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ORIGINAL ARTICLE

Efficacy of topical gabapentin in women with primary macular amyloidosis: A side-by-side triple-blinded randomized clinical trial

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Abstract

Background: Primary cutaneous macular amyloidosis (PCMA) is a chronic pruritic cutaneous disease characterized by heterogeneous extracellular deposition of amyloid protein in the skin.

Aims: This study aimed to evaluate the efficacy of topical 6% gabapentin cream for the treatment of patients with PCMA.

Materials and Methods: In this triple-blind clinical trial, a total of 34 patients, who were diagnosed with PCMA, treated using two different strategies of topical gabapentin as the active group and vehicle cream as the control group.

Results: Pruritus score reduction in both groups was statistically significant compared with the baseline value ($p < 0.001$). There was a significant pigmentation score reduction in intervention group compared with control group after 1 month of the study ($p < 0.001$). The differences of pigmentation score changes between the groups were not significant at month 2 ($p = 0.52$) and month 3 ($p = 0.22$).

Conclusions: The results of this study suggest that topical gabapentin cream may be effective as a topical agent in the treatment of pruritus associated with PCMA without any significant adverse effects. It is recommended to perform similar studies with a larger sample size and longer duration in both sexes.

KEYWORDS
gabapentin, macular amyloidosis, pruritus, topical gabapentin

1 | INTRODUCTION

Primary cutaneous macular amyloidosis (PCMA) characterized by extracellular deposition of heterogenic amyloid proteins in the skin, is a chronic pruritic cutaneous disease.

Itch is one of the characteristic features of PCMA and the symptom can be debilitating. Both cutaneous and neurological components may be involved in the pathophysiology of pruritus in PCMA.[1]

Today there are no standard protocols for the treatment of PCMA. The current concept varies from topical, intralesional, or physical treatment with various efficacy. A variety of treatment modalities including topical corticosteroids, topical dimethyl sulfoxide, topical retinoids, oral cyclophosphamide, oral colchicine, phototherapy, laser therapy, surgical intervention, and transcutaneous nerve stimulation have been used, but no particular treatment is effective for all cases.[2–4]

PCMA is usually associated with pruritus, so one of the important goals of treatment is to control itching and consequently disrupt the vicious cycle of itching and scratching.[5]

Despite numerous developed therapies to control pruritus, treatment of pruritus in PCMA has remained a challenging clinical problem for dermatologists. This might be because the exact mechanism of development of pruritus in PCMA has not been completely understood.[6]

So various treatments are proposed to improve the itching. Gabapentin is a structural analog of gamma-aminobutyric acid (GABA)[7] and can play an inhibitory role by changing glutamic acid decarboxylase activity and restricting the presynaptic release of glutamate. It has been successfully applied for the treatment of various medical conditions.[8,9]

It has been demonstrated that gabapentin can relieve itching especially neuropathic itching and idiopathic pruritus.[10]

Topical gabapentin is probably effective for scalp dysesthesia, a condition that is characterized by scalp burning or pruritus in the absence of any objective findings and may be associated with cervical spine disease.[11]

Also, topical gabapentin is used for relieving pain in post-herpetic neuralgia and other painful neuropathies,[12] and significant pain relief in women with vulvodynia is also seen.[13] Briefly, it could represent an analgesic strategy.

Although various studies have been performed on the efficacy of gabapentin in the treatment of pruritus, the efficacy of this drug and its topical form in the treatment of PCMA has not been studied.

Given that PCMA is usually associated with significant pruritus and can alter the quality of affected individuals' lives, any treatment that leads to improve itching symptoms can help improve the disease.[14]

This study was hence conducted to assess the efficacy of topical gabapentin in the treatment of PCMA in a side-by-side control study.

2 | MATERIALS AND METHODS

2.1 | Overview and patients

A randomized, side-by-side triple-blinded trial was conducted on women with PCMA. The inclusion criteria were patients with bilateral symmetrical PCMA, who were 18 to 50 years old. Patients were excluded from the study if they were hypersensitive to gabapentin, were taking topical or systemic medications to treat PCMA within the past 6 months, or had a history of current or previous neurological and psychological disorders. Pregnant or breastfeeding women were also excluded from the study.

Non-compliant patients, patients who needed other medical interventions, and also patients who did not consent to continue were excluded from the study.

The diagnosis of PCMA was made clinically by two experienced dermatologists.

The Institutional Review Board of the Isfahan University of Medical Sciences approved the study protocol in full compliance with the Declaration of Helsinki. The study was registered in the Iranian registry of clinical trials (http://www.irct.ir; registration number: IRCT20131119015455N4).

Written informed consent was obtained from all patients after a full explanation of the treatment protocol and possible side effects.

2.2 | Study protocol

Each side was randomly assigned and either the right or left side received topical gabapentin and the other side received vehicle cream. All patients were unaware of treatment on either side. A study checklist was used to collect demographic data for each participant, including age, gender, family history, previous medical history and underlying medical conditions, and age at which lesions appeared. Responsible author for this randomization, was not involved in the analysis of the study results. Patients were blinded to receive topical gabapentin (intervention) or vehicle cream (control) on each site. In addition, blinding was maintained so that the assessing dermatologist did not know who was on the intervention or control side. All patients were asked to rub a thin layer of topical cream onto the PCMA area twice daily during the 3-month treatment period. Patients were advised not to take any other topical or systemic medications for the duration of the study. All participants were assessed by an investigator for appropriate use of topical creams.

2.3 | Formulation preparation

Topical gabapentin cream was prepared by a clinical pharmacist in the hospital's pharmacy department according to Good Manufacturing Practice (GMP) standards. To formulate 100 mL of a six percent Gabapentin cream, we dissolved the content of twenty 300 mg hard capsules of the drug (Actopentin, Actover pharmaceutical company), equal to 6 grams of pharmaceutical grade Gabapentin powder in 10 mL of warm (40/C) deionized distilled water and added the result to cold cream (about 75 mL), in a geometric method, to have a consistent 100 mL of the cream. A water in oil topical cold cream was considered as placebo and packaged identically the same to Gabapentin cream.

We used standard BPC codex cold cream as a base for Gabapentin topical cream which is used frequently in our institution in topical products and we did not design this matrix base from scratch which necessitates patch test.

2.4 | Outcomes assessment

All patients were evaluated at baseline, at the end of months 1 and 3 during treatment, and 3 months after the end of treatment. During these assessments, patients were evaluated for response to treatment and possible complications.

At each visit, the severity of pruritus was scored using the 4-Item Pruritus Severity Scale. The total score ranges to 3 (mild pruritus) and a maximum score of 19 (very severe itch).[15]

The questionnaire contains questions about various aspects of pruritus. It delivers data about the extent of pruritus (1–3 points), intensity (1–5 points), frequency (1–5 points), and sleep disturbances (0–6 points) in patients with pruritus.

On each visit, the objective assessment of pigmentation was also evaluated using (FotoFinder Systems GmbH, Germany).

2.5 | Statistical analysis

Means and standard deviations were given to represent numerical variables, and numbers and percentages were given to represent qualitative variables. Normality of numerical variables was checked using the Shapiro–Wilkes test. Wilcoxon Signed Ranks Test was used to compare intervention and control at each time point. The Mixed Model Analysis was used to compare the improvement in pruritis and pigmentation with and without intervention. Analysis of Variance with Repeated Measurements was used to show changes in pruritis and pigmentation scores in each condition. The software used was SPSS-26 and the significance level for statistical tests was set at 0.05.

3 | RESULTS

3.1 | Baseline characteristics

Thirty-four patients with bilateral symmetric PCMA completed the study. The demographic and clinical characteristics of the patients included in the study are summarized in Table 1.

The mean ± (SD) age of the participants was 38.3 (14.5) years (range, 20–72).

Most of the patients had negative family history of PCMA. The mean ± (SD) duration of the diseases was 7.4 (5.3) years (range, 1–27) years. The Mean ± (SD) pruritus score at the base line was 6.8 ± (1.1) (Table 2).

3.2 | Pruritus score

Table 2 showed pruritus score changes in both side of the treatment during the period of the study (Table 2). The reduction in pruritus score was statistically significant in both groups compared to baseline ($p < 0.001$) (Table 2) (Figures 1 and 2).

TABLE 1 Demographic and clinical characteristics of the patients included in the study.

Variables	
Age, year	
Mean (SD)	38.3 (14.5)
Median (min–max)	34 (20–72)
BMI, kg/m^2	
Mean (SD)	24.7 (2.9)
Median (min–max)	25 (3.86)
Duration of disease, year	
Mean (SD)	7.4 (5.3)
Median (min–max)	6 (1–27)
Family history, *n* (%)	
Negative	25 (78.1)
Positive	7 (21.9)
Past history of allergy, *n* (%)	
Negative	19 (59.4)
Positive	13 (40.6)

BMI: body mass index

Mean pruritus scores decreased in both groups compared to baseline, but these changes between groups reached significant levels at all months (Change from baseline to month 1, *p*: 0.005. Change from baseline to month 2, *p*: 0.003. Change from baseline to month 3, $p < 0.001$) (Table 2). Figure 3 demonstrates the estimated means of pruritus score by groups and times (Figure 3).

Stepwise linear regression analysis showed that the decreased in pruritus during study was associated independently with therapeutic intervention with gabapentin ($p < 0.001$) (Table 3).

3.3 | Pigmentation score

Details of changes in pigmentation score was showed in Table 4. There was a significant pigmentation score reduction in intervention group compared with control group after 1 month of the study ($p < 0.001$) (Table 4). Differences in pigmentation score changes between the groups were not significant at month 2 ($p = 0.52$) and month 3 ($p = 0.22$) (Table 4). Figure 4 demonstrates the estimated means of pigmentation score by groups and times (Figure 4).

The results of the stepwise linear regression analysis indicate that prolonging duration of the disease ($p = 0.002$), increasing BMI ($p = 0.03$), and having a positive family history ($p < 0.001$) are independently associated with a decrease in pigmentation improvement (Table 5).

3.4 | Complication

No serious dermatological complications or systemic side effects have been identified with topical use of gabapentin. Only mild topical

Time Point	Grouping			95% CI		p-Value[a] (between)
	Intervention	Control	Diff	Lower	Upper	
Baseline						
Mean ± SD	6.8 ± 1.1	6.8 ± 1.1				–
Month 1						
Mean ± SD	4.8 ± 1.6	5.8 ± 1.4				0.056
Change (baseline—M1)						
Mean ± SD	−1.91 ± 1.2	−0.97 ± 0.93	−0.94 ± 1.01	−1.30	−0.57	**0.005**
p-Within[b]	<0.001	<0.001				
Month 2						
Mean ± SD	3.9 ± 1.6	4.8 ± 1.3				0.053
Change (baseline—M2)						
Mean ± SD	−2.84 ± 1.19	−1.91 ± 0.93	−0.94 ± 0.95	−1.28	−0.60	0.003
p-Within[b]	<0.001	<0.001				
Month 3						
Mean ± SD	2.6 ± 1.9	4.2 ± 1.6				0.002
Change (baseline—M3)						
Mean ± SD	−4.19 ± 1.77	−2.56 ± 1.27	−1.63 ± 1.10	−2.02	−1.23	<0.001
p-Within[b]	<0.001	<0.001				
p-Value[c]	<0.001	<0.001				

[a]Based on Wilcoxon Signed Ranks Test.
[b]Based on one-sample test.
[c]Based on ANOVA with repeated measurements.

TABLE 2 Pruritus score in both groups during the study.

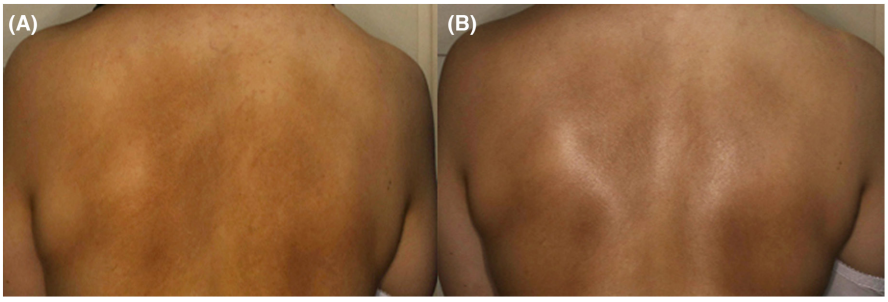

FIGURE 1 Macular amyloidosis: before and after treatment; reduction of itching in the patient after 2 months use of topical gabapentin.

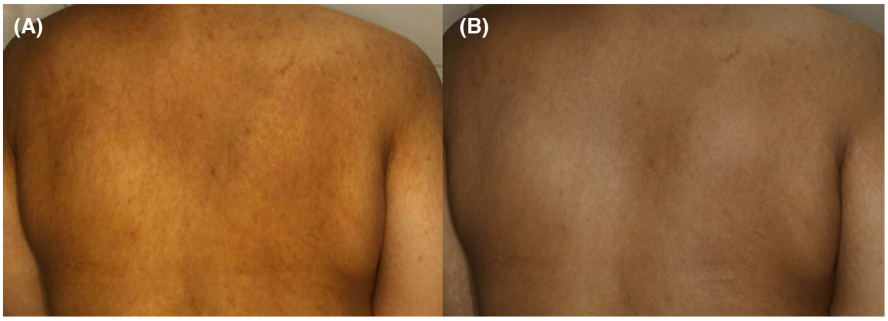

FIGURE 2 Macular amyloidosis: before and after treatment; reduction of itching in the patient after 2 months use of topical gabapentin.

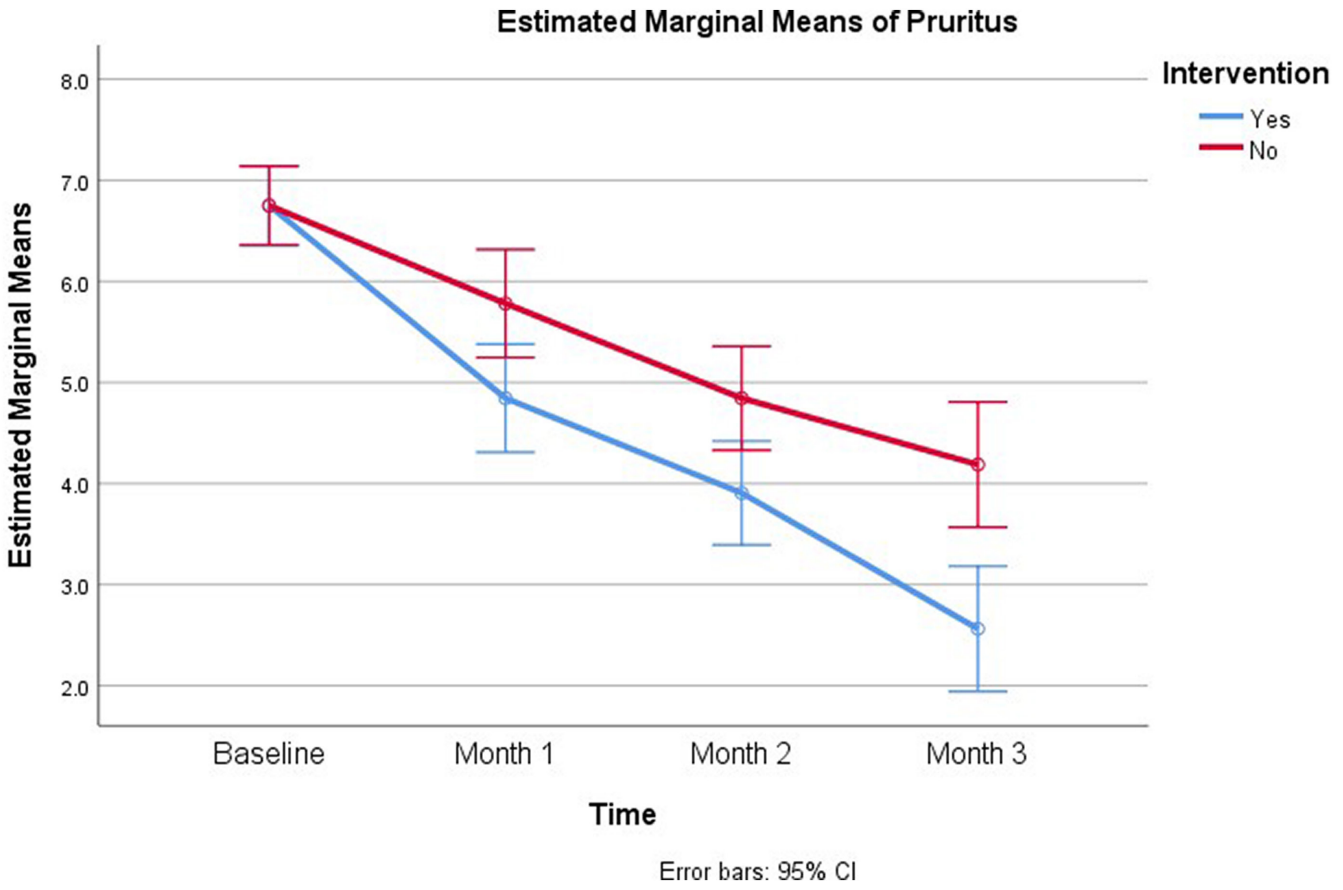

FIGURE 3 The estimated means of pruritus score by groups and times.

TABLE 3 Stepwise linear regression analysis for the association between pruritus changes during study with other parameters.

	Unstandardized coefficients		Standardized coefficients		
	B	Std. Error	Beta	*t*	*p*-Value
Constant	−8.159	1.873		−4.355	<0.001
Intervention (yes)	1.625	0.386	0.473	4.210	<0.001
Age, year	0.015	0.020	0.129	0.765	0.45
Duration of disease, year	−0.053	0.048	−0.162	−1.111	0.27
BMI, kg/m^2	0.077	0.082	0.129	0.939	0.35
Past history of allergy (yes)	0.391	0.460	0.112	0.849	0.40
Family history (yes)	0.450	0.510	0.108	0.882	0.38

adverse effects including mild erythema and irritation were seen. No patient had to discontinue the study due to severe or intolerable side effects.

4 | DISCUSSION

Topical gabapentin is an effective anti-nociceptive and anti-pruritic medication. The use of topical gabapentin especially in elderly and in patients sensitive to the systemic adverse effects of anti-pruritic agents can be more considerable.[16]

The exact mechanism of gabapentin in relieving pruritus is still unclear but there are some probable reported pathways. It may act by inhibiting the release of excitatory neurotransmitters (e.g., dopamine, serotonin, and norepinephrine). Also, gabapentin increases the neuronal excitation threshold. Eventually, it impedes the afferent signals and synaptic transmissions, stabilizes the afferent neurons, and finally blocks the neuropathic afferent pathway.[17,18]

It has been reported that gabapentin inhibits the α_2 subunit of the voltage-dependent calcium ion channel. It is recently shown that gabapentin can reduce the influx of calcium in presynaptic nerve terminals.[19,20] So, it can stabilize neuronal transmissions by blocking the calcium channels.

Gabapentin has also been thought to have a reduction of itch intensity in the central nervous system. So that it can affect the central itch perception.[17]

TABLE 4 Pigmentation score in both groups during the study.

Time point	Grouping			95% CI		*p*-Value[a] (between)
	Intervention	Control	Diff	Lower	Upper	
Baseline						
Mean ± SD	3.5 ± 2.7	3.5 ± 2.7				–
Month 1						
Mean ± SD	3.1 ± 2.6	3.3 ± 2.2				0.41
Change (baseline—M1)						
Mean ± SD	−0.36 ± 1.58	−0.2 ± 1.24	−0.19 ± 0.68	−0.44	0.05	<0.001
p-Within[b]	0.21	0.36				
Month 2						
Mean ± SD	2.9 ± 1.7	3.1 ± 1.9				0.43
Change (baseline—M2)						
Mean ± SD	−0.54 ± 1.77	−0.36 ± 1.84	−0.23 ± 0.46	−0.39	−0.06	0.52
p-Within[b]	0.09	0.23				
Month 3						
Mean ± SD	2.9 ± 2.6	3.1 ± 2.4				0.43
Change (baseline—M3)						
Mean ± SD	−0.56 ± 2.01	−0.4 ± 1.86	−0.19 ± 0.56	−0.40	0.01	0.22
p-Within[b]	0.12	0.21				
p-Value[c]	0.18	0.28				

[a]Based on Wilcoxon Signed Ranks Test.

[b]Based on one-sample test.

[c]Based on ANOVA with repeated measurements.

Also, some studies about the connection between gabapentin and opioid receptors state the probable role of these receptors in relieving itch.[21]

Inhibition of calcium channels, decrease glutamate levels, and inhibition of discharges from peripheral nerves, can be related to the improving itching sensation.[10]

A recent study suggests that short-term use of topical gabapentin can decrease chronic kidney disease-associated pruritus (CKD-AP). It has a positive role to decrease the toxicity induced by systemic gabapentin due to its renal elimination.[22]

This study is a randomized, double-blind, vehicle-controlled study on experimental group (receiving 6% gabapentin) and control group (receiving vehicle) with 15 CKD patients assigned to each group. 11-point visual analog scale (VAS) and 5-D itch scale (degree, duration, direction, disability, and distribution) were used to score the pruritus.[22]

It is the second study, after Boardman et al.,[13] assessing the efficacy of topical gabapentin. These studies both have shown the effectiveness of topical gabapentin in relieving pruritus and pain with no adverse effects.

Based on our literature review, reports on treatment of macular amyloidosis are limited to case reports, and studies of patients treated without a control group.[2] Trials are almost about different types of laser therapy.[3] So, limited randomized clinical trial study is performed on using topical agents for treating macular amyloidosis.

Between topical agents, the use of topical retinoids for the treatment of macular amyloidosis (MA) is controversial. Topical corticosteroids were also used in a patient with no benefit. Only topical dimethyl sulfoxide was reported as an affective topical agent for MA by disappearance of pruritus, flattening of papules, and remission in pigmentation.[2]

A split-sided, individualized, single-blind, randomized clinical trial compared the efficacy of 50% topical dimethyl sulfoxide (DMSO) solution and 0.5% tretinoin cream in treating patients with primary macular amyloidosis. Results showed that DMSO and tretinoin cream had beneficial effects on both hyperpigmentation and pruritus, but DMSO was significantly better at reducing pruritus and thus may be more beneficial than tretinoin. Some side effects such as contact urticaria, desquamation, burning sensation, and garlicky breath have been reported for topical DMSO, mainly when used at high concentrations, but the above study reported no side effects.[23]

Among other methods of treatment, fractional CO2 laser, pulsed dye laser, and Q-switched neodymium-doped yttrium aluminum garnet (Nd: YAG) laser were successful but mostly by reducing pigmentation. Phototherapy with ultraviolet-B (UVB) was effective for management of pruritus. Also, transcutaneous electrical nerve stimulation has been a successful effort to relief MA pruritus.[2]

Our study has several limitations, first a relatively small sample size, second lack of long-term follow-up in the drug-free period for evaluation of relapse of the disease. Third, we used topical gabapentin cream, only for female patients, so the clinical effect of treatment

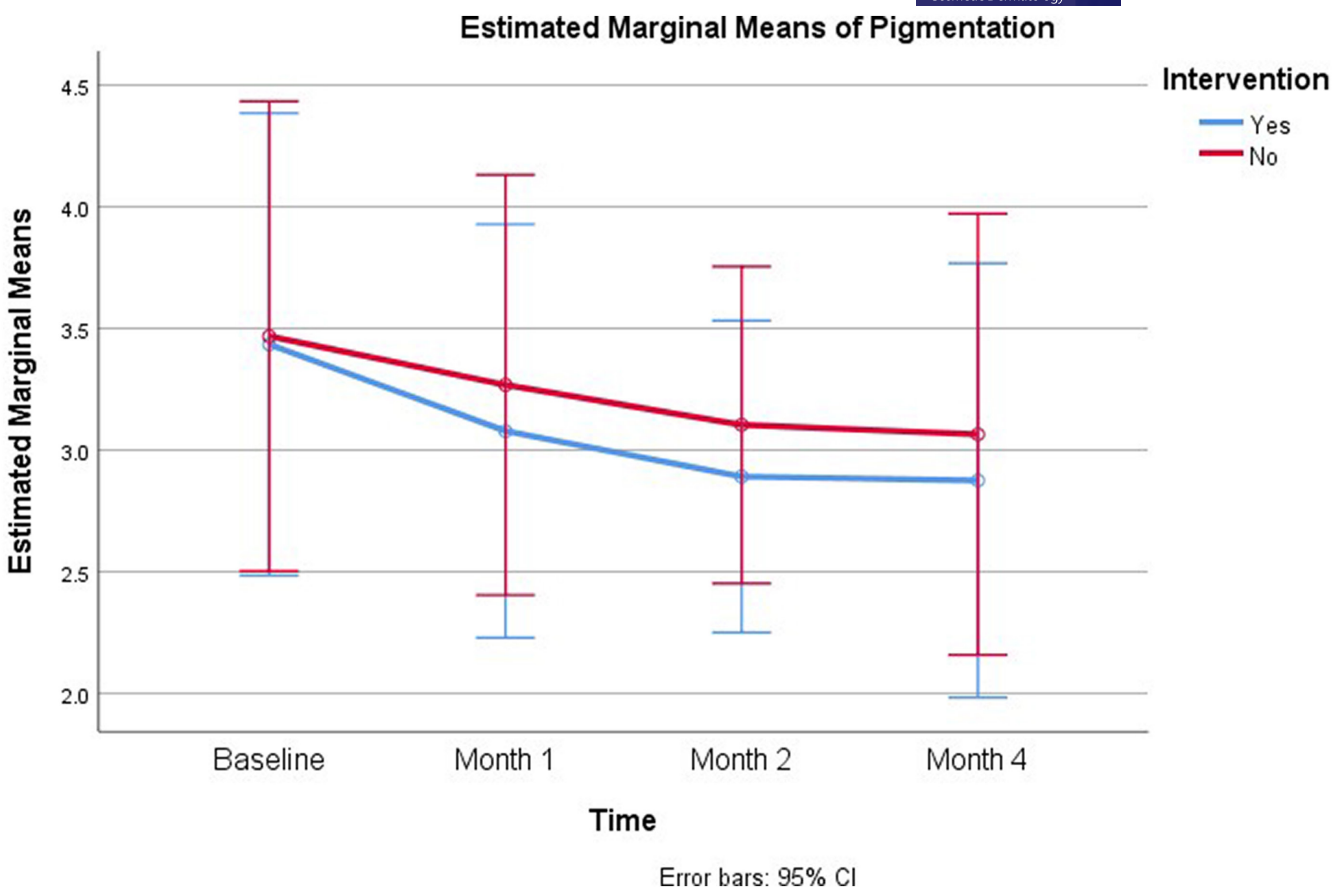

FIGURE 4 The estimated means of pigmentation score by groups and times.

TABLE 5 Stepwise linear regression analysis for the association of pigmentation changes during study with other parameters.

	Unstandardized coefficients		Standardized coefficients		
	B	Std. Error	Beta	*t*	*p*-Value
Constant	−4.895	1.912		−2.560	0.01
Intervention (yes)	0.171	0.396	0.045	0.431	0.67
Age, year	−0.032	0.021	−0.243	−1.558	0.12
Duration of disease, year	0.162	0.049	0.449	3.318	0.002
BMI, kg/m^2	0.186	0.083	0.283	2.230	0.03
Past history of allergy (yes)	0.202	0.470	0.052	0.431	0.67
Family history (yes)	−2.139	0.520	−0.467	−4.117	<0.001

on male individuals is unknown. Withstanding these limitations, our study also has several advantages: (a) side-by-side and controlled design to eliminate the personal confounding variable, (b) we used a vehicle cream as a placebo on the control side leading to no active treatment.

5 | CONCLUSION

Based on the positive findings of the current study we suggest using topical gabapentin for the treatment of PCMA. Selection of the best concentration of topical gabapentin for the control of pruritus needs further study in the future.

AUTHOR CONTRIBUTIONS

B.A.N and G.F designed the concept of the study. Z.S and F.R and M.H performed the data collection. F.P and M.A performed the statistical analysis. J.V and A.M.S designed and formulated the topical drug. B.A.N and G.F and Z.S designed the study. B.A.N and E.H and F.P and F.R drafted the manuscript. The manuscript was revised by G.F and Z.S and J.V and M.H and M.A and A.M.S. All authors revised and approved the final version of this manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available on request from the corresponding author.

ETHICS STATEMENT

This manuscript has been ethically approved by the "Ethics committee of Isfahan university of medical sciences, Isfahan, Iran" and the ethical approval ID is: IR.MUI.MED.REC.1398.366. Also, the IRCT approval ID is: IRCT20131119015455N4.

PATIENTS CONSENT STATEMENT

Written informed consent was obtained from the patients for publication of this study and accompanying images.

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