Long-Term Low-Dose Sucrose May Prevent Migraine: Two Double-Blinded Randomized Controlled Pilot Trials

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Aims: To evaluate the efficacy of sucrose in the prevention of migraine attacks. **Methods:** Two randomized double-blinded pilot trials were conducted, one in college students and one in adults. Migraineurs were randomized into two groups that each received an oral liquid: for students, sucrose 5 g/day (s-group; n = 12) or glucose 2.5 g/day (g-group; n = 10) for 3 months; and for adults, sucrose 5 g/day (s-group; n = 10) or fructose 2.5 g/day (f-group; n = 9) for 6 months. The primary endpoint was the frequency of migraine attacks per month, and the secondary endpoints were mean duration and severity of migraine per attack. Continuous measurements were described as mean ± standard deviation (SD). The overall significance of the effects between different groups was tested using repeated measures analysis of variance (RANOVA), and the efficacy was evaluated using an intent-to-treat analysis. **Results:** Migraine frequency in the students declined significantly in the g-group (mean reduction ± SD: 0.65 ± 0.71; $P < .01$), but not in the s-group (0.33 ± 2.02; $P = .58$). RANOVA results suggested that the secondary endpoints significantly declined over time (all $P < .01$) with no differences between the groups. In the adult trial, mixed-effects model analysis showed that both the primary and secondary endpoints significantly declined over time with no significant differences between the groups. **Conclusion:** Long-term consumption of a 5-g dose of sucrose for adult migraineurs or a 2.5-g dose of glucose for college student migraineurs may be as effective as preventive treatments. *J Oral Facial Pain Headache 2019;33:165–173. doi: 10.11607/ofph.1896*

Keywords: *migraine, prevention, sucrose*

Migraine is a highly prevalent neurologic disease[1] that affects quality of life[2] and is associated with the risk of developing vascular diseases such as hypertension[3] or even stroke.[4] Until now, the cause of migraine has not been clear. Additionally, the application of drugs such as metoprolol,[5] propranolol,[5] topiramate,[5] riboflavin,[6] and magnesium[7] for the prophylaxis and treatment of migraine in adult patients is often limited by exorbitant prices, and drugs have been shown to be invalid in follow-up studies—even amitriptyline and topiramate were associated with higher rates of adverse events in childhood and adolescent migraine.[8–10]

Epidemiologic studies suggest that hunger may trigger a migraine attack.[11,12] McDonald Critchley introduced the dietetic migraine as one of the subtypes of migraine in 1933.[13] A case report described a 56-year-old Italian man who suffered recurrent severe migraine attacks after hypoglycaemia.[14] However, he could prevent a migraine attack by drinking orange juice or administering an intramuscular injection of glucagon. Moreover, a female migraineur could prevent her migraine attack for 3 months by consuming 100 mL of orange juice daily at 4:00 am, and four other migraineurs also reported a benefit from this therapy.[15] In addition, Blau and Pyke[16] described 36 participants who suffered from both diabetes and migraine, and five participants expressed that their attacks had completely disappeared or were moderated at the onset of diabetes. These cases suggest that blood glucose may be related to migraine. In addition, the corresponding author of this paper, who was a migraineur, has experienced that long-term low-dose sugar consumption prevents the onset of migraine unexpectedly and shares this

experience with three other migraineurs. All four migraine cases showed the effectiveness of preventing migraine attacks with long-term low-dose sugar intake. Therefore, the aim of this study was to evaluate the efficacy of sucrose on the prevention of migraine attacks, and two pilot double-blinded randomized controlled trials (RCTs) were conducted.

Materials and Methods

Study Design of Trials and Participants

The Medical Ethics Committee of the School of Public Health, Harbin Medical University approved the studies [No. 2014003 and No. 2015002], and written informed consent was obtained from each subject before enrollment. This study was registered with chictr.org.cn, ChiCTR-IIR-16008864.

Two pilot RCTs were conducted to evaluate the effect of sucrose on the prevention of migraine. The first was a 12-week double-blinded trial to evaluate the efficacy of sucrose 5 g/day (s-group) compared to glucose 2.5 g/day (g-group) as a control in the students at Harbin Medical University, P.R. China. At first, a cross-sectional study was conducted among undergraduates to screen migraineurs according to the Chinese version of the Identification of Migraine screener (ID-Migraine). A total of 395 students were positive and further diagnosed using the International Classification of Headache Disorders-2 (ICHD-2) criteria.[17] After application of the inclusion and exclusion criteria, 22 students participated in this trial and were followed up for 3 months. The second trial was comprised of 19 adults with migraine in Heihe city of Heilongjiang Province, China. Similar to the student trial, two groups separately received sucrose 5 g/day (s-group) or fructose 2.5 g/day (f-group) oral liquid for 6 months.

Inclusion Criteria

Included patients had to be ≥ 18 years of age; diagnosed as having migraine with or without aura according to ICHD-2 criteria; duration of migraine for at least 1 year with two or more attacks per month; migraines with moderate to severe pain (0–10 visual analog scale [VAS] score ≥ 3.6) that affected work and learning; and had taken no prophylactic drugs for migraine such as β-blockers, calcium channel blockers, or antiepileptic drugs in the past 3 months.

Exclusion Criteria

Patients were excluded if they used analgesics more than 10 times every month for migraine attacks; had special types of migraine such as ophthalmoplegic or hemiplegic migraine; had cluster headache, tension-type headache, or secondary headache disorders; had migraine combined with diabetes mellitus, hepatic, renal, or hematopoietic systemic disease, severe mental disease, allergic constitution, or other serious primary disease; or refused to sign the consent.

Randomization and Masking

Statisticians (J.S. for the students, H.Z. for the adults) guarded the computer-based randomization key and generated allocation sequences. Two investigators (X.W. and Y.D.) allocated the participants according to these sequences. All of the oral liquids were packed into indistinguishable brown bottles, and the patients and investigators were masked to the treatment allocation and did not have access to the data. The collection and analysis of follow-up data and the biologic samples were finished prior to unblinding.

Manufacture of Oral Liquids

The sucrose, glucose, and fructose oral liquids were manufactured by Harbin RenHuang Pharmaceutical. Five grams of pharmaceutical grade sucrose or 2.5 g glucose or fructose were dissolved in 10 mL of purified water. The solutions were then put into brown glass bottles, sterilized at 121°C for 15 minutes, and stored at room temperature.

Intervention

The participants were required to drink one bottle of the oral liquid given daily. Researchers monitored the participants by sending text message reminders regularly and put phone calls through to every subject monthly for the information required. After follow-up, fasting blood was collected from each participant, and the composition of the liquid mentioned above was revealed.

Outcomes

The primary efficacy endpoint was the frequency of attacks per month, and the secondary outcomes were the mean duration and severity of each attack, measured in hours and by 0–10 visual analog scale (VAS) score, respectively. A 50% or greater reduction in the endpoints mentioned above compared to the baseline values was defined as effective[12]; therefore, response rate was defined as the proportion of subjects with 50% and greater reduction in that outcome. Additionally, fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) at baseline and at the end of follow-up were evaluated in both trials.

Statistical Analyses

Continuous measurements were described as mean ± standard deviation (SD), and differences were compared using *t* tests. The categorical variables were presented in percentage (%), and the difference between the groups was tested using Pearson

Table 1 Baseline Demographic and Clinical Characteristics

	University students		Adult population	
	Sucrose 5 g/d (n = 12)	Glucose 2.5 g/d (n = 10)	Sucrose 5 g/d (n = 10)	Fructose 2.5 g/d (n = 9)
Demographics				
Age (y), mean (SD)	22.1 (1.70)	21.6 (1.51)	50.70 (10.26)	49.56 (4.80)
Sex, n (%)				
Female	9.0 (75)	9.0 (90)	10.0 (100)	8.0 (89)
Male	3.0 (25)	1.0 (10)	0.0 (0)	1.0(11)
Baseline characteristics				
Type of migraine, n (%)				
With aura	5.0 (42)	2.0 (20)	0.0 (0)	0.0 (0)
Without aura	7.0 (58)	8.0 (80)	10.0 (100)	10.0 (100)
FBG (mmol/L), mean (SD)	4.96 (0.30)	4.91 (0.61)	5.29 (0.46)	4.98 (0.73)
HbA1c, mean (SD)	4.90 (0.25)	5.00 (0.30)	5.80 (0.59)	5.76 (0.46)
Years since onset of migraine, mean (SD)	5.27 (3.46)	7.11 (5.08)	28.70 (15.19)	21.50 (10.98)

FBG = fasting blood glucose; HbA1c = glycosylated hemoglobin.

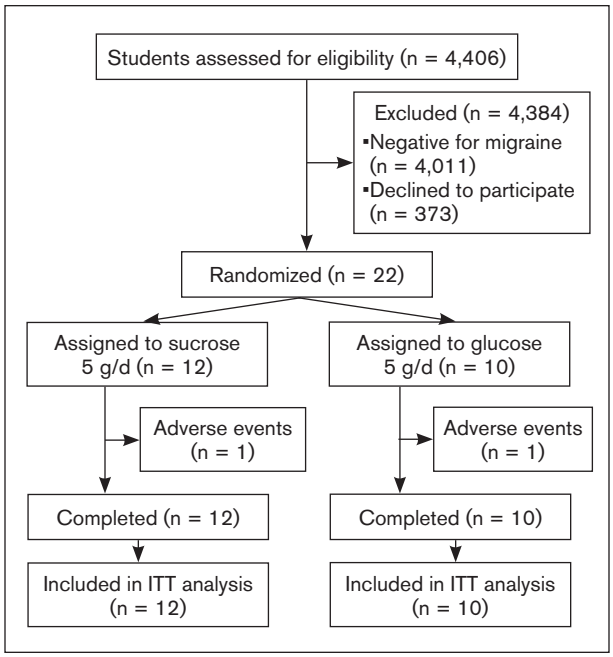

Fig 1 Flowchart of subject inclusion in student trial.

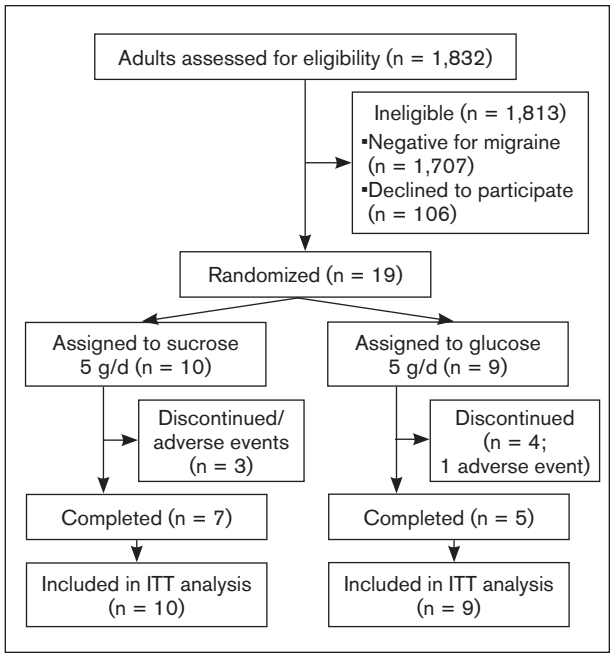

Fig 2 Flowchart of subject inclusion in adult trial.

chi-square tests. The overall significance of the effects between different groups was tested using repeated measures analysis of variance (RANOVA). In addition, a generalized linear mixed-effects model for repeated measures was applied to manage censored data. The efficacy analyses were carried out in accordance with the intent-to-treat (ITT) protocol. For dropouts, the outcome data were computed according to the last observation before discontinuation. Power analysis was conducted using the PASS 11 software with respect to paired means power analysis and time-averaged difference (normal data) power analysis. All statistical tests were two-tailed, and $P < .05$ was considered significant. Statistical analyses were conducted using SAS statistical software, version 9.1 (SAS Institute).

Results

The demographic and baseline characteristics of the patients in both trials are shown in Table 1. The flow diagrams for the student and adult studies are shown in Figs 1 and 2, respectively.

Primary Endpoints

In the student trial, there was a statistically significant reduction in migraine frequency in the g-group

Table 2 Baseline and Follow-up Results in the Student Trial

	Frequency of migraine (no. of attacks per mo)			Duration of migraine (h)			0–10 VAS score		
Follow-up period/ change	Sucrose 5 g/d	Glucose 2.5 g/d	*P* value	Sucrose 5 g/d	Glucose 2.5 g/d	*P* value	Sucrose 5 g/d	Glucose 2.5 g/d	*P* value
Baseline, mean (SD)	1.96 (0.94)	2.10 (1.05)	.74	9.67 (8.45)	8.05 (6.04)	.62	5.25 (1.91)	4.70 (1.77)	.50
1 mo	1.58 (2.19)	2.40 (2.27)	.40	5.42 (10.22)	2.55 (1.91)	.36	2.42 (2.07)	4.15 (2.14)	.07
2 mo	2.13 (3.45)	1.90 (1.81)	.85	0.88 (1.07)	1.75 (2.09)	.25	2.50 (2.50)	2.35 (2.64)	.89
3 mo	1.63 (2.01)	1.45 (1.54)	.82	1.96 (2.23)	2.85 (2.69)	.40	3.63 (2.46)	2.00 (2.05)	.11
Change, mean (SD)									
1 mo	−0.38 (2.54)	0.30 (1.74)	.48	−4.25 (11.96)	−5.50 (6.27)	.77	−2.83 (2.82)	−0.55 (1.95)	.043
2 mo	0.17 (3.60)	−0.20 (1.18)	.75	−8.79 (7.78)	−6.30 (6.21)	.42	−2.75 (3.58)	−2.35 (2.39)	.77
3 mo	−0.33 (2.02)	−0.65 (0.71)	.62	−7.71 (7.68)	−5.20 (6.61)	.43	−1.63 (2.74)	−2.70 (2.31)	.34
No. value of change (% value)									
1 mo	6 (50.0)	3 (30.0)	.34	9 (75.0)	5 (50.0)	.22	5 (41.7)	1 (10.0)	.10
2 mo	5 (41.7)	4 (40.0)	.94	11 (91.7)	8 (80.0)	.43	6 (50.0)	5 (50.0)	1.00
3 mo	5 (41.7)	6 (60.0)	.39	9 (75.0)	6 (60.0)	.45	4 (33.3)	5 (50.0)	.43

VAS = visual analog scale.
Repeated measures ANOVA model up to 3-mo evaluation:
Frequency group effect: F = 0.05; *P* = .83; Time effect: F = 0.45; *P* = .66; Group*time effect: F = 0.46; *P* = .66.
Duration group effect: F = 0.24; *P* = .63; Time effect: F = 8.94; *P* < .01; Group*time effect: F = 0.71; *P* = .52.
VAS score group effect: F = 0.06; *P* = .81; Time effect: F = 7.03; *P* < .01; Group*time effect: F = 2.73; *P* = .05.

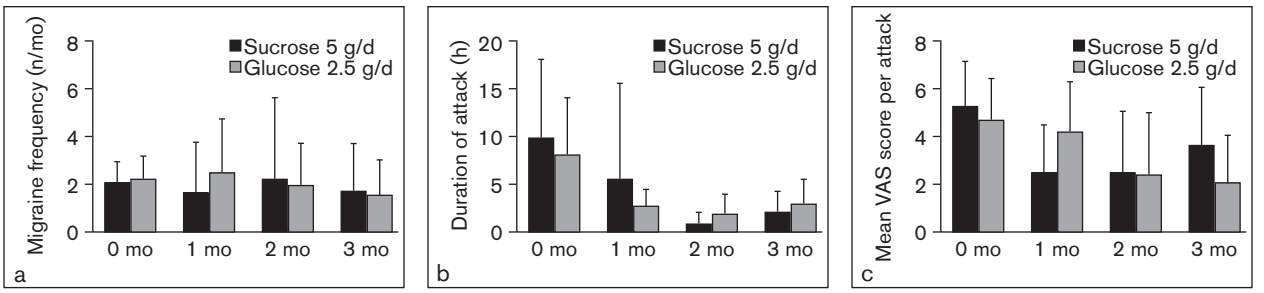

Fig 3 Mean changes in **(a)** migraine frequency, **(b)** duration of migraine attacks, and **(c)** 0–10 visual analog scale (VAS) pain from baseline in the student trial.

(mean reduction ± SD: 0.65 ± 0.71; *P* < .01), but not in the s-group (0.33 ± 2.02; *P* = .58). No significant difference between the groups (*P* = .62) was observed at the end of the third month. In addition, 41.7% in the s-group and 60% in the g-group reported as responders regarding migraine frequency; there was no significant difference between the two groups (*P* = .39). RANOVA suggested that neither group showed a statistically significant reduction in migraine attack frequency with time (time effect: F = 0.45; *P* = .66), and there was no significant difference between the groups (*P* = .83) (Table 2, Fig 3a).

In the adult trial, a statistically significant reduction in migraine attack frequency at the end of 6 months was observed in the s-group, with a mean reduction of 3.5 ± 3.21 attacks per month (*P* = .014), but this was not evident in the f-group (mean reduction 0.67 ± 4.33; *P* = .212). There was no statistically significant difference between the groups (*P* = .278). A total of 70% in the s-group and 55.6% in the f-group reported as responders, without a significant difference between the groups (*P* = .515). Furthermore, the mixed-effects model of repeated measures suggested that the frequency of migraine decreased over the 6-month intervention (time effect: F = 6.48; *P* < .01), without a difference between the groups (*P* = .74) (Table 3).

Secondary Endpoints

For the student trial, in the s- and g-groups, the mean reductions in migraine duration at the 3-month follow-up were 7.71 ± 7.68 hours (*P* < .01) and 5.20 ± 6.61 hours, respectively (*P* = .035). The mean reductions in VAS score were 1.63 ± 2.74 and 2.70 ± 2.31, respectively (both *P* < .01). There was no significant difference in these two outcomes between the two groups. The response rates for duration reduction were 75% in the s-group and 60% in the g-group, without a difference between the groups (*P* = .45). For reduction in VAS score, the response rates were 33.3% in the s-group and 50.0% in the g-group (*P* = .43). RANOVA indicated that the mean duration and the VAS score were significantly

Table 3 Baseline and Follow-up Results in the Adult Trial

	Frequency of migraine (no. of attacks per mo)			Duration of migraine (h)			0–10 VAS score		
Follow-up period/ change	Sucrose 5 g/d	Fructose 2.5 g/d	*P* value	Sucrose 5 g/d	Fructose 2.5 g/d	*P* value	Sucrose 5 g/d	Fructose 2.5 g/d	*P* value
Baseline, mean (SD)	8.80 (11.30)	7.00 (5.10)	.479	12.95 (22.06)	2.28 (1.39)	.172	8.20 (1.16)	6.67 (1.48)	.012
1 mo	5.40 (10.62)	5.00 (5.72)	.275	7.95 (22.56)	1.09 (1.35)	.585	3.60 (3.95)	4.28 (2.71)	.8
2 mo	5.50 (10.58)	3.78 (5.19)	.448	3.20 (7.48)	0.80 (1.35)	.899	3.45 (3.85)	3.72 (2.75)	.737
3 mo	6.50 (12.41)	3.56 (5.34)	.795	1.30 (2.25)	0.76 (1.37)	.795	2.60 (3.50)	3.22 (3.19)	.634
4 mo	6.40 (11.39)	3.56 (5.34)	.791	1.80 (3.90)	0.76 (1.37)	.859	2.60 (3.69)	3.22 (3.19)	.595
5 mo	6.10 (11.39)	5.78 (7.43)	.552	2.40 (4.05)	0.98 (1.40)	.966	3.30 (3.80)	4.00 (3.50)	.701
6 mo	5.30 (10.67)	6.33 (8.70)	.299	0.70 (1.55)	0.98 (1.40)	.387	2.80 (3.88)	4.22 (3.46)	.41
Change, mean (SD)									
1 mo	–2.40 (2.17)	–2.00 (1.73)	.476	–5.00 (28.87)	–1.18 (1.65)	.474	–4.60 (3.63)	–2.39 (2.93)	.114
2 mo	–3.30 (3.33)	–3.22 (4.71)	.709	–9.75 (15.59)	–1.48 (1.57)	.216	–4.75 (3.76)	–2.94 (3.66)	.261
3 mo	–2.30 (2.45)	–3.44 (4.64)	.646	–11.65 (22.09)	–1.52 (1.61)	.186	–5.60 (3.25)	–3.44 (3.93)	.211
4 mo	–2.40 (3.24)	–3.44 (4.64)	.967	–11.15 (22.00)	–1.52 (1.61)	.186	–5.60 (3.25)	–3.44 (3.93)	.211
5 mo	–2.70 (2.31)	–1.22 (2.86)	.356	–10.55 (22.27)	–1.30 (1.67)	.383	–4.90 (3.64)	–2.67 (3.07)	.154
6 mo	–3.50 (3.21)	–0.67 (4.33)	.278	–12.25 (22.43)	–1.30 (1.67)	.193	–5.40 (3.57)	–2.44 (3.12)	.055
No. value of change (% value)									
1 mo	7 (70)	6 (66.7)	.876	6 (60)	4 (44.4)	.498	5 (50)	2 (22.2)	.210
2 mo	6 (60)	6 (66.7)	.764	7 (70)	5 (55.6)	.515	5 (50)	4 (44.4)	.809
3 mo	6 (60)	6 (66.7)	.764	8 (80)	5 (55.6)	.252	8 (80)	4 (44.4)	.109
4 mo	6 (60)	6 (66.7)	.764	8 (80)	5 (55.6)	.252	8 (80)	4 (44.4)	.109
5 mo	6 (60)	5 (55.6)	.845	7 (70)	4 (44.4)	.260	7 (70)	3 (33.3)	.110
6 mo	7 (70)	5 (55.6)	.515	7 (70)	4 (44.4)	.260	7 (70)	3 (33.3)	.110

VAS = visual analog scale.
Mixed-effects model for repeated measures model up to 3-mo evaluation:
Frequency Group effect: F = 0.19; *P* = .67; Time effect: F = 8.60; *P* < .01; Group*time effect: F = 1.2; *P* = .34.
Duration Group effect: F = 2.23; *P* = .15; Time effect: F = 2.93; *P* = .06; Group*time effect: F = 1.1; *P* = .38.
VAS score Group effect: F = 0.06; *P* = .81; Time effect: F = 22.86; *P* < .01; Group*time effect: F = 1.14; *P* = .36.
Mixed-effects model for repeated measures model up to 6-mo evaluation:
Frequency Group effect: F = 0.11; *P* = .74; Time effect: F = 6.48; *P* < .01; Group*time effect: F = 1.07; *P* = .42.
Duration Group effect: F = 2.06; *P* = .17; Time effect: F = 2.74; *P* = .047; Group*time effect: F = 1.07; *P* = .46.
VAS score Group effect: F = 0.11; *P* = .75; Time effect: F = 46.67; *P* < .01; Group*time effect: F = 0.78; *P* = .60.

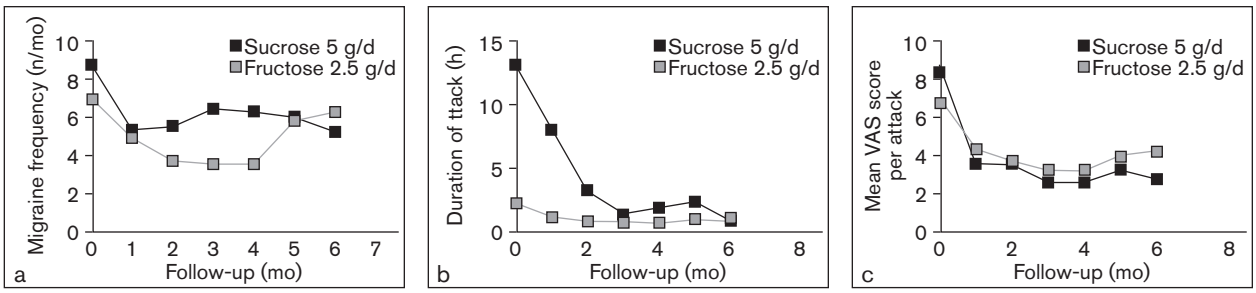

Fig 4 Mean changes in **(a)** migraine frequency, **(b)** duration of migraine attacks, and **(c)** 0–10 visual analog scale (VAS) pain from baseline in the adult trial.

reduced with time (both *P* < .01), with no significant difference between the groups for either endpoint (group effect: *P* = .63; *P* = .81, respectively) (Table 2, Figs 3b and 3c).

For the adult trial, the mean reductions in migraine duration in the s-group and the f-group at the 6-month follow-up were 12.25 ± 22.43 hours (*P* = .002) and 1.30 ± 1.67 hours (*P* = .034), respectively. No statistically significant difference was found between these two groups (*P* = .193). In all, 70% of the s-group and 44.4% of the f-group responded to treatment regarding migraine duration, with no significant difference between the groups (*P* = .260). The mixed-effects model of repeated measures showed that the duration of migraine was reduced (*P* = .05), without a difference between the groups (*P* = .17). The VAS score decreased statistically significantly in the s-group (5.40 ± 3.57; *P* = .003), but not in the f-group (2.44 ± 3.12; *P* = .136); however, no significant difference was detected between the groups (*P* = .055). Besides, 70% of the s-group and 33.3% of the f-group responded to treatment

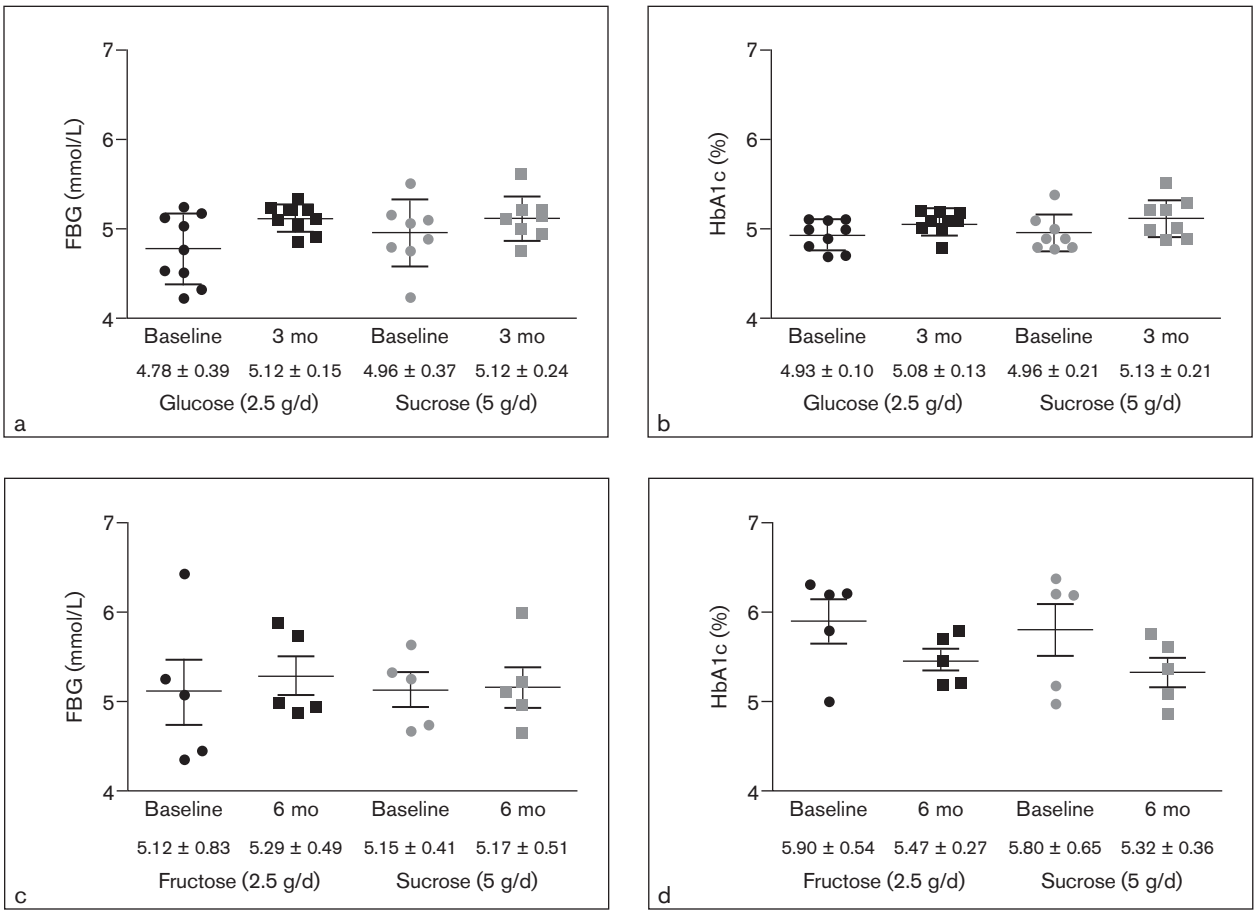

Fig 5 Change in fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) from baseline in **(a, b)** student and **(c, d)** adult trials.

regarding VAS pain, and no statistically significant difference between the groups was indicated (P = .110). The mixed-effects model suggested that the VAS significantly decreased with time (P < .01), without differences between the groups (P = .75) (Table 3, Fig 4c).

Results of Laboratory Analyses

In the student trial and only in the g-group there were increases in both FBG (P = .01) (Fig 5a) and HbA1c (P = .06) (Fig 5b). RANOVA analysis suggested that no significant difference was observed in the change of FBG (P = .48) and HbA1c (P = .63) between the groups.

For the adult trial, neither FBG nor HbA1c changed significantly in either group (Figs 5c and 5d).

Side Effects

During the follow-ups, 1 of the 22 college students in the g-group and 4 of 19 adults (1 in the f-group and 3 in the s-group) reported experiencing nausea after drinking the solution.

Discussion

This is the first study with two pilot RCTs aimed at evaluating the efficacy of sucrose in the prevention of migraine attacks. The findings of both trials showed significant reductions in all three endpoints (the frequency of attacks per month, the duration of the attacks, and the VAS score per attack) in the sucrose groups of the trials after intervention (3 months in students and 6 months in adults). However, no significant differences were observed between the groups in either trial.

According to International Headache Society (IHS) guidelines, the main efficacy parameter for prophylactic treatment studies is a reduction in the frequency of migraine attacks.[18] A systematic review and meta-analysis suggested that if the proportion of responders (subjects who had a reduction of 50% or more in the frequency of migraine attacks) to all subjects was 23.5% or less, the drug may not have a protective effect of any clinical relevance.[19] In these two pilot trials, 41.7% to 70% of migraineurs reported

a reduced frequency of migraine attacks, and the proportions were all above 23.5% in any group. One pharmaceutical study suggested that flunarizine 5 mg/day and topiramate 100 mg/day were effective in 61.6% and 65.9% of the patients, respectively, at the 3-month follow-up.[20] One nonpharmaceutical method, riboflavin treatment (100 to 600 mg/day) administered to migraineurs for 3 months, was reported to be effective in reducing the frequency of migraine attacks in 44.4% to 56% of patients.[21,22]

The mean duration per attack was significantly less than the baseline data in both student and adult trials (Tables 2 and 3). The reductions in the s-group and the g-group of the student trial were 7.71 ± 7.68 hours and 5.20 ± 6.61 hours, respectively; in the adult trial, 12.25 ± 22.43 hours in the s-group and 1.30 ± 1.67 hours in the f-group. A meta-analysis suggested that the migraine days per month were reduced by approximately 2.19 days in a group treated with topiramate.[23] Riboflavin 100 mg/day was associated with a mean reduction of 0.7 hours, and the response rate was approximately 26.2% after a 3-month treatment.[21] High-dose riboflavin (400 mg/daily) was associated with higher effectiveness (59%).[22] In the present study, the response rate ranged from 44.4% to 75%.

The intensity of migraine was lowered significantly in different groups in both trials, and the response rate ranged from 33.3% to 70% (Tables 2 and 3). The VAS reductions in the s-group and the g-group of the student trial were 1.63 ± 2.74 and 2.70 ± 2.31, respectively; in the adult trial, 5.40 ± 3.57 in the s-group and 2.44 ± 3.12 in the f-group. It has been reported that cinnarizin 37.5 to 50 mg/day and topiramate 50 mg/day could reduce VAS scores by 4.7 and 3.0 points, respectively.[24] Migraineurs treated with riboflavin 100 mg/day reported a reduction in VAS score of 1.1, with an effectiveness of 43.2%.[25] In addition, 400 mg/day of riboflavin may reduce VAS scores by 6.0 points.[26]

The corresponding author of this study and three other colleagues (a total of four female migraineurs) experienced improved migraine attack frequency, duration, and severity with the consumption of sucrose in a longer-term and low-dose protocol (details not shown). Their experiences support that there is probably a subtle trade-off effect[16] whereby blood glucose or relevant indicators reflecting long-term glucose level may determine the frequency and severity of migraine attacks. The long-term consumption of low-dose sugar allows accumulation of glucose up to a certain level so that the onset of migraine could be prevented, which leads to the assumption that maintaining the indicators at a certain level or above a threshold where attacks could be stopped after consuming sucrose is required. If the indicators fall slightly, the migraine would still occur but less seriously, and the individual might recover in a short time after taking sucrose. If the indicators are reduced substantially, a migraine episode could recur. This assumption is in accordance with Pearce's 1971 findings that only 1 out of 20 migraineurs developed headache after insulin-induced hypoglycemia, and he suggested that migraine attacks induced by hunger or fasting are unlikely to be directly related to the absolute blood sugar level at the time, as it seems unlikely that such attacks are related to the rapidity of falling in the venous blood sugar.[27]

Although the mechanism of sucrose in the prevention of migraine has been unclear, there is some evidence supporting this phenomenon. It is well known that hunger, delaying or missing meals,[13] and hypoglycemia[15] may trigger migraine. In addition, Blau and Pyke[16] reported that 5 of 36 participants who suffered from both diabetes and migraine responded that their migraine completely disappeared or was reduced at the onset of diabetes. Blau suggested that blood sugar level was a significant contributory factor affecting the migraine threshold in approximately one-third of patients and in some patients the sole triggering factor, but serum glucose levels were not measured in their study. Furthermore, diabetes may protect patients from migraine, especially in the elderly population.[28,29]

Sucrose is broken down into its constituent monosaccharides, namely glucose and fructose, which have the same number of calories but are metabolized differently. Glucose is the main circulating sugar in the blood, whereas the majority of fructose is extracted from the bloodstream into the liver.[25] Therefore, the authors had originally hypothesized that glucose had an active response and fructose acted as a placebo. However, both exhibited similar effects on prevention of attacks. In addition, blood glucose and HbA1c of subjects were tested before and after the intervention. Although both were increased in the sucrose and glucose groups, the increase was not statistically significant in the student trial. In the adult trial, blood glucose increased but HbA1c decreased, and neither change was statistically significant.

The report of analgesic and calming benefits of sweet substances can date back to 632 AD.[30] It was not, however, until the last 20 years that a large amount of papers concerning the analgesic effects of sucrose on acute pain in newborns were reported. The review of the Cochrane Library in 2016 containing 74 RCTs with a total of 7,049 neonates found that sucrose in concentrations between 20% and 30% reduced composite and multidimensional behavioral pain scores, as well as individual behavioral and physiologic pain indicators associated with heel

lance.[31] Although oral sucrose did reduce the observed pain behavior of heel lance, it did not significantly affect the activity of nociceptive circuits in the neonatal brain or spinal cord.[32] Besides, oral sucrose and radiant heat decrease pain in newborn infants undergoing vaccination, which has been identified in an RCT conducted by Harrington.[33] For peripheral intravenous catheter insertion, Cook et al conducted an RCT with a total of 40 neonates, and no statistical difference was found in pain levels between sucrose and placebo.[34] The findings of Harrison et al showed that the analgesic effects of sucrose in small amounts (0.1 mL per dose) can be used for procedural pain management in newborns.[35]

There have been some arguments about whether infant pain could be operating through the same pathway as in adults. Using functional magnetic resonance imaging (fMRI) to identify the network of brain regions, Goksan et al suggested that the experience of infant pain closely resembles that of adults.[36] Ranger and Grunau, however, did not think that infants' painful experience is the same as the adult sensation.[37] Because the extent of brain activation does not directly represent the painful experience (although both are correlated[38]), activated brain regions and self-reports of pain intensity are regarded as complementary information.[37] Similarly, there have been some arguments that pain reflexes and pain perception are frequently correlated in adults,[31] yet the two function independently in infants[24,32]; therefore, the ability of sucrose to reduce clinical observational scores after noxious events in newborn infants should not be interpreted as pain relief.[24,33] There are indeed the descending modulatory effects on pain transmission, however, not developed in newborns.[39]

With regard to the mechanisms of analgesic effects of sucrose, in animal models, a study in neonate rats showed that intraoral sucrose elicits analgesia and reduces inflammatory hyperalgesia as well as allodynia[40,41] without requiring involvement of the forebrain activating brainstem neurons in the periaqueductal gray and nucleus raphe magnus—the two key brainstem sites critically involved in descending pain modulation—by the use of Fos immunohistochemistry identifying the sites relevant to the analgesic properties of sucrose in newborn rats.[39] Moreover, in light of the study by Anseloni et al, sucrose-induced analgesic action could be enhanced by midcollicular transection, which could facilitate nocifensive response in neonate rats, suggesting that descending projections from the mid- or forebrain may facilitate central response to noxious somatosensory input.[39] Therefore, the exact function related to analgesia and mechanisms of oral sucrose should be verified further, with more research either in infants or in adults.

The limitations of this study should be considered. First, the small sample size may have compromised the results. Based on a power analysis, a total sample size of 19 subjects in the adult trial (10 in the s-group, 9 in the g-group) could only achieve a statistical power of 0.36 to detect a difference of 2.8 between the null hypothesis that both group changes in frequency of attack at 6-month follow-up would be 3.5 and the alternative hypothesis that the change in the g-group would be 0.7, with the known group standard deviations of 3.2 and 4.3 and at an alpha level of .05 using a two-sided two-sample *t* test (Table 3). Indeed, the small sample size has negatively affected the outcomes, which could not be ignored. Second, the duration of the RCT of the college students inevitably involved the final examination period, which lasts around 1 month and within which the students had to be nervous, tense, and stressed, even to the point of anxiety, preparing for multidisciplinary exams, more often than not staying up late with large amounts of coffee consumption. Indeed, under the circumstances, the efficacy might be weakened to some extent. Third, there were no real blank controls to evaluate the absolutely preventive effect of the intervention.

Conclusions

Based on the primary outcome, reduction in frequency of migraine attacks, long-term consumption of a 5-g dose of sucrose for adult migraineurs and a 2.5-g dose of glucose for college student migraineurs may be as effective as current preventive treatments. Based on the secondary outcomes, reduction in duration and severity of migraine attacks, long-term consumption of a 5-g dose of sucrose or a 2.5-g dose of fructose for adult migraineurs and a 2.5-g dose of glucose for college student migraineurs may be as effective as current preventive treatments.

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