Efficacy and Safety of Nicotinic Acid for Prophylaxis of Episodic Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Nicotinic acid is a water-soluble vitamin used in dyslipidaemia.

Objective: In this study, 2 doses of nicotinic acid were compared with placebo to explore the effect of this drug in prophylaxis of episodic migraine.

Methods: In this phase 2 trial, adults with episodic migraine attended at Outpatient Department of Bangladesh Medical University were recruited. After a 4-weeks of baseline, 66 eligible participants were randomized to oral Nicotinic acid 500 mg or 1000 mg extended-release tablet or placebo a day for 12 weeks. The primary endpoint was changes in the number of migraine days per 4 weeks from the baseline, was assessed and compared. Trial was registered in the ClinicalTrials.gov with the trial ID number NCT05846373

Results: Nicotinic acid extended-release tablet 500 mg and 1000 mg reduced the number of migraine days per 4 weeks significantly over 1st week to 8th week of double-blind treatment phase (p value < 0.0001 for both Niacin 500 mg and 1000 mg than that of the baseline). Reductions were maintained over 9th to 12th weeks. The number of migraine days were 2.55 ± 2.19 in Niacin 500 mg arm and 2.11 ± 2.05 in Niacin 1000 mg arm were significantly lower than placebo (p = 0.004 among the 3 arms). Most common Treatment-emergent adverse events (TEAEs) experienced in Niacin arm was flushing (42% in 1000 mg arm and 25% in 500 mg arm). They were self-limiting and not much different in Nicotinic acid arms than placebo (p > 0.05).

Conclusion: Nicotinic acid was effective and well-tolerated in prophylaxis of episodic migraine.

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Introduction

Migraine is a prevalent neurological illness that occurs in episodes and has a complex origin. It is characterized by recurring episodes of severe, usually one-sided headaches that often have a pulsating sensation associated with emesis, phonophobia, and photophobia.[1]

According to the Global Burden of Disease 2019 (GBD 2019), the prevalence of migraine estimated was 12.27% to 16.24%. 17.90% women and 10.34% men are affected by migraine. [2] Migraine badly hampers one's quality of life.[3]

The exact etiology and pathophysiology of migraine are unknown. Certain triggers[4] as well as genetic factors are found to be responsible for migraine.[5]

There are several hypotheses about migraine pain generation. In trigeminal ganglion, various inflammatory and vasoactive substances like Calcitonin Gene-Related Peptide (CGRP) and Substance P were found.[6] Trigeminovascular pain pathway is activated on stimulation by these substances when they are released.[7]

Several studies demonstrated neuroinflammation (CRP),[8] and impairment of cerebral mitochondrial energy metabolism in migraine.[9]

Migraine treatment options include acute antimigraine medications, preventive medications, and nonpharmacological therapies.[10] Discontinuation of currently used preventive therapy is high[11] due to poor efficacy and low tolerability. So, effective and well-tolerated oral preventive treatments are needed.[12]

Niacin, which is known as nicotinic acid, or Vitamin B_3, is the precursor of Nicotinamide Adenine Dinucleotide (NAD) or Nicotinamide Adenine Dinucleotide Phosphate (NADP).[13] NAD is produced from dietary tryptophan,[14] and rest of the tryptophan is catabolized to form serotonin (5-HydroxyTryptamine/ 5-HT).[15] It has been found that a low serotonin level is associated with migraine,[16] and injecting serotonin results in relief of migraine headaches. Niacin supplementation accelerates production of 5-HT,[17] thus helps to abolish migraine pain, reduces neuroinflammation,[18] limits cerebral energy shortage.[19] In an observational study performed in the USA, it was found that higher dietary niacin intake is associated with lower migraine risk.[20] Prior to this finding, there were several case reports [15,21] and open-label studies[22,23] showing the beneficial effects of niacin on migraine. But there is no controlled study.[20] So, this study was designed as an attempt to assess the effect of nicotinic acid for prophylaxis of migraine. Further prospective studies are required to establish the preventative benefit of niacin on migraines, as there is currently no placebo-controlled trial specifically focused on nicotinic acid.[20] This study was conducted to evaluate the effects of the impact of extended-release nicotinic acid on the reduction of frequency of headache and improvement in quality of life.

Methods

This Randomized, double-blind, placebo-controlled, parallel-group, single center phase 2 trial was conducted in the Department of Pharmacology and Department of Neurology, Bangladesh Medical University (BMU), Dhaka from March 2022 to January 2024 (actual enrollment started after getting approval from the IRB, i.e., November 2022). 66 potential participants were recruited from the patients attending outpatient department of Neurology and Headache clinic, BMU.

Inclusion Criteria

- Age:18 to 65 years
- Migraine with or without aura according to the International Classification of Headache Disorder, 3rd edition (ICHD 3) criteria,[24] with 4 to 14 qualified migraine headache days per month
- Moderate to severe headache (visual analogue scale score at least 3)
- Receiving Propranolol 40 mg/day
- History of migraine for at least 1 year
- Age at the onset of migraine: less than 50 years.

Exclusion Criteria

- Pregnant and lactating mothers
- Known case of any active liver diseases, diabetes mellitus (DM), gout, peptic ulcer disease, bronchial asthma, bradycardia, peripheral vascular diseases
- Serum ALT > 2 times upper limit of normal range
- Uric acid > 7.00 mg/dl
- Serum Albumin < 32 mg/dl
- Fasting Blood Glucose > 10 mmol/L
- Hypersensitive to niacin
- Taking certain drugs such as lipid lowering agents, antiplatelets and anticoagulants, antihypertensive medications, alcohol or other abusive drugs.

Study procedure

After 28 days open-label baseline period, eligible patients were instructed to visit after overnight fasting. Blood samples were collected for baseline ALT, FBS, Uric acid and albumin estimation. After fulfilling all eligibility criteria, purposive sampling was done and 66 participants entered into the 12 weeks double-blind phase of the study with informed written consent. After baseline assessment, participants were randomly allocated into 3 arms. Each participant was blindly provided a placebo or Nicotinic acid 500 mg or nicotinic acid 1000 mg extended-release tablets containing package, Headache Diary for 3 months, patient compliance form with instructions. 22 of the 66 participants received placebo tablets, 22 received Nicotinic acid extended-release tablet 500 mg/day and 22 participants received Nicotinic acid extended-release tablet 1000 mg/day orally with low fat meal for 84 days. Changes in frequency of headache per 4 weeks, severity of headache using 11-point Visual Analogue Scale (VAS) score, and quality of life using Migraine Specific Quality of Life Questionnaire (Version 2.1) were assessed at the end of 8th and 12th week. A translated and validated Bengali version of this questionnaire was obtained from the website https://eprovide.mapi-trust.org/. For safety analysis, serum Alanine Aminotransferase (ALT), Uric acid, Fasting blood glucose (FBS), and serum albumin were done at the end of 12 weeks. After unmasking, statistical analysis was done.

Statistical Analysis

Statistical analysis was done by Microsoft Office Excel 2019. Chi-squared test was done to see the association between the interventions and the placebo arm. A One-way Analysis of Variance (ANOVA) was done to compare scores among the three arms. Repeated measures ANOVA was done to compare among the baseline, at the end of 8 weeks and at the end of 12 weeks. Unpaired t-test was done to compare between two drug groups. Paired t-test was done to compare the score before and after the intervention. The significant p value is < 0.05.

Results

Figure 1 shows that, at the end of the research, total 8 participants discontinued the trial and 58 patients completed the study. So,19 patients from the placebo arm, 20 patients from nicotinic acid 500 mg arm and 19 patients from Nicotinic acid 1000 mg arm were assessed and evaluated.

At baseline, all the 3 arms were comparable in terms of age, sex, Body Mass Index (BMI) and presence of aura ($p > 0.05$, Table I).

Table II shows that, at baseline, migraine days per 4 weeks, mean 11-point visual analogue scale (VAS) score in 4 weeks and MSQ Version 2.1 scores were not significantly different among the 3 arms ($P > 0.05$).

Figure 2 shows the number of migraine days per 4 weeks throughout the double-blind treatment period. At the end of 12 weeks of treatment, the number of migraine days per 4 weeks significantly decreased from the baseline to 2.55 ± 2.19 in Niacin 500 mg arm ($p < 0.001$, Table II). In Niacin 1000 mg arm, it also significantly decreased to 2.11 ± 2.05 ($p < 0.001$, Table II). Compared to placebo, the reductions were statistically significant in both niacin 500 mg ($p = 0.01$, Table II) and 1000 mg, ($p = 0.004$, Table II) arms.

Pain intensity was reduced in 3 arms from the baseline ($p = 0.003$, Table II). These reductions were statistically significant compared to placebo in both Niacin 500 mg arm ($p = 0.03$, Table II) and Niacin 1000 mg arm ($p=0.003$, Table II).

The number of adverse events of per protocol analysis in the placebo, Nicotinic acid 500 mg and 1000 mg arms are displayed in Table IV. These adverse events were self-limited. No adverse event was considered serious.

Table I: Demographics characteristics of participants

Variables	Placebo (n = 19)	Niacin 500 mg (n = 20)	Niacin 1000 mg (n = 19)	p value
Age (Years)	31.16±10.33	28.8 ±8.41	31.42± 9.32	0.79
Sex				0.28
Male	2 (10.53%)	2 (10%)	5 (26.32%)	
Female	17 (89.47%)	18 (90%)	14 (73.68%)	
BMI (kg/m^2)	23.9 ± 2.31	22.54±3.19	22.11± 3.85	0.2
Presence of aura	5 (26.32%)	3 (15%)	2 (10.53%)	0.41

Data are presented as mean ± SD or n (%).

Table II: Changes in outcome variables from baseline to the end of the 12th week

	Placebo (n = 19)	Niacin 500 mg (n = 20)	Niacin 1000 mg (n = 19)	P value [x]	p value [y]	
					Niacin 500 mg	Niacin 1000 mg
Number of migraine days per 4 weeks						
At baseline	07 ± 2.71	7.45 ± 2.48	7.58 ±2.46	0.76	-	-
At the end of 12 weeks	4.73 ± 3.03	2.55 ± 2.19	2.11 ± 2.05	0.004	0.01	0.004
p value [z]	0.01	<0.0001	<0.0001			
Mean VAS score						
At baseline	7.2 ± 1.33	7.19 ±1.12	7.26 ±1.13	0.98	-	-
At the end of 12 weeks	5.17 ± 2.26	3.43 ± 2.65	2.64 ± 2.58	0.01	0.03	0.003
p value [z]	0.003	<0.0001	<0.0001			
MSQ Version 2.1 Scores						
MSQ Version 2.1 Total score						
At baseline	42.78±17.11	41.36±18.78	41.65±15.98	0.96	-	-
At the end of 12 weeks	41.20±18.17	61.29±28.72	65.71 ± 40.12	0.04	0.01	0.02
p value [z]	-	0.003	0.02			
MSQ Version 2.1 RR Score						
At baseline	35.94 ± 16.7	34.71 ±19.09	37.14 ±15.20	0.91	-	-
At the end of 12 weeks	35.64±18.20	54.14±33.88	62.86 ± 43.87	0.04	0.02	0.04
p value [z]	-	0.002	0.006			
MSQ Version 2.1 RP Score						
At baseline	50 ± 21.86	47 ± 27.74	43.16 ± 19.95	0.67	-	-
At the end of 12 weeks	42.89±28.20	64.25±33.81	63.95 ± 43.7	0.12	-	-
p value [z]	-	0.02	-			
MSQ Version 2.1 EF Score						
At baseline	49.12±23.65	49.33±26.08	50.18 ± 28.05	0.99	NA	NA
At the end of 12 weeks	51.93±28.16	74 ± 26.83	74.74 ± 37.75	0.04	0.02	0.04
p value [z]	-	0.002	0.006			

Data presented as Mean ± SD. [x] Comparison among placebo, Niacin 500 mg and Niacin 1000 mg arms by One-way ANOVA. [y] Comparison between placebo and respective arms by unpaired t test
[z] Comparison between baseline and at the end of 12 weeks by paired t test

Table III: Laboratory parameters in double-blind treatment period

	Placebo (n = 19)	Niacin 500 mg (n= 20)	Niacin 1000 mg (n = 19)	P value [y]
Serum ALT level (U/L)				
At baseline	21.84 ± 6.72	20.85 ± 12.86	22.05 ± 11.73	0.93
At the end of 12 weeks	20.84 ± 17.18	17.35 ± 9.49	18.00 ± 12.78	0.69
P value	0.8	0.37	0.35	
Blood Sugar (FBS) level (mmol/L)				
At baseline	4.63 ± 0.82	4.68 ± 0.87	4.62 ± 0.8	0.92
At the end of 12 weeks	4.56 ± 0.71	4.52 ± 1.06	4.62 ± 0.80	0.3
P value	0.54	0.76	0.24	
Serum Uric acid level (mg/dL)				
At baseline	4.6 ± 1.39	4.49 ± 1.05	5.38 ± 1.76	0.12
At the end of 12 weeks	4.58 ± 0.84	4.44 ± 0.94	4.76 ± 1.17	0.64
P value	0.92	0.93	0.2	
Serum Albumin (gm/L)				
At baseline	46.84 ± 3.76	45.84 ± 2.73	46.26 ± 3	0.65
At the end of 12 weeks	45.57 ± 3.06	44.47 ± 2.95	44.52 ± 2.97	0.55
P value [x]	0.28	0.2	0.11	

Data presented as Mean ± SD.

[x] Comparison between baseline and at the end of 12 weeks by 'paired t-test'

[y] Comparison among placebo, niacin 500 mg arm and niacin 1000 mg arm by One-way ANOVA.

Table IV: Participants with adverse events during 12-week double-blind treatment period

	Placebo (n = 19)	Nicotinic acid 500 mg (n = 20)	Nicotinic acid 1000 mg (n = 19)	*p* value
Flushing	2 (10.53%)	5 (25%)	8 (42.11%)	0.08
Pruritus	2 (10.53%)	5 (25%)	6 (31.58%)	0.28
Dizziness	3 (15.79%)	7 (35%)	4 (21.05%)	0.35
Abdominal pain	1 (5.36%)	2 (10.18%)	1 (5.36%)	0.79

Data presented as n (%)

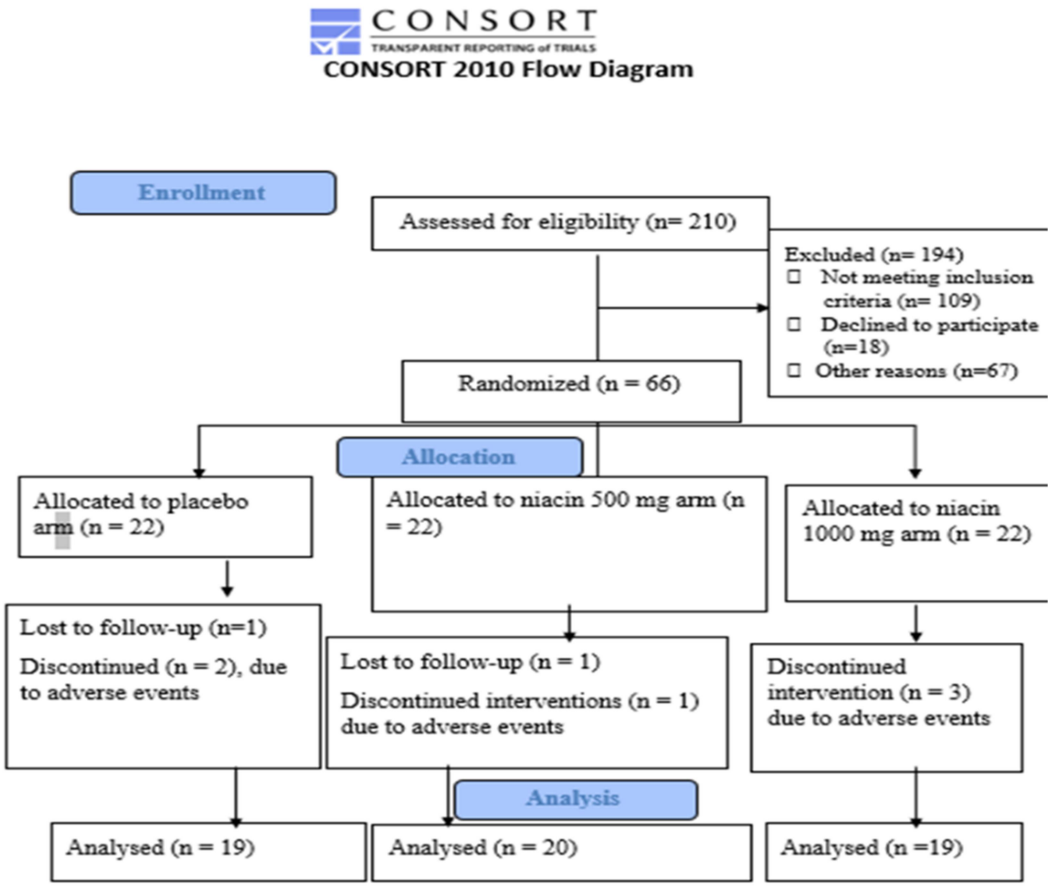

Figure 1. Flowchart of Consolidated Standards of Reporting Trials (CONSORT)

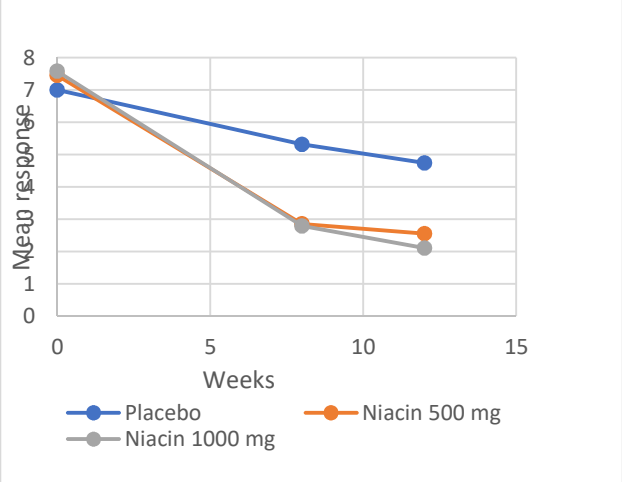

Figure 2. Scattered chart showing the number of migraine days per 4 weeks during the baseline, 8 and 12 weeks of double-blind treatment period.

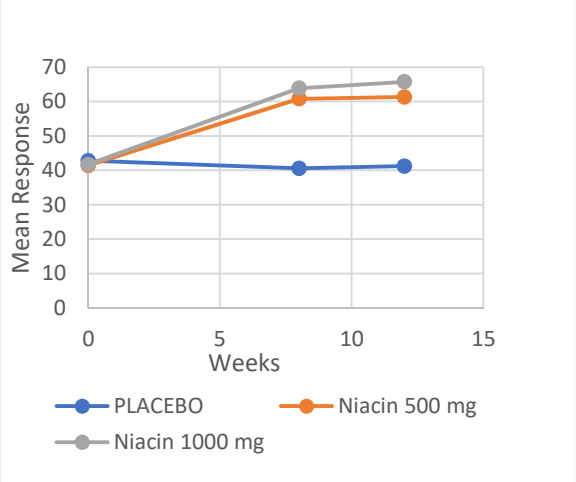

Figure 3. Scattered chart showing MSQ Version 2.1 Total score during the baseline, 8 and 12 weeks of double-blind treatment period.

Discussion

The findings of this study demonstrate that. there is a role of Nicotinic Acid ER 500 or 1000 mg tablet in prophylaxis of migraine. Nicotinic acid demonstrated greater efficacy in preventing migraines compared to placebo. At the end of the 12 weeks, the mean number of migraine days per 4 weeks from baseline were 4.73 $\pm$ 3.03, 2.55 $\pm$ 2.19 (p value = 0.01 versus placebo), 2.11 $\pm$ 2.05 (p value = 0.004 versus placebo) in placebo, Niacin 500 and 1000 mg arms respectively. To the best of the knowledge, this is the first controlled study in adult migraine with Nicotinic acid. Prior to this study, some uncontrolled trials provided results consistent with our findings in different conditions. Some positive results have been also found in paediatric migraines. In an open level study, Supplementing Niacin with some neutraceuticals for 12 weeks were significantly effective in reducing migraine attacks (p = 0.000001) as well as reduction in consuming rescue medications (p = 0.000001).[23] An open-label study with 20 children with magnesium 45 mg, l-tryptophan 175 mg, and niacin 12.5 mg (per dose twice daily) found significant reduction in migraine attacks and lessened the consumption of acute antimigraine drugs (p <0.0001) after 3 months of treatment.[22] There are some case reports supporting the findings of this study. A woman with an uncontrolled headache who started taking Nicotinic acid sustained-release tablet 750 mg per day experienced complete relief after 1 month.[15] Prousky and Sykes described in a case series in 2003 that two patients explored flush with complete pain relief after taking 500 mg of niacin.[21] This result was also consistent with a study performed by Liu et al, 2022, who demonstrated that the higher dietary intake of Niacin is associated with the lower migraine risk.[20]

In low dose, Niacin is well tolerated, helps to limit neuroinflammation[18] and improves cerebral mitochondrial energy metabolism[19] which can provide additional benefit in migraine prophylaxis. To explore this, this randomized, double-blind, placebo-controlled trial was designed.

At the end of the 8 weeks, migraine days per 4 weeks was lowered than the baseline in all the three arms (p <0.05). There was significant improvement in both Niacin 500 mg and 1000 mg arms from that of the placebo arm (p < 0.05), but Niacin 1000 mg arm failed to show significant difference (p > 0.05) than 500 mg arm.

At the end of 12 weeks, the number of migraine days per 4 weeks was lowered from the baseline and that of the end of the 8 weeks in all three arms. The difference between the baseline was significant in the three arms (p < 0.05). But, the difference from the 8 weeks was significant in only in Niacin 1000 mg arm (p < 0.05). There was significant improvement in both Niacin 500 mg and 1000 mg arms from that of the placebo arm (p < 0.05).

It was demonstrated that Nicotinic acid in both 500 mg and 1000 mg reduces migraine attacks, pain intensity more than placebo.

By reducing migraine attacks and providing neuroprotection, Nicotinic acid can help in improving quality of life. It was evaluated using MSQ Version 2.1. At the end of 12 weeks, the improvement in all domains except Role function preventive (RP) were markedly higher than placebo (p < 0.05).

During the treatment phase, there was no serious adverse event in any arm. After 12 weeks of treatment, there was no significant change (p > 0.05) in safety parameters (ALT,

Uric acid, FBS and serum albumin) from that of the baseline. This non-deterioration is due the use of this drugs in small doses.

In this trial, patients with episodic migraine reported improvement in the reduction of frequency of migraine as well as quality of life with addition of Nicotinic acid extended-release tablet at both 500 mg and 1000 mg doses. But we cannot recommend it strongly as our sample size was small and may not be representative of a large population.

Conclusion

Nicotinic acid in both 500 mg and 1000 mg doses significantly reduced migraine frequency. Significant improvement was found in reduction in pain intensity, and in quality of life.

Limitations

The sample size was small and the trial excluded chronic migraine and other subtypes of migraine patients.

Recommendation

A further trial involving a larger sample size and longer duration and more doses needs to be conducted to provide additional data as the long-term effect was not studied.

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