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SHORT REPORT

Differential Effects of Cycling Exercise on Pain Types in Patients with Early Parkinson's Disease: A Subgroup Analysis of a Randomized Pilot Trial

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Background: Pain in Parkinson's disease (PD) is common and arises from both central and peripheral mechanisms, manifesting as distinct subtypes. While physical exercise is considered one of the nonpharmacological treatments for managing pain in PD, it remains unknown how the effects of exercise differ depending on the type of pain.

Objective: To explore the differential effects of cycling exercise on various pain subtypes in patients with early PD.

Methods: In the randomized controlled pilot trial, 22 participants with early PD were initially assigned to the cycling exercise group and 11 to the control group. This exploratory subgroup analysis included 25 patients after applying the inclusion/exclusion criteria, comprising 16 cycling exercise participants and 9 controls. The exercise intervention consisted of 40–60 minutes of cycling, three sessions weekly, for 24 weeks. Pain subtypes were assessed using the King's PD Pain Scale. Changes in pain severity and newly developed pain were analyzed descriptively.

Results: After 24 weeks, a greater proportion of participants in the cycling group showed improvement in fluctuation-related, nocturnal, and orofacial pain compared with controls. However, musculoskeletal pain newly developed in 40% of cycling participants, compared to 20% in the control group. For other pain subtypes, both groups showed similar patterns in pain severity changes and newly developed pain.

Conclusion: Cycling exercise may alleviate fluctuation-related, nocturnal, and orofacial pain in PD but may also increase the risk of musculoskeletal pain in some cases. These observations warrant further large-scale investigations.

Keywords: Parkinson's disease, cycling, exercise, pain, trial

Introduction

Patients with Parkinson's disease (PD) frequently experience pain during the course of the disease.[1] Previous evidence suggests that pain occurs in approximately 25% of patients with PD in Korea.[2] This non-motor symptom in PD can manifest in various forms, with musculoskeletal pain being the most common subtype.[3] Pain has a negative impact on quality of life in patients with PD,[3] but there is insufficient evidence for the efficacy of both pharmacological and nonpharmacological interventions for pain in these patients.[4]

Physical exercise is considered one of the nonpharmacological treatments for managing pain in PD.[5] Exercise may modulate pain through effects on central nociceptive processing, enhancement of descending inhibitory control, and alterations in neurotransmitter signaling,[5] providing a biologically plausible basis for its potential analgesic effects in PD.

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Because pain subtypes arise from differing pathophysiologic mechanisms,[3] it is reasonable to expect that their therapeutic response patterns may vary. However, whether specific pain subtypes show distinct responses to exercise has not been established. To date, no study has systematically evaluated exercise effects according to pain subtype in PD.

Cycling exercise is the most readily accessible and one of the most well-established aerobic exercises shown to be effective in PD.[6] We recently presented results on the effectiveness of cycling exercise on various non-motor symptoms in patients with PD, in which there was no significant improvement in overall pain severity with exercise.[7] However, the interpretation of those findings was limited by the inclusion of patients without pain and the lack of analyses stratified by pain subtype. In this study, we aimed to explore differential effects of cycling exercise on pain types in PD patients who had pain. We hypothesized that pain subtypes would differ in their responsiveness to cycling exercise.

Methods

Study Design and Participants

This was an exploratory subgroup analysis of a single-center, randomized controlled pilot trial.[7] The study design was approved by the Institutional Review Board of the Inha University Hospital (2022-01-030) and registered at cris.nih.go.kr (KCT0007130). Written informed consent was obtained from all enrolled patients. The methodology and details of the trial are available elsewhere.[7,8] Patients with PD were recruited from the Department of Neurology at Inha University Hospital. PD was diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria. Individuals were eligible if they: (1) were 50–80 years of age; (2) had Hoehn and Yahr stage 1 or 2; (3) had a disease duration of <5 years; (4) engaged in less than the aerobic exercise levels recommended by the American College of Sports Medicine (≥20 minutes of vigorous exercise ≥3 days/week or ≥30 minutes of moderate exercise ≥5 days/week);[9] (5) had been on stable dopaminergic therapy for >3 months; and (6) had a score ≥1 on part I of the Movement Disorder Society–Unified Parkinson's Disease Rating Scale. Exclusion criteria were: (1) neurological, orthopedic, or cardiac comorbidities precluding safe aerobic exercise; (2) a Montreal Cognitive Assessment score <18; (3) current use of antipsychotic medications; or (4) unavailability for >10% of the study period.

Thirty-three patients with PD were randomly allocated to high-intensity interval cycling (60% maximum aerobic power for 30–50 seconds with 1 minute rest intervals, n=11), moderate-intensity continuous cycling (50% peak oxygen consumption, n=11), and usual care (n=11) groups. Randomization was performed at the Inha University Hospital Medical Statistics Support Center using a computer-generated random-number sequence (block size of 3). Allocation was concealed through centralized assignment, and the investigators responsible for enrollment were not aware of upcoming allocations. Both exercise groups received supervised aerobic exercise intervention using a cycle ergometer for 40–60 minutes, three days per week, over a period of 24 weeks. The total duration of aerobic exercise per session increased by 10 minutes every 8 weeks. The detailed exercise protocols are presented in Supplementary Box 1. This 24-week cycling protocol is broadly comparable to that used in the Park-in-Shape study,[10] although the exercise duration per session in our program was longer by up to 30 minutes. The original randomized controlled trial was primarily designed to evaluate the effects of high-intensity interval training on non-motor symptoms in patients with PD. However, the present exploratory analysis focused on the effects of cycling exercise as an exercise modality rather than on exercise intensity or mode. Accordingly, the high-intensity interval cycling and moderate-intensity continuous cycling groups were combined into a cycling exercise group (n=22). The control group was allowed to maintain their daily lives without the exercise intervention.

Pain Assessment

We used the King's Parkinson's Disease Pain Scale (KPPS), which is a reliable and valid self-reported questionnaire to assess pain in PD.[11] It consists of 14 items divided into seven domains: musculoskeletal pain (item 1), chronic body pain (items 2 and 3), fluctuation-related pain (items 4–6), nocturnal pain (items 7 and 8), orofacial pain (items 9–11), discoloration/edema and swelling (items 12 and 13), and radicular pain (item 14). The score for each item is calculated by multiplying intensity (0–3) by frequency (0–4), with a total score ranging from 0 to 144.

Statistical Analysis

Considering the exploratory nature of this study, all analyses were performed using per-protocol principles. The Shapiro–Wilk test was performed to test the normality of the data. Baseline characteristics between the groups were compared using the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. To assess the effect of cycling training according to pain type, changes in pain severity at 24 weeks were classified as aggravation, no change, or improvement. Categories of change were defined using a simple direction-of-change approach rather than predefined numerical cutoffs: change scores were calculated as post-intervention minus pre-intervention values, with negative values indicating improvement, zero indicating no change, and positive values indicating aggravation. In addition, we assessed the proportion of newly developed pain in participants who had no baseline pain in each pain subtype. These proportions were compared descriptively between the exercise and control groups because the number of participants in each subgroup was insufficient for statistical analysis. Two-sided p values < 0.05 indicated statistical significance. All analyses were performed using *R* version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 33 patients with PD were enrolled in this trial. Of these, three cycling exercise participants dropped out during the exercise intervention period (one because of the excessive burden of exercise and the others because of musculoskeletal pain). No injuries or falls occurred during the intervention period. Among the remaining participants, three cycling exercise participants and two controls had no pain as indicated by the KPPS at the baseline visit. Finally, this study included 25 patients with PD, comprising 16 cycling exercise participants and 9 controls. There were no significant differences in demographic and clinical characteristics between the groups (Table 1). Attendance rates during the exercise sessions were 95.4%.

Preintervention Assessment of Pain

There were no significant differences between the cycling exercise and control groups in KPPS total scores or in the subscores for musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, discoloration/

Table 1 Baseline Characteristics of Participants

Variables	Intervention	Control	*p* value
Number of subjects	16	9	–
Age, years	67.0 (60.3–74.8)	65.0 (61.5–72.5)	0.718
Male sex, %	6 (37.5%)	5 (55.6%)	0.434
Age at PD onset, years	63.5 (60.0–72.8)	62.0 (58.0–70.0)	0.846
PD duration, years	2.5 (2.0–4.0)	3.0 (1.5–4.0)	0.846
MDS-UPDRS part 1 score	6.0 (4.0–9.5)	4.0 (2.5–7.5)	0.187
MDS-UPDRS part 2 score	2.5 (1.0–8.0)	5.0 (1.0–7.5)	0.760
MDS-UPDRS part 3 score	19.0 (16.0–27.0)	16.0 (14.0–20.0)	0.251
KPPS total score	8.0 (3.3–16.5)	4.0 (3.5–12.0)	0.637
Musculoskeletal pain presence, %	9 (56.3%)	6 (66.7%)	0.691
Chronic pain presence, %	5 (31.3%)	4 (44.4%)	0.671
Fluctuation-related pain presence, %	3 (18.8%)	3 (33.3%)	0.630
Nocturnal pain presence, %	8 (50.0%)	4 (44.4%)	1.000
Orofacial pain presence, %	4 (25.0%)	3 (33.3%)	1.000
Discoloration, edema/swelling presence, %	2 (12.5%)	2 (22.2%)	0.602
Radicular pain presence, %	8 (50.0%)	6 (66.7%)	0.677

Note: Data are n (%) and the median (interquartile range).
Abbreviations: KPPS, King's Parkinson's Disease Pain Scale; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease.

edema and swelling, and radicular pain (Supplementary Figure 1). The proportion of participants with each pain subtype also did not differ between the groups (Table 1).

Postintervention Assessment of Pain

At 24 weeks, a greater proportion of participants in the cycling group showed improvement in fluctuation-related pain, nocturnal pain, and orofacial pain compared with controls (Figure 1A). All participants in the cycling group with these pain types reported improvements from baseline, whereas the control group exhibited mixed outcomes, including no change or worsening of pain. For other pain subtypes, including musculoskeletal pain, chronic body pain, discoloration/edema and swelling, and radicular pain, both groups showed comparable patterns of change, with no apparent between-group differences.

Regarding newly developed pain, musculoskeletal pain emerged in 40% (4 of 10) of cycling participants without prior musculoskeletal pain, a higher proportion than that observed in the control group (20%, 1 of 5) (Figure 1B). The occurrence of newly developed pain in other subtypes was comparable between the two groups.

Discussion

Our results showed the potential efficacy of cycling exercise in alleviating fluctuation-related pain, nocturnal pain, and orofacial pain across various pain subtypes in patients with early PD. Although the exact mechanisms underlying the effects of cycling on these types of pain remain unclear, one possible explanation is that the improvements may be at least partially mediated by dopaminergic pathways. Fluctuation-related pain is closely linked to motor fluctuations, often worsening during the *off*-medication state and, to a lesser extent, during the dyskinetic state.[12] Given that our participants did not experience dyskinesia associated with levodopa, fluctuation-related pain in this study appears to primarily occur during the *off*-medication state. Nocturnal pain is associated with restless legs syndrome (RLS) and periodic leg movements (PLM), as well as nocturnal akinesia. The descending diencephalospinal dopaminergic neurons from the hypothalamus are regarded to play a key role in the pathogenesis of RLS.[13] In PD, degeneration of these neurons, along with nigrostriatal neurons, contributes to RLS development.[13] Additionally, PLM frequently accompany RLS, with nigrostriatal dopaminergic dysfunction implicated in its pathogenesis.[13] These conditions are known to respond well to dopaminergic medications.[14] Notably, a previous randomized controlled trial found that aerobic and lower-body resistance training improved RLS-related symptoms,[15] which may support our findings. Lastly, orofacial pain in PD patients includes grinding pain, chewing pain, and burning mouth syndrome.[11] Positron emission tomography studies reported a reduction in presynaptic striatal dopamine in burning mouth syndrome, similar to that observed in PD.[16] In addition, Previous evidence shows that dopaminergic therapy may reduce complaints of orofacial pain and jaw dysfunction in PD patients.[17] Taken together, these observations suggest that cycling exercise alleviates certain types of pain by modulating dopaminergic pathways, potentially through increased dopamine release, upregulation of dopamine receptors, and enhanced dopamine-related neuroplasticity.[18] Supporting this, the current trial demonstrated that cycling exercise reduced the progression of off-state motor symptoms over 24 weeks.[7]

Alternatively, other neurotransmitters, such as opiates, gamma-aminobutyric acid, norepinephrine, acetylcholine, and serotonin, are involved in pain modulation in PD.[1] Serotonin and norepinephrine regulate pain through descending antinociceptive pathways from the brain to the spinal cord, and agents that enhance these pathways can effectively suppress nociceptive transmission.[19] In addition, acetylcholine functions as a neuromodulator in both the central and peripheral nervous systems and modulates pain perception through pre- and postsynaptic mechanisms mediated by nicotinic and muscarinic receptors.[20] Cholinergic activity also influences multiple pain-processing regions, including the primary somatosensory cortex, insular cortex, anterior cingulate cortex, medial prefrontal cortex, and descending modulatory systems.[20] Cycling exercise may impact these non-dopaminergic systems and contribute to pain relief; however, the differential effects of these neurotransmitters on specific pain subtypes remain unclear.

Despite the above positive findings, our study also revealed that 40% of cycling participants developed new musculoskeletal pain, compared with only 20% in the control group. All exercise sessions were fully supervised and the ergometer settings and workloads were individualized to minimize the risk of overuse injuries, but new musculoskeletal pain still emerged in a notable proportion of participants. In line with this, two participants dropped out of our trial due to worsening musculoskeletal pain following cycling exercise, although they were not included in the final analysis.

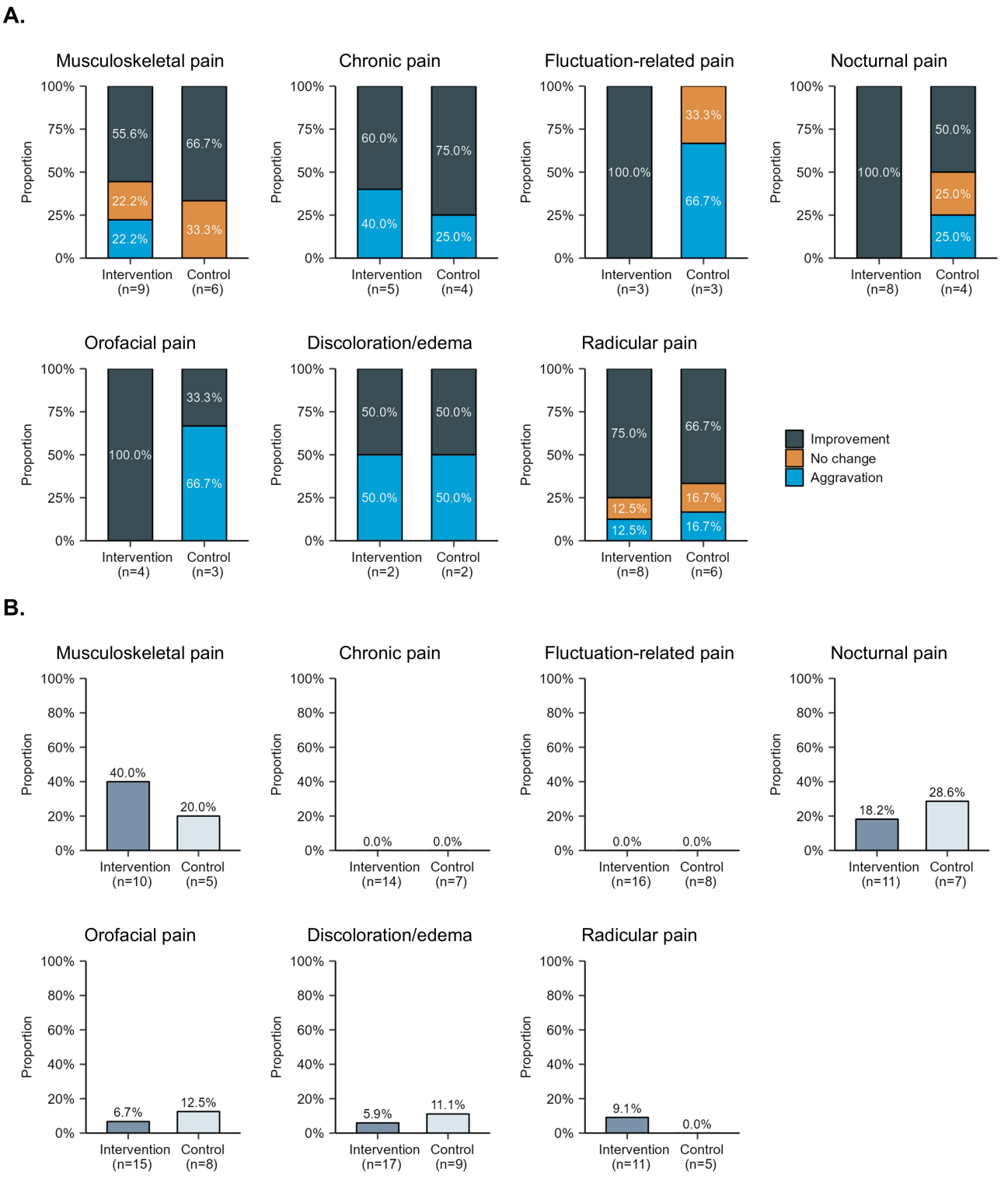

Figure 1 Proportion of pain severity changes (**A**) and prevalence of newly developed pain (**B**) across different pain types after 24 weeks.

These findings may be somewhat surprising because we excluded patients with orthopedic comorbidities that make them unfit to do cycling exercise prior to enrollment. The dropout rate due to musculoskeletal problems in our study was comparable to that reported in previous exercise trials in PD.[10,21] Cycling is a low-impact, non-weight-bearing exercise; however, it can strain joints and muscles, particularly when performed at high intensities or for prolonged durations,

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leading to chronic overuse injuries.[22] Such injuries often result from improper positioning or pressure at the contact points on the bicycle ergometer.[22] The relatively advanced age of our participants and PD-specific motor symptoms may further increase the risk of injury during cycling exercise. These findings may underscore the importance of recognizing potential risks associated with cycling, especially in PD patients who are susceptible to age- or disease-related musculoskeletal strain. In this context, careful monitoring for overuse injuries and individualized adjustments to exercise regimens may be recommended when applying cycling exercise in a clinical setting.

Our study has several limitations. First, small subgroup sizes restricted robust statistical comparisons, necessitating reliance on descriptive analyses. Under these conditions, hypothesis testing and effect-size estimation with confidence intervals were not feasible. Consequently, the current sample size substantially limited statistical power. A post hoc power consideration using our samples indicated that, with 80% power, only large effect sizes (Hedges' $g \approx 0.8$) could be detected.[23] Given this limitation, findings with small effect sizes should be interpreted cautiously, as their clinical implications may be lacking. Second, because we combined high-intensity interval training and moderate-intensity continuous training groups into a single cycling group, it was not possible to investigate whether the effects on pain outcomes differ according to exercise intensity or mode. In particular, the impact of cycling exercise on musculoskeletal pain may be closely related to exercise intensity, but this could not be examined in the present study. Third, the use of analgesic medications may have influenced our findings. In this trial, three participants (18.8%) in the intervention group and one participant (11.1%) in the control group were taking regular analgesics, with comparable proportions between groups. In addition, the study protocol did not allow the initiation or modification of medications that could affect pain or other non-motor symptoms during the study period. Therefore, analgesic use is unlikely to have substantially affected the observed results. Nonetheless, the unsupervised use of nonprescription analgesics outside clinical monitoring cannot be excluded. Fourth, a formally validated Korean version of the KPPS is not yet available, although the scale is widely used in clinical practice and research settings in Korea, including a recent clinical trial.[24] Further validation studies are necessary to ensure its psychometric robustness and cross-cultural applicability. Lastly, this study included only patients with early-stage PD, most of whom reported mild pain severity at baseline. Accordingly, these findings may have limited generalizability to the entire population with PD or those with more severe pain.

In conclusion, this exploratory analysis suggests that cycling exercise may benefit certain pain types, such as fluctuation-related, nocturnal, and orofacial pain, in early PD. However, these potential benefits must be weighed against the notable risk of musculoskeletal pain, which newly developed in a considerable proportion of participants. However, these observations should be interpreted with caution given the small sample size and descriptive nature of the analyses. Further large-scale trials are required to confirm our findings. Moreover, growing evidence indicates that combining physical exercise with noninvasive neuromodulation techniques may produce synergistic effects by enhancing neuroplasticity and functional recovery in individuals with motor disabilities.[25,26] How such combined interventions might influence pain outcomes in PD remains unknown, and future studies exploring these integrated therapeutic approaches are warranted.

Data Sharing Statement

The dataset supporting the conclusions of this article is included within the article. Further enquiries can be directed to the corresponding author, R.K.

Ethics Approval and Informed Consent

The study design was approved by the Institutional Review Board of the Inha University Hospital (2022-01-030) and registered at cris.nih.go.kr (KCT0007130). Written informed consent was obtained from all enrolled patients. The study complies with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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