Effectiveness of Postburn Pruritus Treatment and Improvement of Insomnia—A Randomized Trial

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Postburn pruritus is difficult to assess and treat. Antihistamines used in its treatment provide little relief. Identification of the itch neuronal pathway has inspired new alternatives, including gabapentin, for its management. The study compared the effectiveness of cetirizine, gabapentin, and a combination of gabapentin and cetirizine in treating postburn pruritus. Burn patients were randomly assigned to treatment with Cetirizine (n = 23), Gabapentin (n = 23), or Cetirizine plus Gabapentin (n = 23). A baseline assessment of the intensity or the severity of pruritus was evaluated, after which treatment commenced with standard doses of the 3 study regimens. Quality of sleep was assessed at baseline (day 0) and repeated on day 3, day 7, and day 14. Approximately 97% of participants presented with moderate or severe itch; 69% with acute itch; and the majority (94.2%) experienced pruritus between the first and fourth weeks. Gabapentin reduced itch by 92.9% in 14 days compared to cetirizine's 61.8%. The combined effect of cetirizine and gabapentin was comparable using gabapentin alone. When the itch became protracted over 6 weeks, the effectiveness of cetirizine in controlling itch worsened. It reduced itch intensity by only 37.7%, whilst gabapentin did so at 89.4%. Itch intensity correlated positively with insomnia, and controlling itch intensity improved sleep. Gabapentin was more effective for the treatment of postburn pruritus than cetirizine. Controlling itch intensity improved sleep. In acute and moderate itch, low-dose gabapentin could be added if cetirizine is the drug intended for its treatment.

Key words: postburn pruritus; gabapentin; cetirizine; insomnia.

INTRODUCTION

Pruritus, a common distressing symptom, often compounds the afflictions of burned patients and is an uneasy condition to assess and treat. The origins of pruritus are pruritogenic (from skin), neuropathic (itch along afferent pathway), neurogenic (originating centrally) or psychogenic.[1] Postburn itch is pruritogenic or pruriceptive and has an incidence rate of 100% in children and 87% in adults, irrespective of the size of injury or degree of burn with varying degrees of intensity.[2,3] Although pruritus is experienced early during the healing phase, it could persist for many years. A recent study conducted by Holavanahalli reported that 72% of survivors of severe burns continue to experience itching 17 years after wound healing.[4] Pruritus is a common occurrence with wounds from burns managed either conservatively or by skin grafting. However, compared to ungrafted burn wounds, grafted wounds record higher intensity of itch even though the difference plateaus off at 12 months.[5] Often enervating, pruritus from burns results in skin integrity breach, especially when the patient constantly scratches for relief.[6] Thus, wounds that already take a considerably long time to heal reopen, setting the chain of healing to restart with worsening itch as the wound re-heals. Itch is more pronounced in those with higher percentage burns and long wound healing phases. Even though the mechanism is not well understood, the anatomical site is known to commonly influence pruritus severity. It has been more frequently reported on the lower extremities than anywhere else on the body.[7]

Clinically, pruritus is one of the most disturbing physical complaints of the burn patient.[8] The telling effect of pruritus extends beyond the incessant scratching but gravely affects the quality of life. It affects sleep patterns, alters the patient's

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day-to-day schedules and activities, and causes psychological impairment from anxiety and depression.[5–7,9] The challenge of tackling postburn pruritus could be enormous, especially when the burn injury involves greater total body surface area (TBSA). The frequent scratching for relief leaves in its wake reopened wounds, thus slowing the process of wound healing. Deep dermal burns are particularly prone to developing hypertrophic scars which are notably itchy.[8]

Pruritus is a subjective symptom and, therefore, difficult to quantify and an ideal instrument of measure is hard to find[10–12] and even more troubling has been its treatment. Historically, various agents such as menthol cream and topical vitamin D through immune-suppressing agents such as cyclosporine have been explored for their treatment with unimpressive results.[13,14] With definitive treatment being evasive; psychological therapy has been recommended to complement the other forms of standard therapies already in use.[13,15] Antihistamines, the mainstay of postburn pruritus management and treatment, are limited in efficacy.[16] Worryingly, first-generation antihistamines, which reduce itch in only 20% of postburn itch cases, have the undesired side effect of inhibiting muscarinic and serotonin receptors,[7] thus rendering this first line of treatment with its sedative side effect largely unsatisfactory. Common among the antihistamines are chlorpheniramine and cetirizine. Cetirizine selectively inhibits the peripheral histamine H1 receptors, including those of immune cells, respiratory smooth muscle cells, vascular endothelial cells, and the gastrointestinal tract. Histamine which is stored by mast cells and keratinocytes, binds to H1 receptors on the surface of sensory nerve endings. Antihistamines, additionally, stabilize mast cells and prevent their uncontrolled degranulation.[17] During wound healing, histamine is produced as a byproduct of collagen synthesis.[18] Its synthesis is increased in granulating wounds, explaining why proliferating and remodeling wounds itch the most during acute healing. However, cetirizine largely does not cross the blood–brain barrier and thereby avoids the neurons of the central nervous system, consequently producing minimal sedation compared to many first-generation antihistamines.[19,20]

Centrally acting medications such as gabapentin have been reported to greatly decrease the intensity of postburn pruritus. A prescription anticonvulsant drug that is also used in the treatment of chronic neuropathic pain, gabapentin's utility in itch management has been limited until recently.[21,22] The precise mechanism of action is not well known, but it is thought that its primary action is on the voltage-gated calcium ion channels in the dorsal horn where the itch pathway synapses.[23] This action inhibits the release of excitatory neurotransmitters. Gabapentin increases gamma-aminobutyric acid synthesis, which is an inhibitory neurotransmitter. The release of calcitonin gene-related peptide, a mediator of pruritus, is also inhibited by gabapentin. Additionally, it modulates the central perception of itch by acting on opioid receptors.[21–23] Therefore, gabapentin acts both on the peripheral and central itch pathways.

Gabapentin use for the treatment of pruritus is new, and it is not practiced at the Burns Unit of the Korle Bu Teaching Hospital, where this study was conducted. Antihistamines, particularly cetirizine, are the available postburn pruritus treatment medications at the Burns Unit, and their use in the treatment of healed wounds is often augmented with emollient and compression garments. This treatment modality only provides relief for a small percentage of patients, a situation that has compelled the search for superior alternatives. This study hypothesized that combined treatment with cetirizine and gabapentin for postburn itch would be better than their individual effect(s) due to their different mechanism of action—cetirizine acting peripherally and gabapentin acting centrally. The specific objectives were: (i) to determine the efficacy of cetirizine, gabapentin or their combination for treating pruritus in burn patients over a 14-day period and (ii) to compare the improvement in sleep impairments in postburn patients with pruritus upon treatment with cetirizine, gabapentin or their combination. This study, thus, compared the mainstay (standard-of-care) treatment form (10 mg of Cetirizine + 100 mg vitamin C daily) to the advocated treatment and evaluated their effects on sleep quality.

METHODS

Study design and site

The study was a randomized double-blind study conducted at the National Reconstructive Plastic Surgery and Burns Unit of the Korle Bu Teaching Hospital (KBTH), Accra, Ghana. The experimental intervention (Cetirizine plus Gabapentin) was compared with 2 monotherapy control arms (Cetirizine alone and Gabapentin alone). Even though burn injury is managed in various hospitals across the country, this unit receives referrals from all over the country, especially in the southern part. It sometimes serves neighboring countries. The unit, with a total bed capacity of 20, has an average annual patient admission of about 300. Usually, adults whose injuries exceed 20% of their TBSA are admitted for treatment. Children are admitted with 15% TBSA. On average, 2 cases of adults with severe burns (>20% TBSA) are admitted per week for treatment. However, an average of 5 burn cases are received and treated on an OPD (outpatients' department) basis every week. Those are patients with less than 15% burn. The unit is well-equipped to manage burn patients. The study was approved by the Ethics and Protocol Review Committee of the College of Health Sciences, University of Ghana [Ethical Approval Number: CHS-Et/M.9-P4.3/2016/2017] and was registered with the ISRCTN with the trial registration number ISRCTN10393098.[24]

Study participants and eligibility

The study was conducted on patients with burns involving >15% TBSA who were on admission at the Burn Unit of KBTH. Severe thermal burn was clinically defined as a thermal burn involving >20% TBSA. Eligible patients had to be (1) aged 16–65 years (assessments with VAS was difficult in children and the elderly), (2) have burns involving >15% TBSA (TBSA <15 patients are not admitted for treatment) and (3) were expected to be hospitalized for more than 7 days. Patients with the following conditions were excluded from the study: (1) patients with comorbidities including skin diseases, diabetes, chronic renal diseases, obstructive jaundice, pregnancy, etc., which by themselves caused itching, (2) patients who were septic, (3) patients with impaired cognitive ability, and (4) patients with known hypersensitivity reactions.

Sample size estimation

Based on findings from a previous study,[25] the study was designed to detect at least a 50% reduction in mean VAS scores between the combination and cetirizine-only groups. Based on these assumptions, a sample size of 19 participants per group was required to detect this difference at 95% confidence and 90% power. With an estimated 20% attrition rate, a total of 69 patients (23 participants per group) was recruited.

Participants recruitment, randomization, and concealment

Participants who satisfied the inclusion criteria were selected consecutively into the study after informed consent had been obtained and parental consent with assent in those aged below 18 years and capable of providing assent, ie, 10 years and above.

The selected participants were assigned a code and randomized into 3 groups. The groups consisted of standard treatment [cetirizine arm (Group A)] and interventional arm [gabapentin (Group B) and combined cetirizine and gabapentin (Group C)]. Participants were randomly allocated to one of the 3 arms of treatment by simple ballot without replacement.

The concealment was done by first wrapping the respective drug regimens in a foil before enveloping it in an opaque (brown) envelope and sealed by stapling. All the foil and envelope were of the same make. The patient's code and date were written on the back of the envelope. The sealed envelope was then given to the research assistant (RA), who was a qualified nurse in the unit and instructed on how to administer the drug to the participants. However, the RA was not told of the drug contained in the envelope. In the case of missing or damaged drugs, the pharmacist who carried out the assignment and could identify the number on the envelope replaced the envelope with the same drug.

Drug administration regimen

The standard adult dosage of cetirizine is 5-10 mg daily,[26] while for gabapentin, the recommended dosage for treating pruritus ranges from 300 mg to 900 mg per day, given in divided doses as has been successfully used with no side effects.[25,27] Cetirizine, 10 mg, was administered as a daily dose at 0600 h combined with 100 mg vitamin C to group A participants (cetirizine alone group). The vitamin C was administered again at 14 h and 22 h. The daily dose of cetirizine remained at 10 mg throughout the length of the study, as this was the standard treatment given at the unit where the study was conducted. At maximum dose, gabapentin was administered 300 mg 3 times daily at 6 h, 14 h, and 22 h to the study participants recruited into the gabapentin arm (group B). They also received 100 mg of vitamin C at the same hours. They, however, were started on the standard 300 mg daily dose combined with vitamin C. This dose was increased to 300 mg twice daily (600 mg total dose) if there was no response to treatment as per VAS on day 3 and then increased to the maximum dose of 300 mg 3 times daily (900 mg total dose). However, they were maintained on their current dose if there was an improvement in symptoms until the next review.

The Cetirizine-Gabapentin arm (group C) was administered a combined dosage of the 2 medications. Thus, they were started on 10 mg cetirizine combined with 300 mg gabapentin as a daily dose. The dose of gabapentin was increased to 300 mg twice daily when the VAS score did not change, whilst the cetirizine dose remained 10 mg daily. On the third review day, when the effect of the drug had not increased significantly as per the VAS score, the gabapentin dosage was increased to 300 mg 3 times daily while still maintaining the cetirizine dose of 10 mg daily. They also received 100 mg of vitamin C 8 h in combination.

VAS and AIS deployment

A baseline assessment of the intensity of pruritus was performed using the visual analog scale (VAS). Pruritus was categorized into 4 groups based on the VAS score into the following categories: (i) no itch (VAS 0-1), (ii) mild (VAS 2-4), (iii) moderate (VAS 5-7), and (iv) severe (VAS 8-10). The Athens Insomnia Scale (AIS) was employed to score sleep quality.[28] The patients were followed up and reviewed on days 3, 7, and day 14. At each follow-up day, the improvement or otherwise in itch intensity was assessed using VAS. However, AIS assessment was done on a weekly basis, ie, days 7 and 14. If, on these days, there had been no response to treatment or the symptoms worsened, the dose of the drug was increased as described above until the maximum dosage regimen was reached. Treatment was discontinued if there was no response or worsening symptoms at maximum dosage. Those whose treatment was discontinued were put on the standard treatment offered at the Burn Unit, which comprises cetirizine-only treatments with/without paraffin oil or petroleum jelly for moisturizing. Treatment was discontinued if the participants reported any adverse events.

Adverse event assessment

Adverse events were monitored daily using the Generic Assessment of Side Effects tool.[29] This tool is a 36-item questionnaire that reviews all the body systems. In addition, patients could list and rate any other symptom. A symptom was rated as mild, moderate, or severe.

Statistical analysis

Data was analyzed using IBM SPSS Statistics version 20. Categorical variables, including gender, educational status, and drug side effects, were expressed as proportions, tables, and graphs. Continuous variables, including age, VAS and AIS, were expressed as means and standard deviation and compared using the *t*-test, while categorical variables were expressed as proportions and compared by means of the chi-square or Fischer exact test as appropriate. The primary outcome of the study was to evaluate the effect of the study drugs on pruritus. Comparison among the various regimens (cetirizine, gabapentin or their combination) for treating pruritus burn patients over a 14-day period was done using repeated measures mixed analysis of variance (ANOVA). *P*-value ≤ .05 was deemed statistically significant.

RESULTS

Participant enrollment and overview of the study

During the recruitment period of the study (November 2017–April 2019), 96 patients with varying percentages of burn were eligible for the study. Twenty-seven[27] patients who did not satisfy the inclusion criteria were excluded, and the

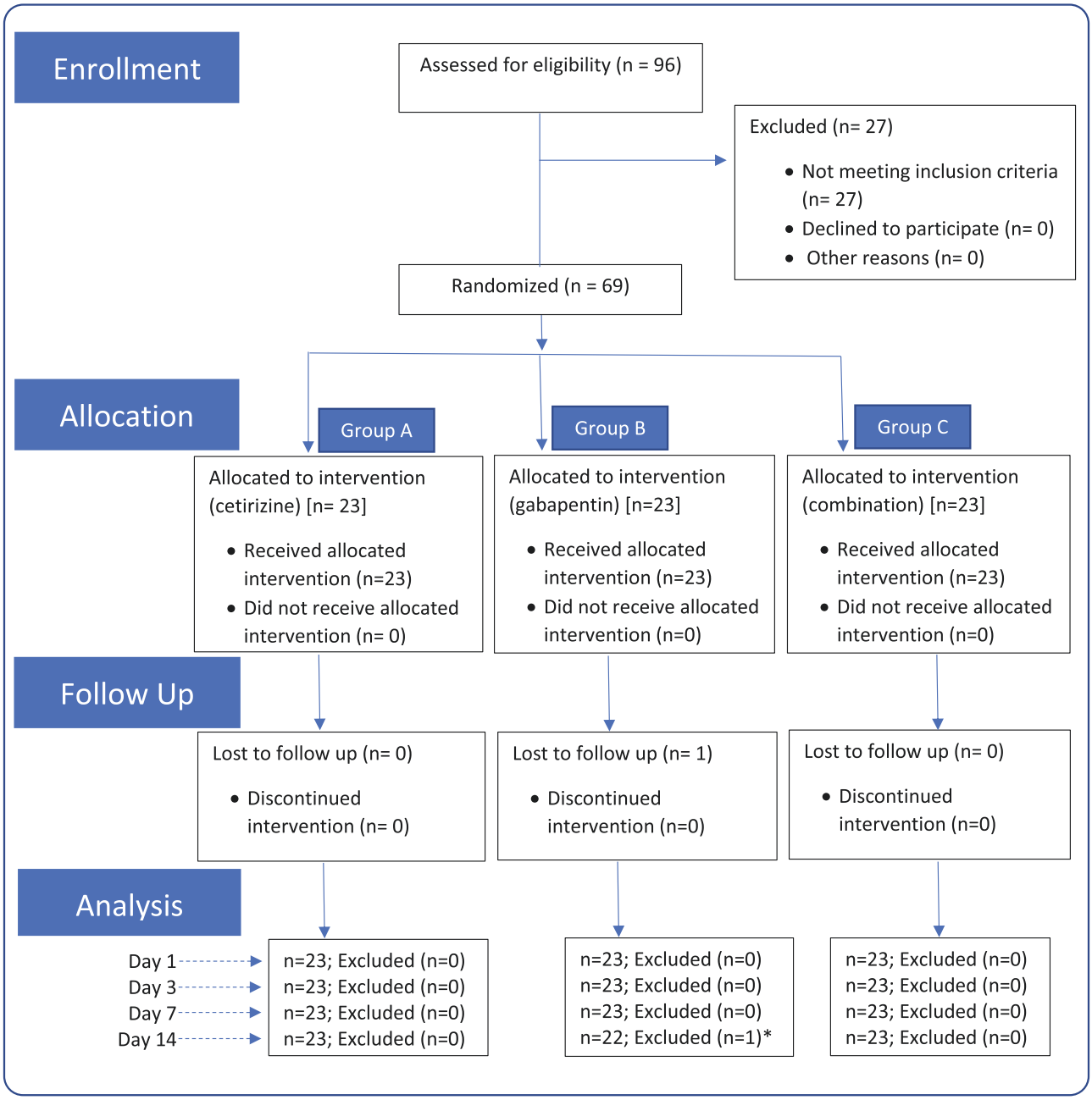

Figure 1. A Flow Chat for the Trial. Ninety-Six Patients Were Assessed for Eligibility, of Which 69 Qualified for Enrollment. The Enrolled Were Randomized into 3 Groups, 23 Patients Each. * Lost to Follow-Up

remaining 69 were randomized (Figure 1) for the study. One participant in the gabapentin arm did not complete the treatment as the participant defaulted to treatment and was lost to follow-up. However, data obtained from that participant for days 0, 3, and 7 were included in the analyses and censored.

Participants' demographics

The 69 participants included in the study consisted of 36 (52.2%) males and 33 (47.8%) females. The average age of the participants was 33.3 (SD = 10.9) years. The youngest participant was a 16-year-old female, and the oldest participant, also female, was 64. The majority of participants were aged between 26 and 35 (Table 1). The mean age between the 3 groups was not significantly different statistically. The number of females in the groups cetirizine (A), gabapentin (B) and combination (C), respectively, were 12 (52.2%), 10 (43.5%) and 11 (47.8%) and for males 11 (47.8%), 13 (56.5%) and 12 (52.2%). Statistically, there was no difference between males and females in the treatment groups (χ^2 = 0.35: P = .840).

Flame burn was the most common cause of burn

The commonest cause of burn amongst the patients was flame burn, the result of an explosion from household use

of liquefied petroleum gas. They constituted 63.8%. Scalding burn from hot water, soups and oils made up 20.3%. Two patients sustained burns from other sources—one fell into a pit of hot ash (charcoal), the other from radiation heat from a blazing incinerator. Chemical burn made up 4.3%. Table 2 details the causes of burns among the 3 arms of the study. Gabapentin and combination groups contributed 21.7%[15] each to the flame burn population, whilst the cetirizine group contributed 20.3%.[14] No patient presented with chemical burn in the cetirizine groups, whilst the combination group reported 2 cases. Scalding burn had the highest representation in the cetirizine group (8.7%). There was no difference in the cause of burns between the treatment groups when it was subjected to statistical analysis (Fisher's = 6.57: $P = .585$).

At the time of enrollment, 53 patients (77%) had not received surgery (skin grafting) or any form of procedure intended to aid wound healing surgically, eg, an integra application. This represented the number of patients whose wounds healed by secondary intention and reepithelialization. However, 23% (16 patients) had skin grafting prior to reporting itch. With regards to the participants who did not receive surgery prior to treatment administration, 20 (29.0%) were in the combination group, whereas the majority of those who received surgery 5 (7.2%) fell into the gabapentin group (Table 2). There was no difference in statistics among those who received surgery before treatment and amongst those who did have surgery before treatment commenced (Fisher's test = 0.66: $P = .918$). The majority (94.2%) of the patients started experiencing pruritus between the first and fourth weeks. Only 5.8% experienced itch after the fourth week of injury. The third-week postinjury was when most participants experienced their first itch (30.4%). Those who experienced itch by the fourth week constituted 23.2%, with 20.3% experiencing it in week 1. Only 1 patient (1.4%) reported that the itch episode started more than 6 weeks after the burn injury. Categorizing the duration of itch, 70% of the patients had endured itch for less than 6 weeks (acute itch), while 30% had endured itch for more than 6 weeks (chronic itch) (Table 2).

Dosage

There was a statistically significant association ($P = .001$) between the dosage given and the treatment groups. In the gabapentin group, 9 out of the 23 persons had received 2 dosages of the drug (ie, 600 mg in 2 divided doses) by the time they were exiting the study. Only 1 person received the full dose of 900 mg administered in 3 divided doses. More than half of the participants in the gabapentin group received only a single dose of the drug. Amongst the combination group, however, 19 out of the 23 persons received a single dose of cetirizine and gabapentin combined, with only 4 receiving a dose comprising a single dose of cetirizine and a double dose (600 mg) of gabapentin. None of the participants in the combination group received 3 doses of gabapentin (900 mg).

Table 1. Age Distribution Among Participants and Treatment Groups

Age distribution of participants		Age (years) distribution between the treatment groups				
Range (years)	**Frequency**	**Group/*n***	**Mean (SD)**	**Min**	**Max**	***P*-value**
15-25	16	Cetirizine (A)/23	31.4(8.3)	16	50	.193
26-35	28					
36-45	17	Gabapentin (B)/23	31.7(10.7)	16	58	
46-55	4					
56-65	4	Combination (C)/23	36.6(12.9)	16	64	

Table 2. Distribution of Causes of Burn, Prior Surgery, and Itch Duration Among Participants

	Treatment group/*n*			
Parameter	**Cetirizine (Group A)/23**	**Gabapentin (Group B)/23**	**Combination (Group C)/23**	***P*-value**
Cause of burn				
Chemical	0 (0.0%)	1 (1.4%)	2 (2.9%)	.585
Electric burn	3 (4.3%)	2 (2.9%)	1 (1.4%)	
Flame	14 (20.3%)	15 (21.7%)	15 (21.7%)	
Scalding	6 (8.7%)	3 (4.3%)	5 (7.2%)	
Other	0 (0.0%)	2 (2.9%)	0 (0.0%)	
Previous surgery				
No	19 (27.5%)	18 (26.1%)	20 (29.0%)	.918
Yes	4 (5.8%)	5 (7.2%)	3 (4.3%)	
Itch duration				
<6 weeks	17 (24.6%)	16 (23.2%)	15 (21.7%)	.814
>6 weeks	6 (8.7%)	7 (10.1%)	8 (11.6%)	

Gabapentin reduced pruritus by 92.9% in 14 days

More than half (52.1%) of the participants presented with severe itch, up to 44.9% with moderate itch, while 2.8% reported mild itch. None of the participants in all 3 groups remained in the severe itch category at the end of the study (Table 3). At the end of the study (day 14), whereas all the participants in the gabapentin group were itch-free, 3 (13%) of the participants within the cetirizine group reported moderate itch, whilst 15 (65.2%) still experienced mild itch. In all, there was a significant difference between the main treatment effect on itch reduction among the study groups (*F*-test = 3.39: *P* = .040). The mean VAS over the duration of the study for cetirizine was 4.7 as compared to 3.7 for the gabapentin group (Figure 2A). There was a significant interaction effect between the time at which the measurement was done and the treatment group on the mean VAS score (*F*-test = 10.16: *P* <.001) with an effect size of 0.24. From Figure 2B, the mean VAS reduced from 7.17 to 2.74 by the end of the study for the cetirizine group. This constituted 61.8% reduction in VAS compared to 92.9% of the gabapentin group, which had reduced from 7.05 to 0.50. On day 7, cetirizine had improved the VAS score by 47.8%, while the gabapentin group had improved by 61.3%. By day 7, the combination groups recorded a percentage itch reduction of 61.6%, and by day 14, they recorded 91.3 % from 8.04 to 0.70.

Pruritus was categorized into acute itch (duration of itch <6 weeks) and chronic itch (duration of itch >6 weeks). The majority of the participants presented with acute itch (69.6%), with chronic itch making up 30.4%. In the acute itch group, there was a statistically significant difference between the main treatment effect and itch reduction (*F*-test = 3.24: *P* = .048). There was a significant interaction between time and the treatment group. On day 14, the effect of reducing itch intensity was different amongst the groups, with cetirizine offering a lower reduction rate (*P* < .001). All the other days of the treatments were not different from each other. In the chronic itch group, there was no difference between the main treatment effects of itch reduction (*F*-test = 3.21, *P* = .064). There was a significant interaction effect between time and treatments with an effect size of 0.84 (*F* = 15.89: *P* < .001). Thus, the effect cetirizine had on reducing the mean VAS score was significantly different from the gabapentin and the combination groups for participants with chronic itch (*P* <.001) on day 14 (Table 3). There was no difference between the gabapentin and the combination group at day 14 (*P* = 1.000). The mean VAS score of the cetirizine group on day 14 was 4.6 compared to 0.86 of the gabapentin group, as shown in Table 3.

Adequate itch control improves sleep

The highest score (AIS) of 22 was recorded on day 1, while the lowest score of 0 was recorded both on days 7 and 14. Table 4 represents the insomnia status of participants among the treatment groups on day 1 and day 14. Even though all the participants in the combination group reported insomnia on day 1, there was no statistical difference between the groups (*P* = .127). However, on day 14, the difference was significant (*P* = .004). The gabapentin group recorded the least number of participants with insomnia at the end of the study (*n* = 1, 1.4%), and cetirizine with the most (*n* = 11, 15.9%). The insomnia score of the participants reduced over the period upon drug administration (*F*-test = 297.96: *P* = .004). However, the main effect of the treatment groups was not statistically significant (*F*-test = 0.46: *P* = .636), though

Table 3. Itch Categorization and Intensity Among Treatment Groups

		Itch intensity estimated by VAS score			
Treatment groups/*n*	**Day**	**No itch**	**Mild itch**	**Moderate itch**	**Severe itch**
Cetirizine	1	0(0.0%)	1(1.4%)	12(17.4%)	10(14.5%)
(Group A)/23	3	0(0.0%)	10(14.5%)	13(18.8%)	0(0.0%)
	7	4(5.8%)	9(13.0%)	8(14.5%)	0(0.0%)
	14	5(7.5%)	15(22.1%)	3(4.4%)	0(0.0%)
Gabapentin	1	0(0.0%)	0(0.0%)	12(17.4%)	11(15.9%)
(Group B)/23	3	0(0.0%)	10(14.5%)	13(18.8%)	0(0.0%)
	7	7(10.1%)	10(14.5%)	6(8.7%)	0(0.0%)
	14	22(32.4%)	0(0.0%)	0(0.0%)	0(0.0%)
Combination	1	0(0.0%)	1(1.4%)	7(10.1%)	15(21.7%)
(Group C)/23	3	1(1.4%)	5(7.2%)	16(23.2%)	1(1.4%)
	7	4(5.8%)	16(23.2%)	3(4.3%)	0(0.0%)
	14	18(26.5%)	5(7.5%)	0(0.0%)	0(0.0%)

Itch classification	**Treatment group**	**Mean VAS at day 1**	**Mean VAS at day 14**	**Percent reduction**
Acute itch	Cetirizine	7.059	2.059	70.8
	Gabapentin	6.533	0.333	94.9
	Combination	7.600	0.467	93.8
Chronic itch	Cetirizine	7.500	4.667	37.8
	Gabapentin	8.143	0.857	89.5
	Combination	8.875	1.125	87.3

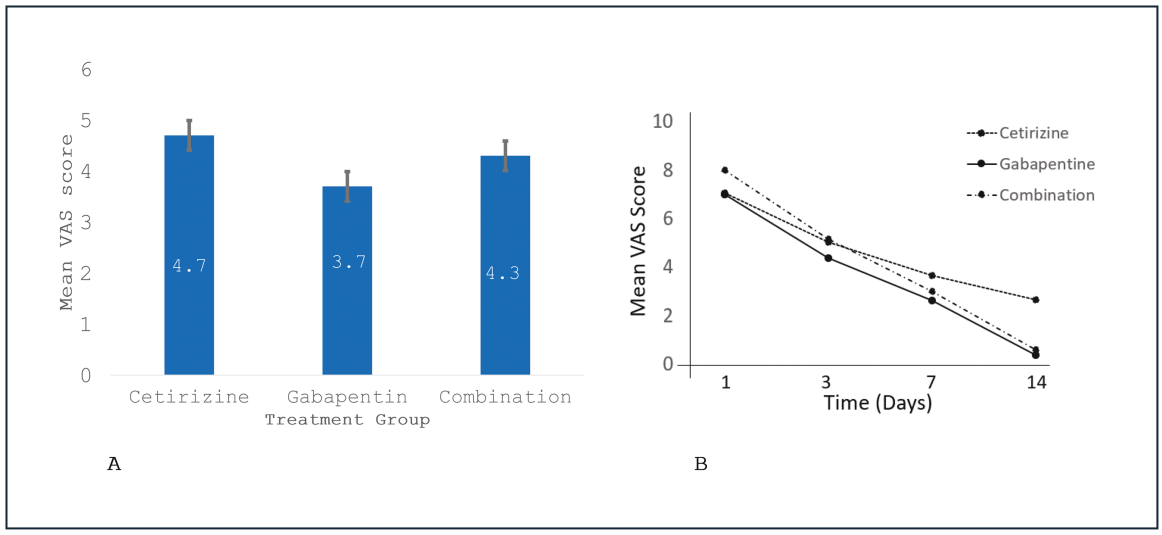

Figure 2. (A) Mean VAS Score Among Treatment Groups. (B) Mean VAS Scores Among Groups in Relation to Time

Table 4. Insomnia Status Among Participants Among Treatment Groups

			Status			
			Normal	Insomnia		
Day		**Treatment group**	***n* (%)**	***n* (%)**	**Chi-square**	***P*-value**
	1	Cetirizine	4 (5.8%)	19 (27.5%)	4.13	.198
		Gabapentin	3 (4.3%)	20 (29.0%)		
		Combination	0 (0.0%)	23 (33.3%)		
	14	Cetirizine	12 (17.4%)	11 (15.9%)	11.28	.004
		Gabapentin	22 (31.9%)	1 (1.4%)		
		Combination	17 (24.6%)	6 (8.7%)		
Mean insomnia score						
Treatment group				Day 1	Day 14	*P*1	*P*2
Cetirizine				11.87	5.30	.002	.001
Gabapentin				13.60	3.77	.001	
Combination				15.00	4.17	.002	

*P*1 is *P*-value obtained by comparing day 1 and day 14 scores within groups.
*P*2 is *P*-value obtained by comparing day 1 and day 14 scores between groups.

the mean scores of all 3 groups decreased significantly from baseline to endpoint (Table 4). There was a strong, significant positive correlation between the VAS score on day 1 and the insomnia score on day 1 ($r = 0.520$: $P < .001$) and on day 14 ($r = 0.591$; $P < .001$) (Figure 3).

Gabapentin provides greater satisfaction after treatment

All patients recorded varying degrees of improvement in their treatment, with the gabapentin group recording the highest level of satisfaction. Of the 22 participants (1 participant did not complete treatment) in the gabapentin group, 12 reported that they were "*very satisfied*" with their treatment at the time they were exiting the study. This constituted 17.4% of the total population. The combination group recorded a close percentage of 14.5% (Table 5). However, none of the participants in the cetirizine group reported that they were "*very satisfied*" with their treatment. The highest level of satisfaction amongst this group was "*satisfied*," constituting 15.9% of the total population. Out of the 23 participants of the cetirizine group, 10 reported that even though their symptoms improved, they were not satisfied with the treatment as compared to 0 and 2 persons in the gabapentin and combination groups, respectively. The total number of "*satisfied*" and "*very satisfied*" patients in the gabapentin and combination groups were 22 (31.9%) and 21 (30.4%), respectively and were higher than in the cetirizine group 11 (15.9%). No patient reported "*no improvement*" in the gabapentin and combination groups. Participants' satisfaction level was highly significant among the treatment groups (Fisher's test = 32.18, $P < .001$).

DISCUSSION

The study compared the effectiveness of 3 postburn pruritus treatment options: cetirizine, a traditional treatment offered

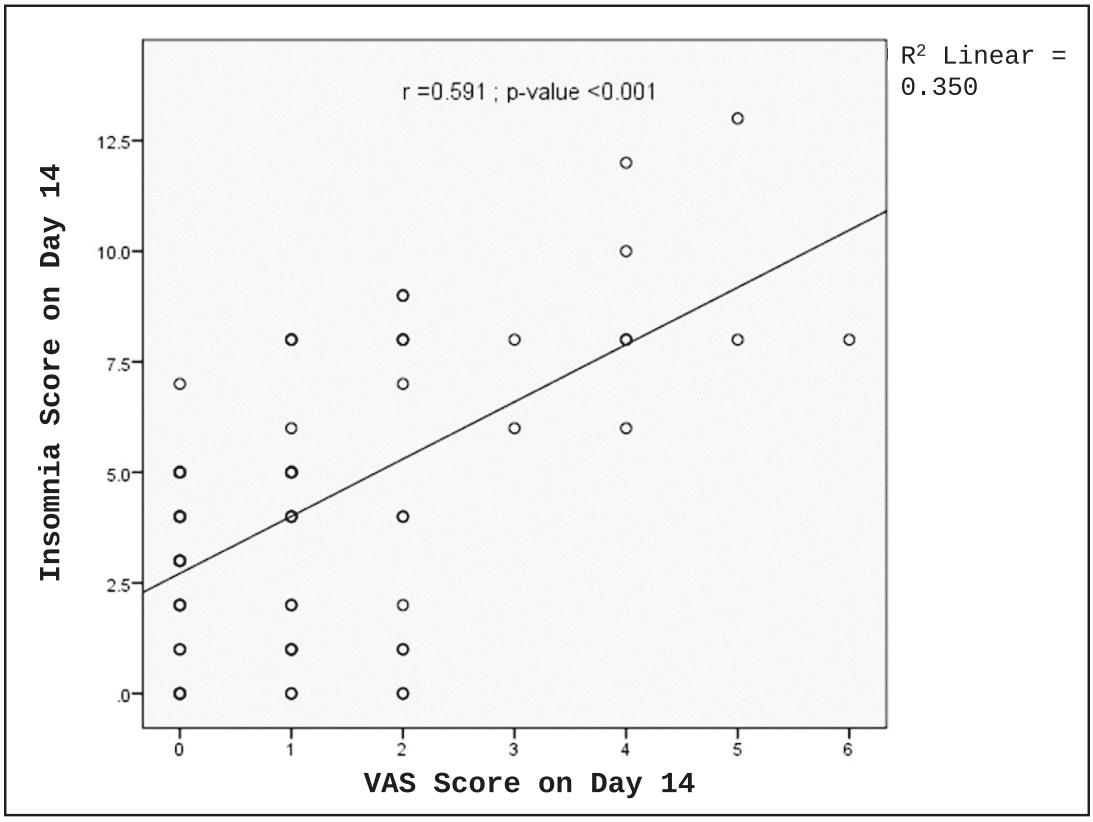

Figure 3. Correlation Between Insomnia and VAS Scores at Day 14

Table 5. Participant Satisfaction Level Among Treatment Groups

	Treatment groups				
Satisfaction level	**Cetirizine**	**Gabapentin**	**Combination**	**Fisher's exact test**	***P*-value**
Itch worsened	0 (0.0%)	0 (0.0%)	0 (0.0%)	32.18	<.001
No improvement	2 (2.9%)	0 (0.0%)	0 (0.0%)		
Improved but not satisfied	10 (14.5%)	0 (0.0%)	2 (2.9%)		
Satisfied	11(15.9%)	10 (14.5%)	11 (15.9%)		
Very satisfied	0 (0.0%)	12 (17.4%)	10 (14.5%)		

at the Burns Unit of the Korle Bu Teaching Hospital, with 2 newer treatment forms—(i) gabapentin and (ii) cetirizine-gabapentin combination. This was based on the hypothesis that combined treatment with cetirizine and gabapentin would have a better effect on postburn pruritus than their individual effect due to their different mechanism of action.

Overall, the intensity of the itch continuously decreased over time independently of the treatment group. However, the itch-reducing effect of cetirizine plateaued earlier than it was seen with the gabapentin or combination groups. Whereas there was no difference between gabapentin and the combination groups in reducing itch intensity, there was a markedly significant difference between cetirizine and gabapentin and between cetirizine and combination. This suggests that the gabapentin and the combination treatments were more efficient at reducing itch intensity than cetirizine alone. The total reduction of the mean VAS score (itch intensity) over the 14-day period was 61.8% for cetirizine, 92.9% for gabapentin and 91.3% for combination. Thus, gabapentin alone can be used as monotherapy for the treatment of itch and combining it with cetirizine is unlikely to provide any additional advantage. Over the first week, when the effect of treatment was evaluated amongst the different groups, gabapentin reduced the intensity of the itch by 61.3% compared to cetirizine by 47.8%. It can be inferred from this finding that gabapentin has a quicker onset of action in itch reduction than cetirizine. Ahuja et al. also reported a similar finding, that the onset of action of gabapentin in reducing itch was dramatic.[25] They reported a reduction of mean VAS score for cetirizine at 52%, gabapentin at 95% and combination at 94%. Their study, however, spanned 28 days, which might contribute to the slightly higher percentages reported. The general trend is realized to be that time has a positive effect on treatment, ie, reducing itch intensity. Therefore, it is safe to assume that if the participants had received medication for 2 more weeks, more patients could have attained "*no itch*" status. Further contributing to the higher percentages

of itch reduction recorded in the Ahuja study is that patients were started on comparatively higher doses of gabapentin, such that participants with VAS scores of 9-10 received 900 mg of gabapentin. Such patients would have received the lowest dose of 300 mg if they were recruited for this study. The percentage reduction of itch amongst the cetirizine group in this study was, however, higher than the percentage Ahuja recorded (61.8% vs 52%, respectively). Considering the higher dosage of cetirizine patients received in the Ahuja et al. study (10 mg BD), a greater response was expected. Participants of the cetirizine group (group A) received a single dose of 10 mg, which is the dose used at the center where the study was conducted. Perhaps the increased itch intensity reduction success in this study was due to the fact that a greater portion of the participants suffered acute itch (69.9%).

The principal indication for the use of gabapentin is for the treatment of seizure disorders. Besides that, it has also been indicated for the treatment of chronic neuropathic pain.[30] All these are deemed greater stimuli than itch. Itch itself is a subjective symptom. Therefore, in this study, the participants began treatment with the lowest dosage, irrespective of their initial VAS score. The dosage, however, was increased if the symptoms did not improve. Only 1 patient required the full dose of gabapentin for the treatment of itch, with only 13 out of 46 (28.3%) patients requiring twice-daily dosing (600 mg) of gabapentin to control their itch. Thus, even though higher daily doses might result in a quicker or better reduction in itch intensity, a daily dose of 300 mg daily was sufficient for most patients. Starting on a lower dose may also be beneficial in reducing side effects, and it is also cost-effective. This emphasizes the need for reevaluation of the patient's symptoms during treatment using the VAS score. The association between dosage and treatment effect was statistically significant, suggesting that higher dosage is likely to result in much better itch control. Interestingly, when combined with cetirizine, the dosage of gabapentin required to produce efficient itch reduction is reduced. Whereas 9 patients in the gabapentin group required a daily dose of 600 mg, only 4 persons in the combination group required 600 mg gabapentin to control itch. This may not show a synergistic effect of cetirizine and gabapentin because gabapentin, when used alone, reduced pruritus by 92.9% as compared to when combined with cetirizine (91.3%).

Pruritus was subclassified into *acute* and *chronic* itch. This was to evaluate the assumption that no difference existed amongst the treatment groups insofar as itch was experienced within 6 weeks and that any difference would have been noted after itch had prolonged into chronicity (more than 6 weeks). However, even though the reduction in the mean VAS score of the cetirizine group was better with acute itch (70.8%), it proved very unsatisfactory within the chronic group—recording a reduction of mean VAS score at only 37.7% over a 14-day period (Table 3). The gabapentin group showed better mean VAS reduction—94.9% for acute and 89.5% for chronic. The performance of the combination was similar to gabapentin. This demonstrates that when itch becomes protracted and chronic, cetirizine is unable to manage it effectively. Gabapentin or combination therapy with cetirizine is a better treatment option in such circumstances.

The findings from the present study suggest that treatment/management of moderate to severe itch with cetirizine is unlikely to result in itch-free status within a 14-day timeframe. Gabapentin or a cetirizine-gabapentin combination will likely do so. Two-thirds of participants in the cetirizine group still reported itch at the end of the study, whereas all the participants of the gabapentin group, including those with severe itch attained "*no itch*" status (Table 3). The study, therefore, revealed that it would be better for the caregiver to classify itch intensity before starting treatment and recommends that severe to moderate itch should be treated with centrally acting medications such as gabapentin. Even when the itch is acute and moderate, a low-dose gabapentin could be added if cetirizine is the drug intended for its treatment.

These observations contributed to patients' responses when evaluating their satisfaction with the treatment they received. Participants in the gabapentin and combination groups were more content with treatment (Table 5). With none of the participants of the cetirizine group reporting that they were "*very satisfied*" with their treatment, most of the gabapentin population recorded otherwise. Most of the cetirizine participants responded that even though their symptoms improved, they were not satisfied with their treatment. Goutos, reviewing the current practices of postburn management in the United Kingdom, stated that antihistamines only partially relieved the symptoms of itch in 60% of his patients, with 20% reporting no relief at all.[31] Once again, the satisfaction in the combination group was comparable to the gabapentin group.

Itch is a discomforting symptom and can deprive the sufferer of their sleep. As much as 89.8% of the participants reported insomnia at the start of the study (Table 4). They affirmed the disturbing influence itch had on the quality of sleep. At the end of the study, though, only 26% of the participants reported still having insomnia. There was a general trend of improvement in sleep disturbance amongst the 3 groups. The cetirizine group, however, had more patients exiting the study still with insomnia than the rest of the groups (Table 4). It was expected that cetirizine would have delivered more somnolence from its side effects, thereby impacting insomnia and improving sleep. Rather, it was the persistence of the itch that influenced whether the patient got a good night's sleep or kept awake scratching his wounds for relief. This reflected the percentage reduction in the mean VAS score. There was a significantly positive correlation between VAS score and insomnia, such that the higher the VAS score, the more severe the insomnia and vice versa (Figure 3).

Postburn pruritus is not the only cause of insomnia in burn patients. Pain, anxiety, depression, and medications all contribute to the cause of insomnia.[32] The constant interruption from hospital staff to either review or administer scheduled medications disturbs the patient's sleep. Medications such as opioid-based drugs, eg, pethidine, morphine, which are commonly used to alleviate pain in burn patients, increase somnolence. With all these at play, it is difficult to say emphatically that controlling itch alone improves insomnia. However, whilst all these factors existed, the patients had sleep disturbances, and it was not until itch was controlled that insomnia improved significantly in this study. On the other hand, since gabapentin is known to effectively control pain, the subjects could have attained relief for both itch and pain at the same time, especially in those who still had open wounds. Thus, the better control of insomnia was seen in the groups whose treatment contained

gabapentin. Raymond et al. studied the interrelationship between quality of sleep and pain in hospitalized burn patients.[33] They found out that burn patients experienced sleep impairment, which correlated with the intensity of pain they bore. Such that, the intensity of pain worsened in the morning after a bad night's sleep. Pain was a determinant of poor sleep as a result. Because pain and itch are shades of the same stimulus, controlling itch should improve sleep.

LIMITATIONS

The instrument used in measuring the intensity of itch, the Visual Analog Scale, although validated, only did so subjectively since there are no known methods for objectively assessing itch intensity. A more objective method of evaluating itch intensity would have provided additional or alternative options for assessing itch intensity. Additionally, the study considered only patients who sustained severe burns and were thus admitted for treatment. Patients whose burns involved TBSA of less than 15% but also experienced itch were not studied. Also, patients <16 and >65 years of age were excluded from the study. Therefore, the effect of treatment on pruritus within this age group could not be evaluated. However, given the random allocation of interventions and minimal losses to follow-up, the efficacy results could be considered approximate to an estimate derived from an intention-to-treat analysis and, therefore, sufficiently robust.

CONCLUSION

The study compared the effectiveness of 3 postburn pruritus treatment options: cetirizine, a standard-of-care treatment offered at the Burns Unit of the Korle Bu Teaching Hospital, with 2 newer treatment forms—gabapentin and cetirizine-gabapentin combination. The results suggest that gabapentin is a better agent for reducing the intensity of itch than cetirizine. Its effectiveness as a monotherapy is comparable to that of a cetirizine-gabapentin combination. Combined therapy of gabapentin and cetirizine, however, yielded a better result at reducing itch intensity than cetirizine alone. The intensity of itch correlates positively with insomnia, such that the greater the VAS score, the greater insomnia and thus, reducing itch intensity improves sleep.

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