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Research Article

Usefulness of classical homeopathy for the prophylaxis of recurrent urinary tract infections in individuals with chronic neurogenic lower urinary tract dysfunction

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Context/Objective: to investigate the usefulness of classical homeopathy for the prevention of recurrent urinary tract infections (UTI) in patients with spinal cord injury (SCI).

Design: prospective study.

Setting: rehabilitation center in Switzerland.

Participants: patients with chronic SCI and ≥ 3 UTI/year.

Interventions: Participants were treated either with a standardized prophylaxis alone or in combination with homeopathy.

Outcome measures: The number of UTI, general and specific quality of life (QoL), and satisfaction with homeopathic treatment were assessed prospectively for one year.

Results: Ten patients were in the control group; 25 patients received adjunctive homeopathic treatment. The median number of self-reported UTI in the homeopathy group decreased significantly, whereas it remained unchanged in the control group. The domain incontinence impact of the KHQ improved significantly ($P = 0.035$), whereas the general QoL did not change. The satisfaction with homeopathic care was high.

Conclusions: Adjunctive homeopathic treatment led to a significant decrease of UTI in SCI patients. Therefore, classical homeopathy could be considered in SCI patients with recurrent UTI.

Trial registration: ClinicalTrials.gov. (NCT01477502).

Key words: Homeopathy, Neurogenic lower urinary tract dysfunction, Spinal cord injury, Urinary tract infections

Introduction

Virtually every patient with spinal cord injury (SCI) suffers from neurogenic lower urinary tract dysfunction (NLUTD). Especially suprasacral SCI frequently leads to elevated bladder storage pressures which are the major risk factor for renal deterioration.¹ The impaired storage and voiding functions of the lower urinary tract are not only risk factors for renal damage, but also for urinary tract infections (UTI).² UTI are one of the most common morbidities in individuals with NLUTD.³ Approximately one in five individuals

with NLUTD suffer from recurrent UTI, which are associated with a considerable morbidity and mortality and affect the quality of life (QoL) substantially.⁴ Common measures to control recurrent UTIs in individuals with NLUTD include optimization of their bladder management and elimination of infection sources, such as bladder stones or foreign bodies.³ Unfortunately, recurrent UTI persist despite these measures in a high percentage of affected patients. Therefore, several preventive or protective measures have been used, but until today, no prophylaxis with evidence-based efficacy exist.⁵ As a consequence, a plethora of different methods are currently used for UTI prophylaxis.

Recently, the usefulness of classical homeopathy as an adjunctive prophylactic measure has been demonstrated

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in a case series.⁶ However, prospective studies for evidence-based evaluation of homeopathic treatment are currently not available.

Therefore, we prospectively assessed the usefulness of classical homeopathy for the prevention of UTI in patients with NLUTD due to SCI and compared the results to a cohort of patients receiving conventional prophylaxis.

Methods

From 12/2011 to 06/2015, each patient with an NLUTD due to SCI who presented to our unit for urodynamic evaluation was, as part of the medical history, was asked for the number of UTI within the last year. Each patient with three or more UTI/year was asked to participate in the study. After screening for exclusion criteria (time since SCI < 12 months, no urodynamically proven NLUTD, age < 18 years, lack of comprehension, ongoing homeopathic treatment), morphologic causes for UTI, e.g. bladder stones, were ruled out and NLUTD was assessed by ultrasound and video-urodynamics, respectively. After having signed the informed consent form, patients were randomized between two groups and received either a standard prophylaxis alone or, in addition, classical homeopathic treatment. As there is no generally accepted standard prophylaxis for UTI, we used the standard prophylaxis applied in our hospital as a standard for this study. It comprised urine acidification with either L-methionine, 3 × 500 mg, or cider vinegar, one teaspoon in 1 glass of water, thrice daily, and cranberry extracts. In patients with recurrent *E. coli* UTI, oral immunotherapy with a commercially available preparation of lyophilized *E. coli* was added. Homeopathic treatment was provided by an experienced, certified homeopath. Classical homeopathy, consisting of treatment with a single substance in high potencies (potencies in which no molecule of the original substance can be traced), was used.⁷ The choice of the homeopathic remedy was based on a case-taking (meticulous medical history) by the homeopath, including the actual bladder management. The study duration was 12 months.

UTI were defined, in accordance with the most recent guidelines^{8,9} as the combination of bacteriuria, leucocyturia, and clinical symptoms. Symptoms were assessed with a previously published data set used by the International Spinal Cord Injury Society for defining UTI,⁸ urinalysis was performed by dipstick testing. As primary outcome measure, we compared the number of UTI reported by the participants during the study period (12 months) with the number of UTI/year before the study. The number of UTI/year before the

study was assessed by standardized history taking, which has been utilized and described previously.¹⁰ During the course of the study, patients received dipsticks for urine testing and a questionnaire describing the clinical signs and symptoms of a UTI in SCI patients.⁸ Patients were asked to perform a dipstick test (Swiss Medical Solution AG, Bürun, Switzerland), only if they suffered from symptoms listed on the questionnaire. Each month, patients sent back the UTI questionnaire reporting the symptoms experienced and the dip stick results. If the dipstick test was positive and the reported symptoms conclusive, the incident was rated as a UTI. The reported UTI were used to determine the number of UTI/year during the study. Furthermore at the end of the study, patients were asked retrospectively concerning the number of UTI during the 12 months course of the study (retrospective UTI/year). In order to ensure the coherence with the prescribed prophylaxis, patients reported their current medication for UTI prophylaxis in a questionnaire at the end of each month.

If an acute UTI was diagnosed, initial treatment was based on patients' preference (antibiotics, phytotherapy, or homeopathic remedies). If fever persisted for more than 48 hours and/or symptoms did not resolve after 5 days, antibiotic treatment was established.

As secondary outcome parameters, we evaluated the general health-related quality of life (QoL), using the validated German version of the EuroQol five dimensions questionnaire (EQ-5D), which is validated in German language,¹¹ and the Satisfaction with Life Scale (SWLS). For the LUT-related psychometric properties, the validated German version of the King's Health questionnaire was used.¹² The scores for the different dimensions were calculated as described in the literature.¹³ The attitude towards homeopathy was assessed with a standardized questionnaire and the satisfaction with homeopathic care and with the effects of homeopathic treatment was evaluated with a visual analogue scale (VAS). Although the "Qualiveen" questionnaire (Coloplast, Humlebaek, Denmark) has been validated for the assessment of QoL in patients with NLUTD, we decided not to use this questionnaire for two reasons. First, its domains did not cover exactly the areas we were interested in. Second, in our experience, the return rate of the questionnaire was unsatisfactory.

The study had been approved by the local ethics committee (PB_2016-00054) and was registered on ClinicalTrials.gov. (NCT01477502). All applicable institutional and governmental regulations concerning the ethical use of the data were followed.

Statistical analyses

A sample size of 25 in each group was determined to be sufficient to detect a 25% difference in the number of UTI/year between the two groups (clinically relevant difference) in the presence of a 30% variance with a power of 80% and a significance level of 5%.

The group allocation was blinded for the statistical analyses. The median and 95% confidence intervals (CI) or proportions were calculated. The effects of treatment (homeopathy or control) and time (pre- / post-treatment) on the number of UTI/year and the secondary outcome parameters were investigated using the method described by Brunner *et al.*¹⁴ for the nonparametric (rank-based) analysis of longitudinal data in factorial designs. The Wilcoxon signed-rank test and the Wilcoxon rank-sum test were used to investigate the differences between the time points and the groups at the specific time points, respectively. Differences in proportions between the groups were tested using Fisher's exact test. The statistical analyses were performed using the R software environment (version 3.3.0, Copyright 2016, The R Foundation for Statistical Computing) and the package „nparLD". A p-value of < 0.05 was considered significant.

Results

From 12/2011 to 06/2015, a total of 46 patients provided written informed consent. The recruitment was stopped before the full number of study participants was enrolled, because the majority of potential study participants refused written informed consent because they did not want to be randomized to the control group. The recruitment was therefore closed after ten patients from the control group had completed the study. Consequently, treatment allocation by randomization was abandoned.

Four participants of the control and two participants of the homeopathy group did not provide any data (questionnaires were not returned). During the course

of the study, three and two patients in the control and homeopathy group, respectively, terminated study participation. The data of these study participants were excluded from analysis. Thus, the data of 35 individuals were evaluated (control group 10, homeopathy group 25). There were no significant differences in the characteristics of the study participants between the two groups (Table 1).

Bladder management

19 patients (76%) in the homeopathy group and 8 patients (80%) in the control group performed intermittent catheterization (IC), whereas the remaining patients used either reflex micturition or (2 patients in the homeopathy group) a suprapubic catheter (table 1). In all patients, bladder function was assessed urodynamically and treated appropriately prior to inclusion in the study. None of the patients performing IC demonstrated significant detrusor hyperactivity, the patients with reflex micturition voided with a leak point pressure below 40 cm H₂O.

Homeopathic remedies

As homeopathy aims at treating the individual person, not a certain disease or bacteria, medication was chosen individually. Consequently, not a single, but several different remedies were used. All remedies were used as liquids in high potencies (LM-potency).¹⁵ In the 16 men receiving homeopathic treatment, 6 different remedies were used (Staphysagria, Nux-vomica, Lycopodium clavatum, Hypericum, Sulphur and Acidum nitricum) with Staphysagria and Nux-vomica being the most frequently used medications. In the 9 female participants, more and different remedies were used (Causticum, Staphysagria, Medorrhinum, Nux-vomica, Sulphur, Sepia, Lycopodium clavatum Thuja, Silicea und Kalium- carbonicum), and the medication had to be changed more frequently within the course of the study.

Table 1 The characteristics of the evaluated individuals.

		Control	Homeopathy	P
Sex (n / %)	women	3 / 30%	9 / 36%	0.9
	men	7 / 70%	16 / 64%	
Age (years)		47 (37-73)	47 (22-71)	0.3
Duration SCI (years)		23.9 (3.6-49.9)	13.8 (1.4-45.0)	0.1
Bladder evacuation	IC	8 / 80%	19 / 76%	0.9
	SPC	0 / 0%	2 / 8%	
	reflex	2 / 20%	4 / 16%	

The data are presented as the median and the range where appropriate. SCI, spinal cord injury; IC, intermittent catheterization; SPC, suprapubic catheterization; Reflex = triggered reflex voiding; Electrostimulation = sacral anterior root stimulation or sacral neuromodulation.

Urinary tract infections

The treatment had a significant ($P < 0.0001$) effect on the number of UTI/year. In the homeopathy group, the number of UTI/year decreased significantly from, both when considering the number of UTI/year that was retrospectively collected at the end of the study (from 9 UTI/year to 2 UTI/year, $P < 0.001$), and in the prospective assessment (from 9 UTI/year to 6 UTI/year, $P = 0.008$). The pre-treatment (i.e. baseline) number of UTI/year was significantly ($P = 0.001$) lower in the control (3 UTI/year, 2-5 UTI/year) compared to the homeopathy group, and there was no change in the number of UTI/year, neither over time (3 UTI/year, 1-7 UTI/year; $P = 0.9$) nor considering the retrospectively collected data (table 2).

Medication for prophylaxis of UTI

The most prophylactic treatment included phytotherapy (cranberries) or urine acidification. Prophylactic measures remained unchanged during the study period in all patients

QoL measures

Neither the treatment ($P > 0.9$) nor the time ($P > 0.3$) had a significant effect on the general QoL measures used (EQ-5D, SWLS). The treatment had a significant effect on three domains of the KHQ: incontinence impact ($P = 0.038$), social limitations ($P = 0.022$) and emotional problems ($P = 0.007$). Furthermore, the time had a significant ($P = 0.001$) effect on the domain incontinence impact. Based on these results, post-hoc analyses have been performed. In the homeopathy group, there was a significant ($P = 0.035$) improvement in the domain incontinence impact from pre- to post-treatment. In control group, the scores in the domains social limitations and emotional problems were significantly ($P \leq 0.017$) lower (i.e. limitations and problems less severe) compared to the homeopathy group.

Attitude towards homeopathy

The attitude toward homeopathy was a median 5 (95% CI 4-6) (i.e. positive) out of a maximum of 6 (i.e. very

positive) and did not change significantly ($P = 0.23$) over time. The median VAS for the satisfaction with the homeopathic care and the effects of the homeopathic treatment were 90 (95% CI 90-100) and 77.5 (95% CI 50-90), respectively.

Discussion

UTI persists to be one of the most difficult complications to diagnose, treat and prevent in patients with NLUTD. Numerous guidelines point out that asymptomatic bacteriuria should not be treated, and there is broad consensus that UTI should be treated with narrow spectrum antibiotics, if possible, for the shortest duration that is clinically safe.⁵ Recommendations for UTI prevention, however, are less clear-cut, and currently, no evidence-based recommendation exist.⁹ Our study is the first prospective evaluation of homeopathic treatment for the prevention of UTI in patients with SCI. According to our results, homeopathic treatment led to a significant and clinically relevant reduction of UTI, whereas the UTI rate in a control group remained unchanged. The clinical relevance of the improvement is mirrored by the satisfaction of the participants with homeopathic care.

A major cause for the current lack of successful preventive measures for UTI is the multitude of factors contributing to its pathogenesis. Besides impaired bladder function and morphologic causes, e.g. stones, the bladder evacuation method is the main predictor for symptomatic UTIs in individuals with NLUTD. Transurethral catheters showed the highest odds of symptomatic UTI.¹⁰ Furthermore, SCI-related changes in host response may also be responsible for the increased risk for UTI in this group of patients. It has been demonstrated that SCI induces an immune deficiency syndrome that is sufficient to propagate clinical relevant infections in these patients.¹⁶

Only a minority of the underlying causes can be treated effectively. Therefore, if bladder management has been optimized and morphologic reasons for UTI have been removed, prophylaxis resorts to medical or procedural

Table 2 Urinary tract infections.

	Homeopathy (n = 25)	Control (n = 10)
UTI pre study/year (medical history)	9	3
UTI end of study (medical history)	2	3
UTI end of study (questionnaire)	6	3
Difference UTI pre-post (medical history)	$P < 0.001$	n.s.
Difference UTI pre-post (questionnaire)	$P = 0.008$	n.s.

UTI, urinary tract infections; Pre = before the beginning of the study; Post = at the end of the study.

interventions. Antibiotic prophylaxis is not recommended due to the lack of efficacy and the increase in bacterial resistance.⁵ The use of cranberry products is also not supported by the results of prospective studies.¹⁷ Insufficient evidence exists for the effectiveness of urine acidification,¹⁸ or immunostimulation.¹⁹ Bacterial interference seems to be a promising option, but sufficiently powered trials are lacking.²⁰

Although the exact mode of action needs to be further elucidated, homeopathy is based on stimulating autoregulatory and self-healing processes.²¹ The homeostasis of any complex system is based on the equilibrium of antagonistic activities of different substances or different receptors for the same substance. This homeostasis may become chronically disrupted. To reverse this condition, it may be necessary to trigger an endogenous therapeutic reaction with a specific pathogenic substance contained in the small doses of a homeopathic remedy.²² The hypotheses regarding the action mechanisms of highly diluted/dynamized solutions include sensitivity to bioelectromagnetic information, participation of water chains in signaling and regulation of bifurcation points of systemic networks.²³

As the high incidence of UTI in patients with SCI seems to be caused not merely by the presence of aggressive bacteria, but also by an impaired host defense, the stimulation of these processes may be a possible mode of action of homeopathic prophylaxis.

Whereas treatment and control group were not statistically different in the demographic parameters, there was a significance difference in the number of UTI/year at the beginning of the study. The number of UTI at the end of the study was not statistically different between the two groups, but it remained unchanged in the control group whereas it was significantly reduced in the treatment group. One may speculate that a high UTI frequency may reflect a more severe immune dysfunction due to SCI, and the autoregulatory processes stimulated by homeopathy were responsible for the reduction of UTI. However, as it is not possible to reliably quantify immune dysfunction today,¹⁶ this hypothesis cannot be proven. Furthermore, as there are multiple possible reasons for UTI development in persons with SCI, it is not possible to determine if this difference had an effect on the results.

In our study, we used classical homeopathy. This term comprises that a single remedy was selected based on the totality of signs and symptoms of the individual patient.⁷ Thus, no general remedy for UTI exists, but each patient was treated with the drug most suitable for him. The fact that many different homeopathic

remedies have been used in this study underlines the importance of individual counselling and treatment.

As mentioned before, ultra-high potencies were used, in which no molecule of the original substance can be traced. Despite this fact, reproducible effects of these drugs have been demonstrated in numerous studies,²⁴ including case series of UTI prevention in SCI patients.⁶

SCI leads to a multitude of secondary health and social problems that interfere with the QoL. Not surprisingly, general QoL is worse in patients with chronic SCI than in the general population.²⁵ The results of the general QoL questionnaire reflect these findings. Although UTI can significantly impair the QoL of the affected patients, it was not very likely that UTI treatment alone would have improved general QoL.

The KHQ is a validated questionnaire that has been used in patients with NLUTD and has demonstrated to reliably document the impact of urinary dysfunctions, including UTI, on QoL.²⁶ Our results demonstrated that homeopathic treatment led to a significant and improvement of the incontinence impact, one domain of the KHQ. One can only speculate if this is due to the reduction in UTI or if homeopathy has an additional impact on QoL.

Although this is the first study to prospectively evaluate the usefulness of homeopathic treatment for the prevention of UTI in SCI patients, it has some limitations. First, as we were not able to complete recruitment for the control group, the study is underpowered regarding a statistically sound comparison between the two groups. Nevertheless, it could be demonstrated that homeopathy had an impact on UTI frequency, whereas standard prophylaxis had not. Secondly, it may be criticized that the study was not blinded. Previous studies that used a randomized, placebo-controlled setting²⁷ attributed the clinical improvements to the homeopathic consultation, not to the remedy. As we wanted to assess homeopathy as a therapeutic method and not the efficacy of a single homeopathic remedy, we decided not to include an experimental group with homeopathic consultation and placebo treatment. Thirdly, it was striking that the number of UTI documented prospectively by dipstick and questionnaire was different from the UTI rate reported by the patients retrospectively. One possible explanation is the high incidence of bacteriuria in SCI patients,^{2,4} which leads to a positive dipstick test in the majority of patients. As the symptoms of the questionnaire were not specific for UTI alone, but may also be caused by other pathologies, e.g. bowel dysfunction, pressure ulcers, or other infections, a substantial number of patients may have had other underlying causes for the symptoms. Thus, in a

follow-up study, all patients that present with the suspicion of a UTI should be examined clinically in order to exclude other reasons. Furthermore, we cannot exclude that the fact that we did not change prophylactic measures in the study arm had some influence on the results, but as we aimed at comparing the value of an adjunctive homeopathic treatment, any changes in the basic prophylactic treatment would have made a comparison between the groups more difficult.

In our setting, treatment with classical homeopathy was beneficial regarding reduction of UTI in SCI patients. To achieve satisfying results, well-trained homeopaths with experience in the treatment of SCI patients are needed. As homeopathy relies on the signs and symptoms of an individual, and SCI leads to a loss of sensory and motor function, the number of symptoms is limited and often unspecific. The experience our homeopaths gathered from a permanent consult service in our center may have contributed to the positive results.

Conclusion

Our prospective study demonstrates that adjunctive homeopathic treatment lead to a significant decrease of UTI in patients with SCI although the statistical analysis were limited by not achieving the recruitment numbers. Satisfaction with the treatment was high. Therefore, classical homeopathy could be considered in SCI patients with recurrent UTI.

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Disclaimer statements

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Declaration of Interest The authors declare that they have no conflict of interest.

Conflicts of interest The authors declare no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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