
Physiotherapy (in accordance with the Regulations Governing the Prescription of Remedies)	29 (97%)	35 (95%)	64 (96%)

IQR: interquartile range.
[a]Data are *n* (%) or mean (standard deviation (SD)) unless stated otherwise.

Table 2. Results for primary endpoint Berg Balance Scale[a].

		Baseline	Week 6	Week 12	Difference between groups at 12 weeks[b]
LOCF ANCOVA					2.33 (0.03–4.63), $p=0.047$
Mean (SD)	Control ($n=37$)	42.1 (10.9)	44.9 (9.8)	45.1 (10.9)	
	Intervention ($n=30$)	40.6 (11.5)	45.4 (9.3)	47.0 (8.7)	
Change	Control ($n=37$)	0	2.9 (4.7)	3.1 (5.1)	
Mean (SD)	Intervention ($n=30$)	0	4.8 (5.1)	6.4 (5.4)	
MMRM					3.07 (1.00–5.14), $p=0.004$
EMM (95% CI)	Control	0	2.5 (1.9–4.0)	2.9 (1.5–4.4)	
	Intervention	0	4.3 (2.5–6.1)	6.0 (4.2–7.8)	

LOCF: last observation carried forward; ANCOVA: analysis of covariance; MMRM: mixed-model repeated-measures; EMM: estimated marginal mean; CI: confidence interval.
[a]Data are mean (SD) or mean (95% CI).
[b]Difference between groups in change of Berg Balance Scale from baseline to 12 weeks derived from ANCOVA or MMRM.

Discussion

This study provides class I evidence that weekly hippotherapy plus standard care in comparison with standard care alone may improve balance function after 12 weeks.

The balance as measured by BBS improved in both groups, but to a significantly different degree. For patients in the intervention group receiving hippotherapy, the increase was 6.4 points (SD: 5.4) on average versus 3.1 points (SD: 5.1) in the control group under ongoing standard care. The preplanned ANCOVA of the modified ITT set detected a mean difference of 2.33 points (95% CI: 0.03–4.63, $p=0.047$) between groups. Applying an MMRM analysis taking into account the intermediate assessment confirmed the results.

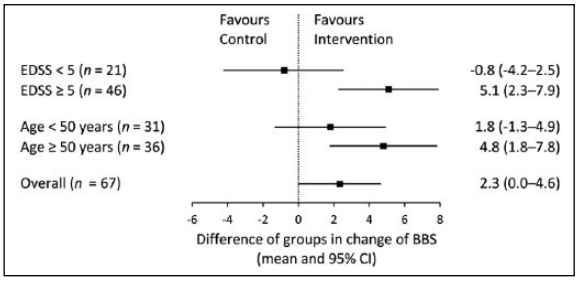

Figure 2. Subgroup analyses of the change in Berg Balance Scale (BBS) after 12 weeks. Results are shown as difference between groups in change of BBS (mean, 95% CI; ANCOVA models of LOCF data).

Furthermore, a positive effect on quality of life and other MS-specific symptoms such as fatigue and

spasticity could be found. With all findings pointing in the direction of the intervention, we interpret the results as an indication for an overall benefit for the patients.

In order to understand whether the results have a relevant effect on patients' daily lives, they need to be interpreted in light of the minimal clinically important difference. In a validation study, Stevenson[20] pointed out that a minimum detectable change score of ±6 BBS points "is necessary to be 90% confident of genuine change." In a systematic review based on 11 studies and 668 subjects, Downs et al.[21] concluded that there was "little specific guidance as to how confident one can be that a real change in balance has occurred between tests across time for individual patients." They inferred that a change between 3 and 7 should be interpreted as a real change in balance for baseline scores of between 20 and 56. In our trial, participants had baseline values around 41 points (Table 2). Beauchamp et al.[22] stated that "anchor-based estimates of the MCID ranged from 3.5 to 7.1." Lord et al.[23] set 6 points on the BBS as the minimal clinically important difference for people with MS.

We therefore think that the change of 4.8 after 6 weeks and of 6.4 points after 12 weeks for the intervention group reflect a relevant change. We are aware that the difference of 3.07 points between the intervention and control group after 12 weeks as result of the MMRM analysis does not reach the threshold of a minimal clinically important difference. In addition, we observed significant effects on the secondary outcomes of spasticity, fatigue, and quality of life. Especially on the results for quality of life, we assume that the improvement on the BBS is noticeable by patients in their daily activities. However, this may be an association and we cannot be sure about a causal relationship. The PP analysis detected a difference of 4.57 points (1.32–7.82) ($p = 0.007$) between the two groups. This finding suggests that a hippotherapeutic regimen which follows the protocol may have a clinically relevant positive effect. With a difference of 5.1 points in change on BBS between groups, the subgroup of patients with EDSS $\geqslant 5$ strongly benefitted from hippotherapy (Figure 2).

Secondary endpoints were chosen as they represent common general symptoms in MS as confirmed by clinicians.[24–26] Furthermore, institutions which perform health technology assessments and deliver guidance for decision-making on reimbursement of therapeutic regimens strongly advocate the inclusion of direct patient-relevant outcomes including quality of life.

Positive effects could be found for all but one secondary endpoint. The minimum clinically important differences of 1.5 and 2.5 points for the MSQoL-54 physical and mental scales were surpassed by far.[27] Although we admit that there was an effect of positive expectation in the hippotherapy group, the effect with 10 points and more is beyond a positive expectation. FSS and NRS improvements point to a positive effect for the intervention group. When using a sum score of 36 as the cutoff for the presence of severe fatigue,[14] the proportion of patients with no severe fatigue increased from baseline to week 12 from 10% to 33% in the intervention group and from 14% to 19% in the control group. The effect on fatigue may be not causal but could be attributed to an altered perception of fatigue based on a better quality of life. These findings are in accordance with a recent Cochrane review.[28] According to 36 trials, exercise therapy may reduce fatigue in patients with MS. These results could not only be observed for endurance training but also for mixed or other training (e.g. yoga). At baseline, pain as measured by VAS was lower in the intervention group than in the control group, but similar after 12 weeks. This finding is in contrast to the other results of the trial. We assume that low initial pain scores and a high variance may explain these results. This is in accordance with Sager et al.,[5] who found a reduction in the perception of pain with a 6-week hippotherapy and a high variance.

Throughout the study, pharmacotherapy was reported by the patients themselves and thus underlies the constraints of patient-reported data (supplementary table e-4). Drug treatment was stable in both groups (93% of the hippotherapy group reported no changes and 84% of the control group, supplementary table e-5). Yet, some data are missing, especially in the control group. Patients with a confirmed MS with spasticity of the lower limbs were eligible for inclusion. Yet, spasticity was not quantified.

The results of this first randomized controlled multicenter trial in the field of hippotherapy for MS patients indicate the positive effect of this therapy on balance and other relevant functions. We demonstrated that for complementary approaches, trials following GCP guidelines can be undertaken in settings that are not familiar with research. Hence, for the benefit of patients, we encourage health professionals and independent foundations to be more proactive regarding research in non-pharmacological interventions. We

hope that with the necessary funding, future trials will be undertaken to extend the study period and to prolong the follow-up.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Vanessa Vermöhlen reports receiving personal fees from the Willi Drache Stiftung during the conduct of the study. Petra Schiller is employed at the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), which concluded an agreement with Willi Drache Stiftung. Marion Drache is honorary chairwoman of the Willi Drache Stiftung (she had no role in data collection and data analysis). Vanessa Vermöhlen and Petra Schiller had full access to all of the data in this study. Both take complete responsibility for the integrity of the data and the accuracy of the data analysis. Sabine Schickendantz, Sabine Hussack, Andreas Gerber-Grote, and Dieter Pöhlau declare that there is no conflict of interest.

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