ORIGINAL RESEARCH

Patent Foramen Ovale Closure for Migraineurs with Massive Right-to-Left Shunt and White Matter Lesions: An Exploration on Curative Effects

Shuai Yan, MM; Ning Wang, MM; Huizhe Liu, MM; Yunying Wei, MM; Xin Liu, MM; Luxuan Wang, MM; Yuqing Huang, MM; Meilin Lin, MD

ABSTRACT

Objective • This study aims to investigate the therapeutic efficacy of patent foramen ovale (PFO) closure in migraine patients with a massive right-to-left shunt (RLS) and white matter lesions (WMLs).

Methods • The research focused on migraine patients with a massive RLS who underwent PFO closure in our hospital from June 2020 to June 2021. The study included 51 patients without WMLs (control group, CG) and 27 patients with WMLs (observation group, OG). A 12-month postoperative follow-up survey was conducted to assess headache episodes (frequency and duration), evaluated using the Headache Impact Test-6 (HIT-6) and the Pain Intensity Visual Analog Scale (VAS). The psychological state was also evaluated using the Hamilton Anxiety and Depression Scale (HAMA, HAMD). Adverse reactions during the follow-up were recorded.

Results • No significant differences in perioperative and prognostic adverse reactions were observed between OG and CG ($P > .05$). Both groups showed a reduction in postoperative headache episodes and pain intensity. However, the OG exhibited higher frequency and duration of headache episodes and elevated HIT-6 and VAS scores, resulting in lower clinical efficacy ($P < .05$). Postoperatively, both groups demonstrated reductions in HAMA and HAMD, with CG showing lower scores compared to OG ($P < .05$). Logistic regression analysis identified the course of the disease, HIT-6 score, and the presence of WMLs as independent risk factors for the efficacy of PFO closure ($P < .05$).

Conclusions • PFO closure proves effective and safe in treating migraine patients with RLS. However, for those with WMLs, clinical attention should be directed toward the treatment of WMLs. (*Altern Ther Health Med.* [E-pub ahead of print.])

Shuai Yan, MM; **Huizhe Liu**, MM; **Xin Liu**, MM; **Luxuan Wang**, MM, Department of Neurological Examination; Affiliated Hospital of Hebei University; Baoding, Hebei; China. **Ning Wang**, MM, Department of Rehabilitation; Affiliated Hospital of Hebei University; Baoding, Hebei; China. **Yunying Wei**, MM, Department of Integrated Traditional Chinese and Western Medicine; Affiliated Hospital of Hebei University; Baoding, Hebei; China. **Yuqing Huang**, MM, Department of Mental Health; Guiyang Provincial Center for Disease Control and Prevention; Guizhou, Guiyang; China. **Meilin Lin**, MD, Department of Laboratory; Affiliated Hospital of Hebei University; Baoding, Hebei; China.

Corresponding author: Meilin Lin, MD
E-mail: linmeilin89@126.com

INTRODUCTION

Migraine is a prevalent, recurrent condition, often localized on one side and characterized by episodes of paroxysmal throbbing pain. Symptoms frequently include nausea, vomiting, dizziness, photophobia, and phonophobia.[1] The incidence of migraine is notably high, reaching 10-12% among individuals over 50 years of age.[2] Research indicates that migraine can contribute to various neurological disorders, including stroke, cerebral infarction, and long-term ischemia and reperfusion injuries. Consequently, migraine is recognized as the third most chronically disabling disease globally.[3]

Individuals suffering from migraines face a 2-4-fold increased risk of developing white matter lesions (WMLs) compared to the general population.[3,4] This heightened risk significantly increases the likelihood of cognitive dysfunction and intensifies the challenges associated with treatment.[4] Currently, growing evidence indicates that patent foramen ovale (PFO) plays a pivotal role in the etiology of migraines, with approximately 55-65% of migraine patients exhibiting varying degrees of PFO.[5,6]

In recent years, PFO closure, involving the implantation of an occluder in the heart to obstruct the patent foramen ovale and consequently prevent abnormal blood flow through the heart, has emerged as an important approach in clinically treating and ameliorating migraines.[6] Despite previous studies suggesting the clinical effects of PFO closure for migraines, significant variations exist in the reported efficacy of this intervention.

Tobis, et al.[7] suggested that PFO closure can effectively alleviate the pain experienced by migraineurs. In contrast, Hildick-Smith, et al.[8] speculated that the therapeutic efficacy of PFO closure is not as optimal as conservative treatment, resulting only marginally satisfactory safety outcomes. Consequently, the present utilization of PFO closure in migraine treatment remains a subject of controversy, with its practical clinical application lacking robust research support.

Furthermore, in the ongoing clinical studies on PFO occlusion, researchers have extensively compared the varying efficacies for different types of migraine patients, including those with acute or chronic migraines and migraines with or without aura headaches.[9,10] However, there is a noticeable gap in the literature concerning the impact of WMLs on the therapeutic effectiveness of PFO occlusion. The scarcity of reliable research support and guidance in this specific context is a significant contributing factor to the persistently low clinical application rate of PFO occlusion.

Since 2020, PFO closure has been adopted as a treatment option for migraines at our hospital, and a substantial number of cases have been accumulated to date. Therefore, this study aims to comprehensively investigate the clinical efficacy and safety of PFO closure in treating migraines with massive right-to-left shunt (RLS). The objective is to evaluate the effectiveness of PFO closure as a viable treatment for migraines, offering a new avenue for clinical intervention and ensuring the health and safety of patients.

MATERIALS AND METHODS

Study Design

A total of 78 migraineurs who underwent PFO closure at our hospital between June 2020 and June 2021 were chosen as the subjects for retrospective analysis. Within this cohort, 51 patients without WMLs constituted the control group (CG), while the remaining 27 patients with WMLs formed the observation group (OG). Ethical approval was obtained from our hospital, and all research participants provided informed consent, signifying their agreement to participate in the study.

Criteria for Patient Inclusion and Exclusion

Criteria for patient inclusion were as follows: (1) Age > 18; (2) Confirmed diagnosis of PFO with RLS-positive migraine according to the International Classification of Headache Disorders;[11] (3) Confirmation through Doppler contrast-enhanced ultrasound, contrast-enhanced transthoracic echocardiography (cTTE), magnetic resonance imaging (MRI), and other imaging examinations; (4) Presence or absence of WMLs, determined by hyperintense T2WI and fluid-attenuated inversion recovery (FLAIR) signal intensities in the white matter area, and isointense or hypointense T1WI signal intensities; (5) Complete case data availability; (6) Willingness to participate in and cooperate with the investigation.

Criteria for patient exclusion: (1) Presence of other cardio-cerebrovascular diseases, autoimmune deficiency diseases, mental illness, and neoplastic diseases; (2) Liver and kidney dysfunction or disorders; (3) Pregnancy or lactation; (4) Transfer of patients to other hospitals after treatment, rendering them unable to complete follow-up.

PFO Closure Procedure

The PFO closure procedure was uniformly conducted by the dedicated treatment team at our hospital for both the control and observation groups. (1) Anesthesia and Venipuncture: Femoral venipuncture and sheath placement were performed under local anesthesia using 2% lidocaine. (2) Hemodynamic Measurements: Measurements of the pulmonary artery, right atrium, and pulmonary vein pressures were obtained using 7F catheters during right heart catheterization.

(3) Transthoracic Echocardiography (TTE): TTE was employed to assess the position of the atrial septum and foramen ovale. (4) Occluder Selection and Delivery: An appropriately sized PFO occluder (25/25mm or 30/30mm) was chosen and threaded into a sheath catheter after careful preparation. (4) Delivery and Fixation: The sheath catheter facilitated the delivery of the occluder along the femoral vein-inferior vena cava-right atrium-foramen ovale-left atrium-left superior pulmonary vein trajectory. Subsequently, the catheter was withdrawn after securing the conveying rod. (5) Confirmation and Separation: Confirmation of the well-positioned occluder and absence of abnormal shunt was ensured through traction experiments and TTE. The occluder was then separated by rotating the conveying rod counterclockwise.

Postoperative Medication

After discharge, patients were prescribed Clopidogrel Bisulfate Tablets (75mg/d orally) for three months and Aspirin Enteric-coated Tablets (100mg/d) for six months.

Postoperative Follow-Up

After discharge, patients underwent a comprehensive 12-month follow-up through regular hospital reexaminations, ensuring intervals did not exceed one month.

Imaging Reexamination. First Month (T1): Transthoracic Echocardiography (TTE) reexamined the occluder's position. Sixth Month (T2): Contrast-enhanced Transthoracic Echocardiography (cTTE) assessed residual shunts postoperatively.

Clinical Evaluation. (1) Headache Assessment: Headache episodes (frequency and duration) were assessed using the Headache Impact Test-6 (HIT-6)[12] at various time points: before the operation (T0), and at 1 month (T1), 3 months (T2), 6 months (T3), and 12 months (T4) after treatment. HIT-6 scores range from 36 to 78, with higher scores indicating a more severe impact of headaches on patients' quality of life. (2) Pain Evaluation: Pain intensity was evaluated using the Pain Intensity Visual Analog Scale (VAS)[13] at the same time points. VAS scores range from 0 to 10, with higher scores indicating more severe pain.

Psychological Status Evaluation. The Hamilton Anxiety and Depression Scale (HAMA, HAMD)[14] assessed patients' psychological status. Higher scores on HAMA and HAMD

are associated with more severe anxiety and depression in patients.

Adverse Reactions (ARs) Monitoring. The occurrence of adverse reactions during the follow-up, including stroke, myocardial infarction, and atrial fibrillation, was recorded. The incidence of adverse reactions was calculated as the number of ARs divided by the total number of people multiplied by 100%. Incidence Rate = number of ARs/total number of people ×100%.

Statistical Analysis

Data were analyzed using SPSS 21.0 software (IBM, Armonk, NY, USA). The significance level for this study was set at $P < .05$. Counting data were analyzed as [n (%)]. The chi-square test (χ^2) was employed to analyze counting data. Measurement data ($\bar{x} \pm s$) was analyzed as mean± standard deviation, independent samples t test was utilized for between-group comparisons, and variance analysis and the Bonferroni correction test were applied for multiple group comparisons. Logistic regression analysis was conducted to identify related factors influencing the study variables.

RESULTS

Comparison of Clinical Baseline Data

When comparing gender, basic diseases, family history, and other data between the OG and CG, no significant differences were observed ($P > .05$). However, there were notable distinctions in age, Body Mass Index (BMI), and the number of individuals with aura headaches, with OG showing higher values than CG ($P < .05$), see Table 1.

Table 1. Comparison of Clinical Baseline Data

Variables	Control Group (n=51)	Observation Group (n=27)	t or χ^2	P value
Gender			2.912	.088
Male/female	13/38	12/15		
Age	29.35±10.75	38.33±14.29	3.124	.003
BMI	22.46±1.38	23.61±1.69	3.236	.002
Family History Of Disease			1.087	.297
Yes/No	2/49	0/27		
Smoking			3.525	.061
Yes/No	5/46	7/20		
Hypertension			0.002	.962
Yes/No	2/49	1/26		
Diabetes Mellitus			-	-
Yes/No	0/51	0/27		
Hyperlipidemia			1.416	.234
Yes/No	1/50	2/25		
Course of Disease	7.62±7.91	10.30±8.82	1.368	.175
With Aura Headache			4.311	.038
Yes/No	16/35	15/12		
Acute And Chronic Classification			0.033	.856
Acute/Chronic	46/5	24/3		

Note: Age, BMI, and Course of Disease are presented as mean ± standard deviation. Gender, Family History of Disease, Smoking, Hypertension, Diabetes Mellitus, Hyperlipidemia, Aura Headache, and Acute and Chronic Classification are presented as count/percentage.

Comparison of Surgical Results and Adverse Reactions (ARs)

In the OG, only one patient experienced atrial fibrillation within 3 hours postoperatively, which later converted to sinus rhythm. No other adverse reactions occurred in the remaining patients during the perioperative period. At one-month post-surgery, none of the patients exhibited abnormalities in the occluder device or thrombosis. CTTE reexamination at 6 months post-surgery revealed no moderate or large shunts. However, small right-to-left shunts were observed in 1 case in OG and 2 cases in CG, respectively.

Throughout the follow-up, neither group encountered complications such as occluder displacement, stroke, myocardial infarction, or peripheral vascular embolism. However, both groups experienced common postoperative symptoms, including insomnia, anorexia, and frequent vomiting. Notably, there was no significant difference in the incidence of adverse reactions between the two groups ($P > .05$), see Table 2.

Table 2. Surgical Results and Adverse Reactions

Group	n	Postoperative Atrial Fibrillation	RLS Shunting	Insomnia	Anorexia	Frequent Vomiting	Overall Incidence
Control Group	51	0 (0.0)	2 (3.92)	3 (5.88)	2 (3.92)	2 (3.92)	17.65%
Observation Group	27	1 (3.70)	1 (3.70)	2 (7.41)	1 (3.70)	1 (3.70)	22.22%
χ^2							0.238
P value							.626

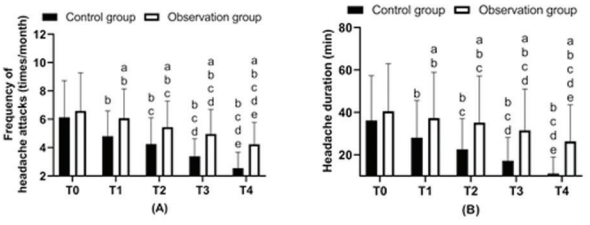
Note: Values for adverse reactions are presented as count (percentage).

Abbreviation: RLS, Right-to-Left Shunt

Comparison of Migraine Episodes

The frequency and duration of headache attacks in both groups at T1 were significantly reduced compared to those at T0, reaching their lowest values at T4 ($P < .05$). There was no significant difference in the baseline headache frequency at T0 between the OG and CG ($P > .05$). However, from T1 to T4, the frequency and duration of headaches were consistently higher in OG compared to CG ($P < .05$), see Figure 1.

Figure 1. Comparison of Migraine Episodes. A. Comparison of the Frequency of Headache Attacks Between the Two Groups. B. Comparison of Headache Duration Between the Two Groups. vs. Control Group

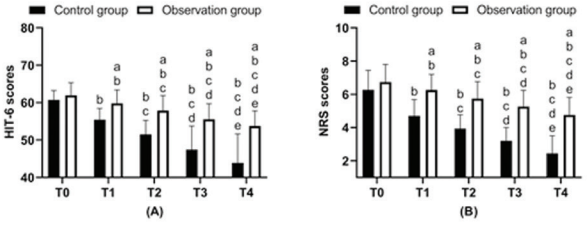


[a]$P < .05$; vs. T0
[b]$P < .05$; vs. T1
[c]$P < .05$; vs. T2
[d]$P < .05$; vs. T3
[e]$P < .05$

Comparison of Pain

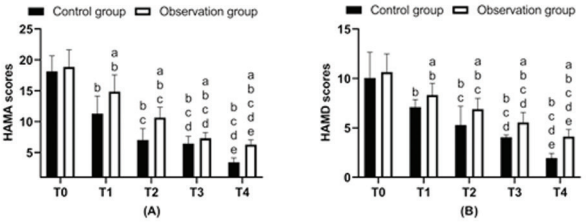
The HIT-6 and VAS scores did not significantly differ between groups at T0 ($P > .05$). However, at T1-T4, both HIT-6 and VAS scores were consistently higher in the OG than in the CG ($P < .05$). Postoperatively, HIT-6 and VAS scores in both groups gradually decreased over time, reaching their lowest values at T4 ($P < .05$), see Figure 2.

Figure 2. Comparison of Pain. A. Comparison of HIT-6 scores Between the Two Groups. B. Comparison of VAS Scores Between the Two Groups. vs. Control Group,



[a]$P < .05$; vs. T0
[b]$P < .05$; vs. T1
$P < .05$; vs. T2
$P < .05$; vs. T3
$P < .05$.

Figure 3. Comparison of Negative Psychological Emotions. A. Comparison of HAMA Scores Between the Two Groups. B. Comparison of HAMD Scores Between the Two Groups. vs. Control Group



[a]$P < .05$; vs. T0
[b]$P < .05$; vs. T1
[c]$P < .05$; vs. T2
[d]$P < .05$; vs. T3
[e]$P < .05$

Table 3. Univariate Analysis of Variables Influencing the Efficacy of PFO Closure

Variables	Group A (n=47)	Group B (n=25)	*t* or χ^2	*P* value
Gender			0.535	.465
Male/Female	13/34	9/16		
Age	27.98±9.85	40.00±12.88	4.421	<.001
BMI	22.25±1.18	23.86±1.72	4.682	<.001
Family History of Disease			1.094	.300
Yes/No	2/45	0/25		
Smoking			3.274	.070
Yes/No	4/43	6/19		
Hypertension			0.212	.645
Yes/No	1/46	1/24		
Diabetes Mellitus			1.906	.167
Yes/No	0/47	1/24		
Hyperlipidemia			1.409	.235
Yes/No	1/46	2/23		
Course of Disease	6.84±6.85	10.92±9.26	2.124	.037
With Aura Headache			0.251	.616
Yes/No	16/31	10/15		
Acute and Chronic Classification			3.064	.080
Acute/Chronic	44/3	20/5		
HIT-6 Score	44.51±8.41	52.56±4.26	4.480	<.001
WMLs			28.790	<.001
Yes/No	6/41	19/6		

Note: HIT-6 score is the score at 12 months after surgery. The values for continuous variables are presented as mean ± standard deviation, and categorical variables are presented as count/percentage.

Table 4. Multivariate Analysis of Variables Influencing The Efficacy of PFO Closure

Variables	OR	B	S.E.	Wald χ^2	*P* value	95%CI
Age	1.342	0.816	0.369	11.534	<0.001	0.942-2.860
Course of Disease	1.624	-0.056	0.034	5.679	<0.001	1.142-3.226
BMI	1.242	0.642	0.924	2.642	0.171	0.642-25.061
HIT-6 Score	1.162	0.113	0.069	14.324	<0.001	1.064-1.634
Presence of WMLs	1.364	0.284	0.134	8.763	<0.001	1.152-5.664

Note: The statistical significance level is set at $P < .05$.

Comparison of Negative Psychological Emotions

After the analysis, the results of HAMA and HAMD scores indicated no significant difference between the scores of both groups at T0. However, at T1-T4, HAMA and HAMD scores were consistently higher in the OG than in the CG ($P < .05$). Notably, the scores for both groups began to decrease at T1, reaching their lowest values at T4, see Figure 3.

Univariate Analysis of Variables Influencing the Efficacy of PFO Closure

At T4, five patients were lost to follow-up, resulting in a final analysis of relevant factors for 72 patients. These patients were then categorized into two groups for further analysis: Group A (headache frequency ≤ 3, n=47) and Group B (headache frequency > 3, n=25), using the median frequency of headache attacks at T4 as a cut-off.

Upon comparing the data between the two groups, it is evident that there were no significant differences in age, gender, cerebrovascular risk factors, migraine with or without aura headache, and acute and chronic classification composition ($P > .05$). However, Group A exhibited a shorter age, disease course, BMI, lower HIT-6 scores, and a higher incidence of WMLs compared to Group B ($P < .05$), see Table 3.

Multivariate Analysis of Variables Influencing the Efficacy of PFO Closure

Logistic regression analysis was performed on the single-factor indices. The results revealed that the duration of the disease, HIT-6 score, and the presence of WMLs were independent factors influencing the frequency of headache attacks after PFO closure treatment ($P < .05$), see Table 4.

DISCUSSION

Clinical support for PFO closure in cryptogenic stroke cases has grown, with the embolization theory related to RLS acquiring attention from experts in cardiology and neurology.[15,16] However, the underlying mechanism of migraine caused by PFO remains incompletely understood. The controversy surrounding the clinical application of PFO closure in migraine treatment persists, mainly due to its infrequent utilization. As closure surgery becomes more mature and widely applied, confirming the therapeutic effect of PFO closure for migraine becomes pivotal for the future well-being of migraine patients.

In this study, we explored the treatment of migraine patients with RLS through PFO closure. Notably, the incidence of perioperative and prognostic ARs was low, indicating the high safety of PFO closure in migraine treatment. Our findings align with previous studies,

reinforcing the safety of PFO closure in treating stroke or transient cerebral ischemia.[17] This safety can be attributed to technological advancements and increased clinical experience in closure surgery. Moreover, both groups exhibited postoperative improvements in headache episodes and pain, consistent with prior evidence,[18] highlighting the effectiveness of PFO closure for migraine treatment.

However, the final total effective rate of clinical treatment in the OG and CG was 73.33% and 94.44%, respectively, significantly lower than reported in some previous studies.[19,20] This discrepancy may result from the shorter observation time in our study, conducted at 6 months postoperatively, compared to the one-year observation time recommended for PFO closure surgery.[21]

Our inter-group comparisons reveal that the improvement in headache attacks and pain relief was less significant in OG, indicating that PFO closure is more effective for migraine patients without WMLs. Analyzing related factors, we identified that the course of the disease, HIT-6 score, and the presence of WMLs were independent factors influencing the frequency of headache attacks after PFO closure treatment. Given the abundance of studies emphasizing the significance of HIT-6 as a primary observational index for migraines, its discussion is omitted here.[22,23]

Patients with a longer disease course tend to have more serious intracranial vasomotor disorders, decreased cerebral perfusion, and aggravated local inflammatory reactions, potentially leading to poor treatment effects.[24] WMLs are clinically considered to result from microemboli blocking microcirculation, inducing recurrent migraine episodes and local blood flow hypoperfusion. Our findings suggest that the presence of WMLs is a critical factor affecting the clinical outcome of migraine patients undergoing PFO closure.

If the embolus is sufficiently large and persists, it may lead to damage in brain tissue, particularly the white matter, which is known for its sensitivity to ischemia.[25] Following the onset of WMLs, abnormal embolism may induce cerebral ischemia, giving rise to the formation of microthrombosis that obstructs arterioles. This, in turn, causes regional cerebral blood perfusion insufficiency, subsequent white matter demyelination, and neural network remodeling. Such processes contribute to the aggravation of migraine development, forming a detrimental cycle.[26]

This cycle could potentially be the primary reason for the unsatisfactory clinical outcomes observed in migraine patients with WMLs. However, specific reasons require further analysis and confirmation through additional experiments. Additionally, the enduring nature of recurrent pain in migraine patients often predisposes them to negative emotions such as anxiety and depression, significantly impacting their overall quality of life.[27]

In our supplementary assessments, we employed the HAMA and HAMD scores. The findings indicated a decrease in scores for both groups starting from the first month after the operation, with relatively higher scores observed in the OG. This can be attributed to a more substantial pain relief experienced by both groups during the initial postoperative month. Moreover, the superior treatment efficacy in the CG likely contributed to the lower scores observed in that group.

These findings collectively contribute to the ongoing discourse on the clinical application of PFO closure in managing migraine, paving the way for more informed and tailored treatment approaches.

Study Limitations

Several limitations are inherent in this study that warrant consideration and improvement. Firstly, the retrospective nature of the analysis introduces a level of subjectivity in patient follow-up, potentially leading to recall bias. To mitigate this, future studies should prioritize prospective designs with standardized protocols. A randomized controlled trial would be particularly valuable to provide more robust evidence and confirm the observed effects of PFO closure in migraine treatment. Secondly, the study's sample size was limited, and the follow-up duration was relatively short. Expanding the number of cases and extending the follow-up period would enhance the statistical power and strengthen the reliability of the findings. Addressing these limitations in future research will contribute to a more comprehensive understanding of the outcomes associated with PFO closure in treating migraine patients.

CONCLUSION

In conclusion, this study affirms the effectiveness and safety of PFO closure as a viable treatment option for migraine patients with RLS. The findings support the potential integration of PFO closure into future migraine treatment strategies. However, for patients presenting with both migraine and WMLs, a nuanced approach is recommended. Clinical attention should prioritize the treatment of WMLs before considering PFO occlusion. This progressive approach is essential for optimizing patient outcomes and improving the overall prognosis of individuals with migraine and concomitant WMLs. Future research and clinical endeavors should continue exploring and refining these treatment protocols for more tailored and effective management of migraine patients.

CONFLICT OF INTERESTS
The authors report no conflict of interest.

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AUTHORS' CONTRIBUTIONS
Meilin Lin designed the study, Shuai Yan and Ning Wang wrote the manuscript, Huizhe Liu and Yunying Wei collected and analyzed data, Xin Liu, Yuqing Huang and Luxuan Wang revised the manuscript, Shuai Yan and Ning Wang made equal contributions in this work.

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None

AVAILABILITY OF DATA AND MATERIALS
The data supporting the findings of this study are available from the corresponding author upon request, subject to reasonable conditions.

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