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Original Article

Transcutaneous tibial nerve stimulation combined mirabegron therapy significantly improves benign prostatic hyperplasia and overactive bladder: a prospective randomized controlled trial

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Abstract: Objective: To evaluate the efficacy and safety of combining transcutaneous tibial nerve stimulation (TTNS) with mirabegron for treating benign prostatic hyperplasia (BPH) and overactive bladder (OAB) in male patients. Patients and methods: A total of 62 participants were prospectively randomized into two cohorts: the control group to receive oral mirabegron (50 mg daily), while the combination group to receive combined TTNS and mirabegron. The primary outcomes were changes in voiding frequency and urgency severity, assessed using a 3-day voiding diary. Secondary outcomes included the International Prostate Symptom Score (IPSS), the Overactive Bladder Questionnaire (OAB-q), Health-Related Quality of Life (HRQoL) score, symptom severity, and urodynamic parameters at weeks 6 and 12. Results: Of the 62 participants, 30 received TTNS along with mirabegron, and 32 received mirabegron alone. At both timepoints, the combination group demonstrated significantly greater reductions in lower urinary tract symptoms (LUTS), including urgency, increased urinary frequency, and incontinence episodes, than the control group ($P < 0.05$). Furthermore, the combination group exhibited significantly higher OAB-q HRQoL scores and lower IPSS, OAB-q symptom bother, and Overactive Bladder Symptom Score (OABSS) values (all $P < 0.05$). No substantial differences were observed in drug-related adverse events or urodynamic parameters between groups ($P > 0.05$). Conclusion: Combined TTNS and mirabegron therapy significantly improved BPH and OAB symptoms and enhanced quality of life, without increasing adverse effects compared to mirabegron monotherapy.

Keywords: Transcutaneous tibial nerve stimulation, overactive bladder, benign prostatic hyperplasia, mirabegron

Introduction

Benign prostatic hyperplasia (BPH) is the most common cause of urinary disorder in males over the age of 50 [1]. Hyperplasia of prostatic stromal and glandular tissue results in prostate enlargement, which compresses the urethra, obstructs the bladder outlet, and causes lower urinary tract symptom (LUTS) [2]. These symptoms typically include increased urinary frequency, urgency, nocturia, and difficulty urinating [3]. The pathogenesis of BPH primarily involves age-related changes of androgen metabolism, abnormal cell proliferation and apoptosis, altered growth factors and inflammatory cells, and abnormalities in neurotransmitters and genetic risk factor [4]. Epidemical data indicate a positive correlation between BPH prevalence and age, with the condition commonly affecting men over the age of 40 [5]. Approximately 50% of men over 60 and 83% of men over 80 experience prostatic enlargement [6].

BPH-associated LUTS are typically divided into three categories: storage, voiding, and post-urination symptoms. Storage symptoms, including

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increased urinary frequency, urgency, nocturia, and urgency urinary incontinence (UUI), greatly affect patients' quality of life and are thus a major concern [7, 8]. Nocturia affects 40%-60% of patients, leading to sleep disturbances, daytime fatigue, cognitive decline, and an increase risk of falls in people over 60 years old [9, 10]. Moreover, urgency and UUI are associated with increased social withdrawal, anxiety, depression, and occupational limitations, with rates significantly higher than in healthy individuals [11]. The International Prostate Symptom Score (IPSS) shows a 62% reduction in quality of life for those with moderate to severe symptoms compared to asymptomatic ones [12].

Current therapeutic strategies primarily aim to modulate bladder sensation and inhibit detrusor overactivity. Muscarinic receptor antagonists, such as solifenacin, and β3-adrenergic receptor agonists, such as mirabegron, suppress involuntary contractions and promote bladder relaxation [13]. However, 30%-40% of patients report suboptimal responses and may experience side effects with long-term use, including dry mouth and urinary retention. Consequently, non-pharmacological interventions, such as transcutaneous tibial nerve stimulation (TTNS), have gained attention. TTNS stimulates the sacral nerve reflex arc (S2-S4) via the ankle, providing a non-invasive alternative to traditional sacral nerve modulation without the associated infection risks [14]. Preliminary studies have reported up to a 45% reduction in urgency episodes with TTNS [15].

Given the limitations of current treatment options, combination therapy emerges as a promising strategy for enhancing therapeutic efficacy. Evidence suggests that TTNS reduces excessive bladder afferent signaling and mirabegron targets the β3 receptors located on detrusor muscle cells, potentially creating a synergistic effect [16]. To test this hypothesis, we designed a prospective randomized trial to evaluate the combined efficacy of TTNS and mirabegron in patients with BPH and overactive bladder (OAB). This method aims to refine individualized treatment protocols and provide an evidence-based framework to incorporate neuormodulation with pharmacotherapy.

Patients and methods

Study design

This was a prospective randomized clinical trial conducted between January and December 2023, registered on 13/02/2022 in Chinese Clinical Trial Register (ChiCTR2200056752). The study was approved by the Clinical Research Ethics Committee of the Affiliated Jiangning Hospital of Nanjing Medical University (Approval number: 202200137). All procedures followed the ethical standards of our institution and adhered to the 1964 Helsinki Declaration. Informed consent was obtained from all participants after fully informing them of the study's purpose, procedures, risks, and potential benefits.

Participants

Inclusion and exclusion criteria

Participants were eligible for inclusion if they met the following criteria: 1. Male participants > 50, diagnosis of OAB and BPH; 2. Presence of OAB symptoms, including increased frequency and urgency for at least 3 months, with or without incontinence; 3. An IPSS score of ≥ 8, indicating 8 or more micturitions per day or 2 or more urgency episodes per day, as recorded in a voiding diary; 4. Urgency episodes rated 3 or 4 on the urgency scale for any 3 consecutive days recorded in the diary.

Participants were excluded based on the following criteria: 1. Post-void residual (PVR) volume > 200 mL; urinary tract infection (UTI); hematuria; chronic urinary tract infection; stress urinary incontinence; 2. Use of anticholinergic or β-3 adrenergic agonist use (within 4 weeks) or previous botulinum toxin (Botox) injection or chronic elctrostimulation within the last 12 months; 3. History of any lower urinary tract surgery, intermittent catheterization, and any cancer of the lower urinary tract or prostate, including neurogenic bladder; 4. Any of the following conditions: urethral stricture, bladder neck stenosis, stones, or diagnosed diabetes.

All participants underwent a comprehensive pre-treatment evaluation, which included gathering personal and medical histories, a physical examination, laboratory tests, and imaging studies. A total of 70 eligible male participants

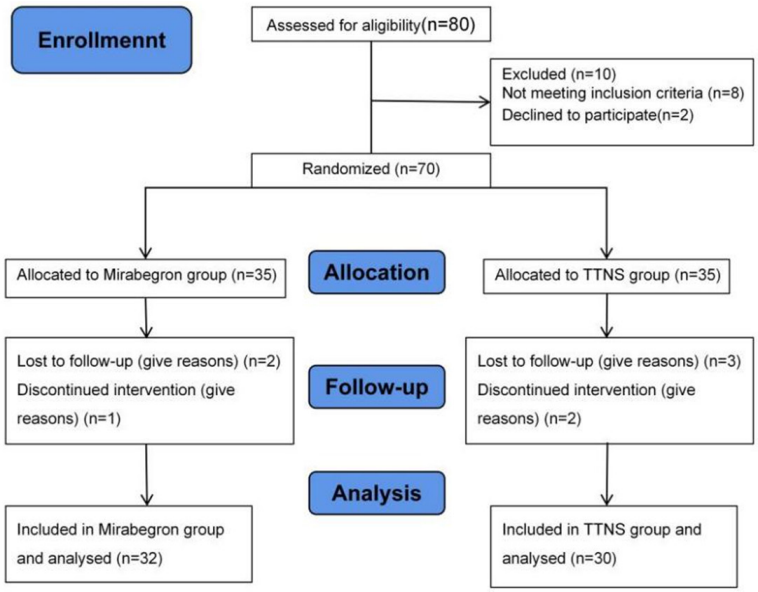

Figure 1. Flowchart for case selection.

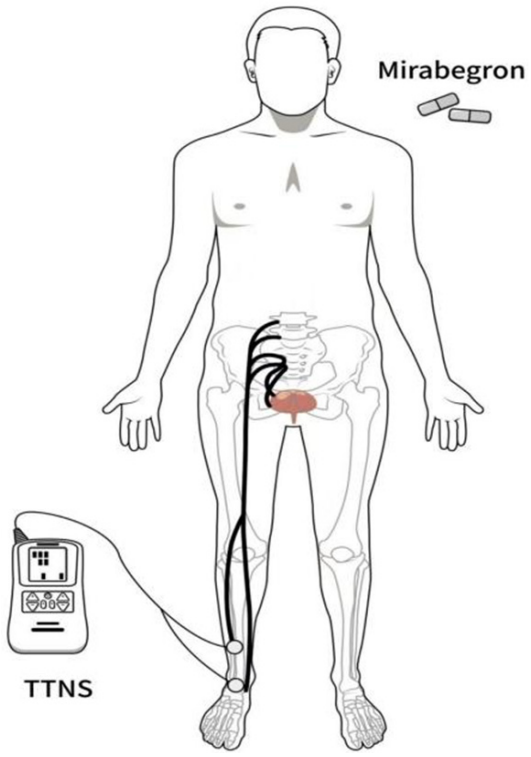

Figure 2. TTNS combined with Mirabegron (TTNS modulates bladder function through activation of the tibial nerve). TTNS, transcutaneous tibial nerve stimulation.

provided informed consent (**Figure 1**). Using a computer-generated randomization table, the participants were randomized (1:1) into two groups for a 12-week treatment protocol. The control group received 50 mg of mirabegron daily, while the combination group received the same daily dose of mirabegron and twice-weekly TTNS.

Procedures

In the combination group, participants received 50 mg of mirabegron daily and underwent TTNS twice weekly for 12 weeks, delivered using the UroCure neurostimulator (Shanghai Kangduo Medical Equipment Co., Ltd., Shanghai, China). Before treatment, all participants were given a detailed explanation of the procedure. Electrical stimulation was applied via two self-adhesive surface electrodes, each approximately 3 cm in diameter. Correct placement was confirmed by eliciting the bunion reflex: one electrode was positioned 2 cm posterior to the medial malleolus, and the other approximately 10 cm above (**Figure 2**). Stimulation parameters included a frequency of 10 Hz, pulse width of 200 μs, and a duration of 30 minutes, with current intensity individually adjusted (0-50 mA). A single physician administered all ATTNS sessions throughout the study, ensuring procedural consistency. Participants were instructed to maintain a weekly 3-day voiding diary, documenting fluid intake, urine output, urgency episodes, incontinence events, voiding frequency, and incontinence severity. They were also advised to continue any medications unrelated to OAB management.

In the control group, participants received 50 mg of mirabegron daily for 12 weeks and completed the same 3-day voiding diary protocol.

At baseline, week 6, and week 12, validated questionnaires were distributed, and objective measurements, including maximum urine flow rate (Qmax) and PVR volume, were recorded. Participants were encouraged to report any treatment-related concerns. If discomfort persisted or outcomes remained suboptimal at the

end of the follow-up, additional therapeutic options were considered.

Outcome measures

Primary outcomes

Primary outcomes were evaluated using a 3-day voiding diary, which recorded daily urinary frequency, urgency, and UUI episodes.

Secondary outcomes

1. The Overactive Bladder Questionnaire (OAB-q) to assess the level of symptoms (with a score of 0 indicating no symptoms and 100 representing the most severe symptoms); A health-related quality of life (HRQoL) score, with a score of 100 indicating optimal quality of life and 0 indicating poor quality of life. 2. The Overactive Bladder Symptom Score (OABSS), which consists of seven items scored from 0 (asymptomatically) to 28 (most symptoms). 3. The IPSS, which classifies the severity of BPH symptoms: 0-7 (mild), 8-19 (moderate) or 20-35 (severe). 4. Adverse Events and urodynamic parameters.

Sample size estimation

A prior study reported that tibial nerve stimulation significantly reduced the number of incontinence episodes from 4.1 ± 1.8 to 1.8 ± 1.1 in the percutaneous tibial nerve stimulation (PTNS) group, compared to a decrease from 4.2 ± 2.1 to 3.8 ± 1.6 in the control group [17]. Based on these findings, a sample size of 18 participants per group was required to detect a 50% reduction in daily incontinence episodes with 95% confidence ($\alpha = 0.05$) and 80% power ($\beta = 0.20$), accounting for a 10% dropout rate. Therefore, a total of 80 male participants were targeted to accommodate potential withdrawals. Random allocation was performed in a 1:1 ratio.

Statistical analysis

Statistical analysis was performed using SPSS software for windows (version 22. 0, IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± SD and tested using Student's t test. Categorical variables were expressed as rate or percentages and compared using Chi-square test. Statistical significance was set at $P < 0.05$.

All statistical analyses were performed by a statistician with expertise in biomedical research. For comparisons involving multiple groups, pairwise comparisons were conducted using repeated-measures ANOVA with Bonferroni post hoc tests following a one-way ANOVA. Appropriate statistical tests were selected based on the distribution of the data and the study design.

Results

Patient demographics and baseline characteristics

Seventy patients were enrolled and randomized equally into two groups: 35 received mirabegron (control group), and 35 received combination therapy with TTNS and mirabegron (combination group). During the treatment and follow-up period, eight participants withdrew, leaving 62 patients for the final analysis of primary outcomes.

Table 1 presents the demographic and baseline characteristics, showing no significant differences between the two groups regarding age, BMI, symptom duration, or medical history. Subgroup analysis by OAB subtype also revealed comparable distributions between groups.

Primary outcomes: voiding diary data

Bladder diary data are shown in **Table 2**. At baseline, no significant differences were observed between groups in frequency of micturition, urgency episodes, or UUI episodes (all $P > 0.05$). By weeks 6 and 12, the combination group showed significantly greater reductions across all three parameters compared with the control group (all $P < 0.05$).

Secondary outcomes: symptom scores and adverse events

As presented in **Table 3**, compared to the control group, patients in the combination group showed significantly greater improvements in IPSS, OAB-q symptom scores, OAB-q HRQoL, and OABSS at both 6 and 12 weeks (all $P < 0.05$). There were no significant differences in the incidence of adverse events or in urodynamic parameters between groups (all $P > 0.05$) (**Table 4**).

Table 1. Comparisons of baseline demographics and clinical characteristics between the two groups

Variables	Control group (n = 32)	Combination group (n = 30)	t/x^2	*P*-value
Age (years)	61.2 ± 2.3	60.8 ± 2.6	0.66	0.412
BMI (kg/m^2)	24.74 ± 3.95	24.19 ± 3.83	0.65	0.258
Duration of symptoms (months)	29.81 ± 3.54	30.27 ± 3.21	0.54	0.538
Hypertension history				
No	20 (62.5)	21 (70)		-
Yes	12 (37.5)	9 (30)	0.49	0.483
Diabetes history				
No	26 (81.3)	25 (83.3)		-
Yes	6 (18.7)	5 (16.7)	0.06	0.812
Constipation				
No	27 (84.4)	22 (73.3)		-
Yes	5 (15.6)	8 (26.7)	1.22	0.237
Smoker				
No	2 (6.2)	4 (13.3)		-
Yes	30 (93.8)	26 (86.7)	0.95	0.348
Hyperlipidemia				
No	23 (71.9)	22 (73.3)		-
Yes	9 (28.1)	8 (26.7)	0.02	0.892
Type of OAB				
Mixed urinary incontinence	21 (65.6)	20 (66.7)		-
OAB-wet	9 (28.1)	8 (26.7)		-
OAB-dry	2 (6.3)	2 (6.6)	0.10	0.953

BMI, body mass index; SD, standard deviation; OAB, overactive bladder.

Table 2. Comparison of OAB-S clinical symptoms between the two groups

Variable	Control group (n = 32)	Combination group (n = 30)	t	*p*-value
Micturitions				
Baseline	14.81 ± 4.05	15.50 ± 3.50	-0.68	0.250
6 weeks	12.02 ± 2.80*	9.04 ± 1.82*	4.76	0.010
12 weeks	11.50 ± 3.21*,#	7.16 ± 2.31*,#	6.09	< 0.001
Episodes of urgency				
Baseline	5.54 ± 1.73	6.20 ± 2.10	-1.36	0.400
6 weeks	4.80 ± 1.41*	3.10 ± 1.21*	4.39	0.018
12 weeks	4.31 ± 1.62*	1.54 ± 0.61*,#	8.45	< 0.001
Episodes of UUI				
Baseline	3.10 ± 1.42	3.32 ± 1.54	-0.58	0.320
6 weeks	2.53 ± 1.13*	1.56 ± 0.52*	4.12	0.015
12 weeks	2.11 ± 0.95*	0.81 ± 0.31*,#	6.90	< 0.001

*P < 0.05, vs baseline in same group; #P < 0.05 vs week 6 in same group. OAB-S, overactive bladder syndrome; UUI, urgency urinary incontinence.

Discussion

The study innovatively investigated the clinical efficacy and safety of transcutaneous tibial nerve stimulation (TTNS) combined with mirabegron in men with benign prostatic hyperplasia (BPH) and overactive bladder (OAB). Our results showed that combination therapy produced significantly greater improvements in urinary symptoms compared to mirabegron monotherapy, without increasing adverse effects. These findings imply that TTNS combined with mirabegron may represent a promising treatment option for men suffering from BPH and OAB, particularly for those who fail to adequately react to ordinary therapies.

Recently studies have increasingly highlighted the role of TTNS in OAB management. For example, Vecchioli et al. [18] reported that TTNS combined with bladder training (BT) improved outcomes in women with idiopathic OAB, show-

Table 3. Comparisons of IPSS score and OAB symptom severity score between the two groups

Variables	Control group (n = 32)	Combination group (n = 30)	*P*-value	RM-ANOVA
IPSS score				
Baseline	21.02 ± 1.84	20.51 ± 2.16	0.475	Time: F (2, 120) = 68.45, P < 0.001
6 weeks	16.51 ± 2.92*	12.03 ± 2.32*	0.018	Group × Time: F (2, 120) = 35.72, P < 0.001
12 weeks	13.83 ± 3.25*	8.55 ± 2.36*,#	< 0.001	
OAB-q symptom score				
Baseline	58.54 ± 3.27	56.07 ± 3.51	0.198	Time: F (2, 120) = 75.32, P < 0.001
6 weeks	42.81 ± 3.83*	36.53 ± 3.06*	0.030	Group × Time: F (2, 120) = 42.18, P < 0.001
12 weeks	30.54 ± 3.46*	23.52 ± 3.34*,#	0.006	
OAB-q HRQoL score				
Baseline	45.41 ± 2.76	46.14 ± 2.95	0.362	Time: F (2, 120) = 82.16, P < 0.001
6 weeks	63.23 ± 4.76*	70.36 ± 4.12*	0.048	Group × Time: F (2, 120) = 38.45, P < 0.001
12 weeks	76.67 ± 5.45*	83.52 ± 4.37*,#	< 0.001	
OABSS				
Baseline	14.51 ± 1.78	13.81 ± 1.45	0.540	Time: F (2, 120) = 71.89, P < 0.001
6 weeks	9.01 ± 2.17*	7.34 ± 2.26*	0.017	Group × Time: F (2, 120) = 40.13, P < 0.001
12 weeks	5. 05 ± 1. 85*	3. 54 ± 1. 42*,#	0.002	

*P < 0.05, vs baseline in same group; #P < 0.05 vs week 6 in same group. IPSS International, Prostate Symptom Score; OAB-q, overactive bladder questionnaire; HRQol, health-related quality of life; OABSS, overactive bladder syndrome score.

Table 4. Comparison of urodynamic parameters and complications

Variable	Control group (n = 32)	Combination group (n = 30)	*P*-value	RM-ANOVA
Maximum flow rate (Qmax) (ml/sec)				
Baseline	13.92 ± 2.57	14.28 ± 2.31	0.631	Time: F (2, 120) = 1.24, P = 0.292
6 weeks	14.83 ± 2.06	15.14 ± 2.13	0.572	Group × Time: F (2, 120) = 0.87, P = 0.421
12 weeks	15.24 ± 2.43	15.63 ± 2.21	0.514	
Post-voided residual (PVR) (ml)				
Baseline	48.54 ± 10.18	50.27 ± 11.35	0.541	Time: F (2, 120) = 1.05, P = 0.353
6 weeks	44.72 ± 9.54	45.91 ± 10.28	0.640	Group × Time: F (2, 120) = 0.92, P = 0.402
12 weeks	42.36 ± 8.81	43.81 ± 9.17	0.523	
Related adverse events				0.911
Dry mouth	2	1	-	
Tachycardia	0	1	-	
Hypertension	1	1	-	
Constipation	1	0	-	
Dizziness	1	2	-	
Urinary retention	0	0	-	

ing better patient satisfaction and cost-effectiveness compared to PTNS. Our findings are consistent with these results, as TTNS and mirabegron provided superior improvements in symptom scores and patient-reported outcomes compared to drug therapy alone. However, their study focused exclusively on women. Similarly, Liao et al. [19] carried out a multi-center trial on a wearable TTNS device, demonstrating a notable decline in voiding frequency after 4 weeks of treatment. In our study, a more pronounced improvement was noted in our study after 6 weeks, with the OABSS decreasing by 6.5 points. This finding suggests that extending the treatment duration may yield more substantial clinical benefits.

Moreover, Xu et al. [20] and Zhao et al. [21] both confirmed that the combined use of TTNS with mirabegron in female OAB patients showed better outcomes than monotherapy, which is consistent with our findings in male patients. Stanley et al. [22] also reported that the addition of a β-3 agonist to TTNS improved both objective and subjective outcomes in patients with refractory urgency urinary incontinence, further supporting the synergistic potential of combining TTNS with pharmacotherapy. Our study extends these observations to the male population, demonstrating that the TTNS combined with mirabegron provides comparable or even greater improvements in symptom control.

Regarding urodynamic parameters, Vecchioli et al. [18] reported that TTNS alone increased the maximum urinary flow rate (Qmax) by 1.5-2.0 mL/s in OAB patients, whereas in our study, the Qmax increased by 1.4 mL/s following TTNS plus mirabegron therapy. This result is in line with Zhao et al. [21], who also observed greater improvement in Qmax with combination therapy. These findings suggest that the beneficial effects of TTNS and mirabegron may be additive or even synergistic, possibly attributed to complementary mechanisms: TTNS modulates sacral reflexes and suppresses bladder hyperactivity, while mirabegron relaxes the detrusor muscle and increases bladder capacity [23].

TTNS, as a non-invasive neuromodulation technique, has shown promise in the management of OAB, particularly in patients who are not suitable for or unresponsive to pharmacotherapy. Necmettin Yildiz and Merve Arbay Celtek [24] reported that TTNS improved quality of life and clinical outcomes in drug-native and drug-resistant women, further supporting its potential utility in diverse patient populations. Our study extend this evidence to men with BPH and OAB, adding to the growing body of evidence supporting its broader application.

As for safety, there was no significant increase in adverse events when compared to mirabegron monotherapy, and the safety profile of TTNS was favorable. Unlike the well-known side effects of anticholinergics such as dry mouth and constipation, TTNS offers a safe, patient-friendly, and non-invasive option [25]. Its portability and ease of use also suggest better long-term adherence compared to PTNS, which is more invasive and less convenient.

Despite these encouraging results, several limitations should be acknowledged. First, this was a single-center study with relatively small sample size and short follow-up period, which may limit the generalizability of the findings. Second, the absence of blank control group preclude the placebo effect. Third, the long-term efficacy and sustainability of TTNS combined with mirabegron remain unclear. Future large-scale, multicenter randomized controlled trials with extended follow-up are needed to validate these findings and to better understand the long-term benefits and safety of combination therapy.

Conclusion

In short, TTNS plus mirabegron is a safe and effective noninvasive treatment option for men with BPH and OAB. This combination significantly alleviates urinary symptoms and improves health-related quality of life through complementary neuromodulatory and pharmacological mechanisms. Such an approach may be particularly valuable for patients who have shown inadequate response to conventional therapies. Nevertheless, further larger-scale, multicenter studies with extended follow-up are warranted to confirm the long-term benefits, clarify underlying mechanisms, and establish standardized protocols for the integration of TTNS with pharmacotherapy in clinical practice.

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Disclosure of conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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