Preventive effect of a heparinoid-containing product on the application site reaction of the rotigotine transdermal patch in Parkinson’s disease: A pilot randomized clinical trial (the SkinHeRo study)

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Abstract

Introduction: The rotigotine transdermal patch (RTP) is a dopamine agonist used to treat Parkinson’s disease (PD) but is sometimes discontinued because of application site reactions (ASRs). We aimed to investigate the effect of a heparinoid-containing product (HCP) for preventing ASRs due to the RTP by conducting a randomized controlled pilot trial.

Methods: Twenty patients with idiopathic non-demented PD were randomized to the skin care group using a HCP (group H) and the non-skin care group (group N). The primary outcome was the change in the baseline Skindex-16 score (ΔSkindex-16) at week 4. In addition, skin symptoms were also evaluated using the Dermatology Life Quality Index (DLQI) and International Contact Dermatitis Research Group (ICDRG) system for clinical scoring allergic patch test reactions up to week 8.

Results: The ΔSkindex-16 score at week 4 tended to be lower in group H than in group N, although the difference was not statistically significant (−1.5 ± 2.0 vs 1.3 ± 10.9, p = 0.53). When the patients with baseline Skindex-16 scores ≥ 7 were excluded, the ΔSkindex-16 at week 4 was significantly lower in group H (−1.5 ± 2.0 vs 6.1 ± 8.6, p = 0.042). The DLQI also tended to be lower in group H at weeks 4 and 8, but not significantly (p = 0.066 and p = 0.077, respectively). The ICDRG score at week 4 was significantly lower in group H (p = 0.044).

Conclusion: We suggest that the HCP has a preventive effect against ASRs caused by the RTP.

1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disease. As still no radical treatment has been established, the main patient care is symptomatic treatment with dopamine replacement therapy. Although levodopa has played a central role in dopamine replacement therapy, dopamine agonists are also needed as treatment options owing to their benefits from their levodopa-sparing effects, continuous dopaminergic stimulation, and ability to improve depression or apathy [1,2]. Among dopamine agonists, the rotigotine transdermal patch (RTP) can particularly achieve continuous dopaminergic stimulation by continuous transdermal absorption. Furthermore, because its dopamine receptor stimulation profile is similar to that of dopamine [3], it is expected to have fewer side effects than other dopamine agonists.

Although rotigotine has various uses, its clinical use has a specific problem of application site reactions (ASRs). A previous study revealed that 44% of patients experienced ASRs [4]. Neurologists often encounter ASRs that cause discontinuation of RTP use. In general, ASRs by transdermal preparation can be divided into “physical” and “chemical” irritations. ASRs can sometimes occur as allergic reactions to rotigotine but are often caused by exfoliation of the keratin or mechanical irritation. Especially in elderly patient with PD, the skin barrier mechanism is reduced, which leads to an increase in the occurrences of skin disorders. Therefore, appropriate skin care is important to prevent and reduce ASRs. However, this has not been thoroughly investigated.

Heparinoid-containing products (HCPs) have long been used to manage various skin conditions. HCPs increased stratum corneum hydration and accelerated permeability barrier recovery in mice and young and aged humans [5]. Topical glucocorticoids are also used for ASRs caused by rotigotine [6] but can induce atrophogenic side effects during long-term use. Recently, a topical HCP has also been reported to have a preventive effect against glucocorticoid-induced alterations of...
the epidermal permeability barrier homeostasis and atrophy [7].

Although HCPs might be useful agents for reducing ASRs caused by the RTP, only few clinical studies have been conducted on the topic so far [8]. Thus, in present study, we aimed to investigate the effect of a HCP for preventing ASRs due to RTP by conducting a randomized control pilot trial.

2. Methods

2.1. Study design

This was a pilot study conducted to examine the efficacy and safety of HCPs for the prevention of ASRs by the RTP in patients with PD. Patients who were indicated to receive rotigotine in clinical use were randomly assigned to the skin care group using a HCP (group H), and those who did not receive heparinoids were assigned to the non-skin care group (group N), and the severity of skin symptoms was compared. The rotigotine dose was adjusted for normal clinical use. In an 8-week clinical trial, clinical symptoms were evaluated at weeks 1, 4, and 8 after the start of the rotigotine therapy. This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Wakayama Medical University Ethics Committee (approval No. 2373) and was registered at the University hospital Medical Information Network (UMIN) clinical trials registry (UMIN000033409).

2.2. Participants

We consecutively enrolled 20 patients with idiopathic PD. The exclusion criteria were (1) severe dementia that caused inability to answer the questionnaire accurately, (2) any severe skin disorders that affect the determination of the ASRs by rotigotine, (3) past history of severe allergic reactions to rotigotine or HCP, and (4) patients who were judged as unsuitable for participation in this study. All the participants provided written informed consent.

2.3. Intervention

In group H, HCP (Hirudoid cream 0.3%, Maruho, Osaka, Japan) was applied once daily on the sites (shoulder, upper arm, abdomen, thigh, and buttocks on both sides) where RTPs were to be applied. HCP application was started 1 week before rotigotine use. The patients were instructed to use the HCP in sufficient amounts as follows: one fingertip unit (approximately 0.5 g) for the area on both palms, or approximately 25 g/week. In group N, no HCP was used. The participants were prohibited to use any other skin care products on the sites where RTPs were to be applied and other new patches. For randomization, we used the permuted block method without adjustment factors and the randomization list was generated from code in statistical software R (https://www.R-project.org/).

2.4. Outcome measures

The primary outcome was the change in the baseline Skindex-16 [9] score (ΔSkindex-16) at week 4. Skindex-16 is a brief version of Skindex, which is a questionnaire that measures the effects of skin diseases on patient quality of life (QOL), consisting of 16 questions presented as a seven-grade scale. The responses were then transformed to a 100-point linear scale ranging from 0 (never bothered) to 100 (always bothered), and a global score was calculated by averaging the scores of each item. As a secondary outcome, the Skindex-16 and ΔSkindex-16 scores at each visit were also evaluated.

Dermatology Life Quality Index (DLQI) score [10] is also an evaluation index of QOL specialized for skin diseases. The total score (0–30 points) of each item is calculated, and the higher the score, the worse the QOL. The International Contact Dermatitis Research Group (ICDRG) system for clinical scoring of allergic patch test reactions [11] was also used to assess for objective macroscopic findings. The ICDRG score was evaluated on a 6-point scale according to the skin condition of the most recent rotigotine application site as follows: negative reaction (−), doubtful reaction (?+), weak (non-vesicular) positive reaction (+), strong (vesicular) positive reaction (++), extreme positive reaction (+++), and irritant reaction (IR). For evaluation of the PD symptoms, the unified PD Rating Scale (UPDRS) and PD Questionnaire-39 (PDQ-39) were used.

2.5. Statistical analysis

Statistical analysis was performed using the JMP Pro 14 software. Continuous variables are presented as mean ± standard deviation and 95% confidence intervals. Categorical variables are presented as numerals. For group comparisons, the Student t test or Fisher exact test was performed, depending on the type of variable.

3. Results

3.1. Participants

All 20 potential participants screened met the eligibility criteria. Both groups were randomly allocated with 10 participants. Both groups were similar in demographic and clinical characteristics at baseline, although the mean age and proportion of women tended to be higher in group H (Table 1). The participants randomized to group H used sufficient heparinoid doses as directed throughout the trial (2.4 ± 1.0 g/day). Four participants dropped out of the trial for the following reasons: withdrawal of consent before the start of RTP application, admission to another hospital because of pelvic friction, exacerbation of preexisting depression and irritation even without ASRs, and exacerbation of pitting edema due to the adverse effect of rotigotine (Supplementary Fig. 1). No participant used any topical corticosteroids or other skin care products during the study period. No other adverse effects were reported.

3.2. Skindex-16

The primary outcome, the ΔSkindex-16 score, and the Skindex-16 score at week 4 tended to be lower in group H than in group N, although not statistically significantly (Table 2). When the patients with baseline Skindex-16 scores ≥ 7 were excluded to eliminate the effects of other skin symptoms, the ΔSkindex-16 score was significantly lower in group H as follows: H (n = 7), −1.5 ± 2.0 [−3.3, 0.3]; N (n = 7), 6.1 ± 8.6 [−1.9, 14.1]; p = 0.042, t = 2.3. At week 8, both the ΔSkindex-16 and Skindex-16 scores also tended to be lower in group H (Table 2). Even at week 1, excluding one case of outlier (the case of dropout before week 4 because of depression: Skindex-16 score of 53 at week 1 without ASRs), the Skindex-16 score also tended to be lower in H group (1.2 ± 2.2 vs 7.4 ± 10.4, p = 0.11).

3.3. Other secondary outcomes

The DLQI also tended to be lower in group H at weeks 4 and 8, although the difference was not statistically significant (Table 2). The

### Table 1

| Demographic characteristics of the patients. | Heparinoid group | Non-skin care group | p |
|-----------------|-----------------|---------------------|---|
| Age, years      | 72.5 ± 8.2      | 70.6 ± 7.7          | 0.60 |
| Sex, female/male| 6/4             | 2/8                 | 0.17 |
| UPDRS part 3    | 20.3 ± 8.7      | 24.3 ± 9.3          | 0.34 |
| Skindex-16      | 2.4 ± 2.8       | 4.8 ± 6.7           | 0.30 |
| DLQI            | 0.6 ± 0.7       | 1.2 ± 1.5           | 0.27 |
| PDQ-39 summary index | 25.0 ± 17.6 | 25.2 ± 13.5         | 0.98 |
In this study, the HCP group tended to be older. As the skin barrier for improving clinical symptoms, even a low dose of rotigotine could unexpectedly show a sufficient effect.

Another reason is that the rotigotine dose was less than the maximum rotigotine dose is as low as 6 mg/24 h, and the effect of HCPs at high doses of rotigotine is unknown. Finally, it was an 8-week short-term study, so long-term effects could not be determined.

Transdermal preparations have merits such as stable blood concentration and independence on swallowing function. Therefore, transdermal preparations may be further developed for the treatment of various diseases. In this context, controlling ASRs is important for improving medication adherence, particularly in elderly patients. The HCP skin care method in this study may be applicable when using other patches, and future studies are needed.

In conclusion, we suggest that the HCP introduced in this study have preventive effects against ASRs caused by the RTP. For verification, a placebo-controlled randomized controlled trial is required after estimating the sample size based on this study.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2021.100105.

**References**

[1] L. Agüera-Ortiz, R. García-Ramos, F.J. Grandas Pérez, J. López-Alvarez, J. M. Montes Rodríguez, F.J. Olazarin Rodríguez, J. Olivera Pueyo, C. Pelerín Valero, J. Porta-Etessam, Focus on depression in parkinson’s disease: a delphi consensus of experts in psychiatry, neurology, and geriatrics, Parkinsons Dis. 2021 (2021) 6621991.

[2] R.A. Hauzer, J. Slawek, P. Barone, E. Dohin, E. Surmann, M. Asgharnejad, L. Bauer, Evaluation of rotigotine transdermal patch for the treatment of apathy and motor symptoms in Parkinson’s disease, BMC Neurol. 16 (2016) 90.

[3] M. Wood, V. Dubois, D. Scheller, M. Gillard, Rotigotine is a potent agonist at dopamine D1 receptors as well as at dopamine D2 and D3 receptors, Br. J. Pharmacol. 172 (2015) 1124–1135.

[4] J. Jankovic, R.L. Watts, W. Martin, B. Boroojerdi, Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease, Arch. Neurol. 64 (2007) 676–682.
[5] Y. Yao, P. Guo, X. Feng, C. Shen, J. Huang, J. Zhang, P.M. Elias, L. Hu, M.Q. Man, A topical heparinoid-containing product improves epidermal permeability barrier homeostasis in mice, Exp. Dermatol. 28 (2019) 956–960.

[6] M. Furue, H. Terao, W. Rikihisa, K. Urabe, N. Kinukawa, Y. Nose, T. Koga, Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis, Br J Dermatol. 148 (2003) 128–133.

[7] S. Wen, J. Wu, L. Ye, B. Yang, L. Hu, M.Q. Man, Topical applications of a heparinoid-containing product attenuate glucocorticoid-induced alterations in epidermal permeability barrier in mice, Skin Pharmacol. Physiol. 34 (2021) 86–93.

[8] Y. Yasutaka, S. Fujioka, H. Shiboguchi, F. Kiyomi, K. Hara, K. Ogata, Y. Tsuboi, H. Kanmura, Efficacy of topical agents for symptomatic treatment of rotigotine patch-induced skin disorders, Brain Nerve. 69 (2017) 1047–1053.

[9] Y. Higaki, K. Kawamoto, T. Kamo, N. Horikawa, M. Kawashima, Chren., The Japanese version of Skindex-16: a brief quality-of-life measure for patients with skin diseases, J Dermatol. 29 (2002) 693–698.

[10] N. Takahashi, Y. Suzuki, M. Nakamura, Y. Miyachi, J. Green, Y. Ohya, A. Y. Finlay, S. Fukuhara, Japanese version of the dermatology life quality index: validity and reliability in patients with acne, Health Qual. Life Outcomes 4 (2006) 46.

[11] U. Ivens, J. Serup, K. O’goshi., Allergy patch test reading from photographic images: disagreement on ICDRG grading but agreement on simplified tripartite reading, Skin Res. Technol. 13 (2007) 110–113.

[12] I. Zucker, B.J. Prendergast, Sex differences in pharmacokinetics predict adverse drug reactions in women, Biol Sex Differ. 11 (2020) 32.