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NEW RESEARCH PAPERS

NEUROMODULATION

Effect of Yoga on Clinical Outcomes and Quality of Life in Patients With Vasovagal Syncope (LIVE-Yoga)

Gautam Sharma, MD, DM,[a] Venkatakrishnan Ramakumar, MD, DM,[b] Mohd Sharique, MSc,[c] Rohit Bhatia, MD, DM, DNB,[d] Nitish Naik, MD, DM,[b] Sriloy Mohanty, BNYS,[c] Aman Agarwal, MSc,[c] Mohini Meti, MSc,[e] Akriti Shukla, BNYS,[b] Siddharthan Deepti, MD, DM,[a] Raghav Bansal, MD, DM,[a] Anunay Gupta, MD, DM,[f] A. Shaheer Ahmed, MD, DM,[f] R.M. Pandey, PhD,[g] Rajiv Narang, MD, DM,[b] Sundeep Mishra, MD, DM,[b] Anita Saxena, MD, DM,[b] Rajnish Juneja, MD, DM,[b] on behalf of the LIVE-Yoga Investigators

ABSTRACT

OBJECTIVES This study aims to determine the impact of yoga as an adjunct to standard therapy versus standard therapy alone on the symptomatic burden in patients with recurrent vasovagal syncope (VVS).

BACKGROUND There is a significant reduction in the quality of life (QoL) of patients with recurrent VVS. Existing management therapies have been largely ineffective. Recent trials have demonstrated the efficacy of yoga in diseases with autonomic imbalance, suggesting its possible utility in VVS.

METHODS Patients with recurrent VVS were randomized to receive either a specialized yoga training program in addition to current guideline-based therapy (intervention arm, group 1) or current guideline-based therapy alone (control arm, group 2). The primary outcome was a composite of the number of episodes of syncope and presyncope at 12 months. Secondary outcomes included QoL assessment by World Health Organization Quality of Life Brief Field questionnaire (WHOQoL-BREF) scores and Syncope Functional Status Questionnaire scores at 12 months, head up tilt test, and heart rate variability at 6 weeks.

RESULTS A total of 55 patients underwent randomization. The mean number of syncopal or presyncopal events at 12 months was 0.7 $\pm$ 0.7 in the intervention arm compared to 2.52 $\pm$ 1.93 in the control arm ($P < 0.01$). In the intervention arm, 13 (43.3%) patients remained free of events versus 4 (16.0%) patients in the control arm ($P = 0.02$). QoL at 12 months showed significant improvement of all Syncope Functional Status Questionnaire scores and 2 domains of WHOQoL-BREF scores ($P < 0.05$).

CONCLUSIONS Yoga as adjunctive therapy is superior to standard therapy alone in reducing the symptomatic burden and improving QoL in patients with recurrent VVS. (J Am Coll Cardiol EP 2022;8:141–149) © 2022 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, Centre for Integrative Medicine and Research, All India Institute of Medical Sciences, New Delhi, India; [b]Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India; [c]Centre for Integrative Medicine and Research, All India Institute of Medical Sciences, New Delhi, India; [d]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India; [e]Department of Pulmonary Medicine & Sleep Disorders, All India Institute of Medical Sciences, New Delhi, India; [f]Department of Cardiology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India; and the [g]Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

HRV = heart rate variability

HUTT = head up tilt test

NYHA = New York Heart Association

PCM = physical counterpressure maneuvers

QoL = quality of life

SFSQ = Syncope Functional Status Questionnaire

VVS = vasovagal syncope

WHOQoL-BREF = World Health Organization Quality of Life Brief Field Questionnaire

Vasovagal syncope (VVS) is a common clinical condition with an estimated lifetime prevalence of 35% (1,2). Although VVS is not associated with an increased rate of mortality, there is a significant deterioration in the quality of life (QoL) in conjunction with the severity and frequency of recurrences (3,4). Existing pharmacological and nonpharmacological therapies for VVS have, if at all, a modest efficacy (5,6).

Yoga is one of the most common forms of complementary and alternative medicine therapies and is increasingly being practiced worldwide. Yoga, an ancient Indian practice based on the principles of mind-body medicine, has been observed to have a beneficial effect in hypertension, atrial fibrillation, and post-myocardial infarction rehabilitation (7–9). Several studies have shown yoga to favorably modulate the autonomic system by balancing the central and peripheral sympathetic-parasympathetic drives (10). Mindful practice and meditation, both integral to yoga, help in reducing stress (11,12). VVS is a type of reflex syncope mediated by emotional or orthostatic stress and is associated with an increased and imbalanced autonomic activation (13). Recent studies have shown the benefit of yoga in patients with VVS (14,15). This randomized controlled trial (RCT) was conducted to assess the effectiveness of yoga as adjuvant therapy in patients with VVS.

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METHODS

This was a single-center, pre-preliminary phase II, open-label, RCT to evaluate the efficacy of yoga on the clinical outcomes of patients with VVS. Eligible patients were randomized into the intervention or control groups in a 1:1 ratio. Data analysis was performed by the trial statistician. All investigators and the trial statistician vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol.

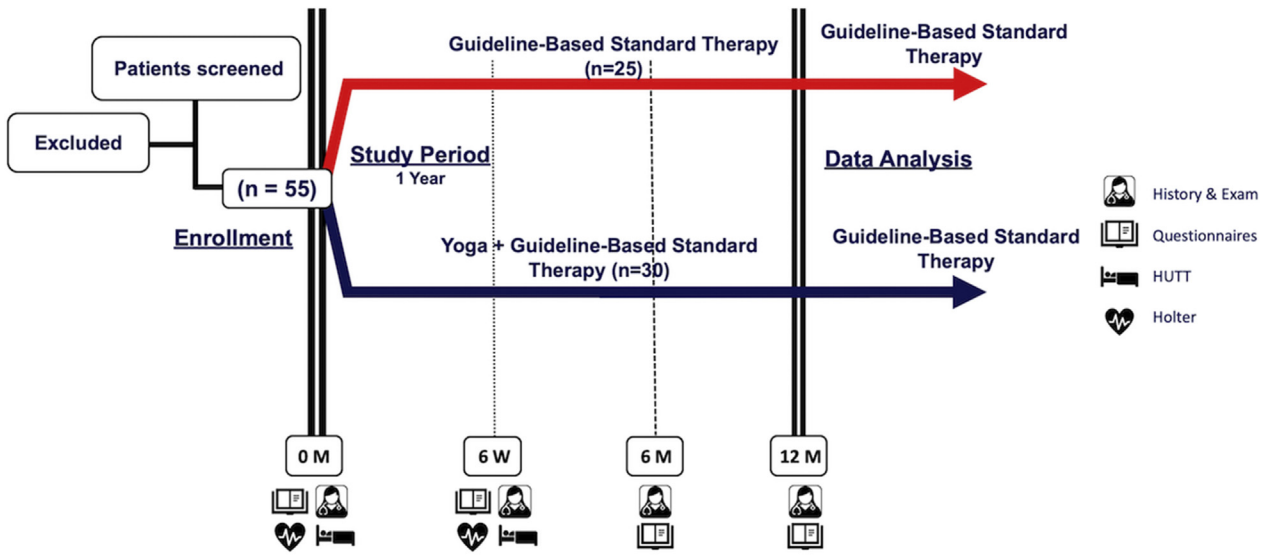
ELIGIBILITY. The study included adults between 15 and 70 years of age who were diagnosed to have VVS, and who had a positive head-up tilt test (HUTT) within 3 months, with at least 2 syncope or presyncope events in the 3 months before enrollment. Only those who were willing and able to practice yoga were enrolled. All secondary causes of syncope were ruled out and patients with structural heart disease, accelerated hypertension, and underlying neurological disorders were excluded. Inclusion and exclusion criteria are listed in Supplemental Table S1.

RANDOMIZATION AND TRIAL PROTOCOL. The study protocol was approved by the institutional ethical committee (Ref. No.: IEC-642/03.11.2017) and was registered online with the Clinical Trials Registry-India (CTRI/2017/12/010917). Written consent was obtained from all participants. Patients were randomized using random sequence generation and allocation concealment using sequentially numbered, opaque, sealed envelopes. Participants were enrolled from the Out-Patient Department of the Cardiothoracic Sciences Center at the All India Institute of Medical Sciences (AIIMS), New Delhi, India. The patients in the control group underwent the standard therapy as per the treating clinician for the same period. Standard care included physical counterpressure maneuvers (PCMs) (Supplemental Table S2), avoidance of known triggers, and salt and water intake augmentation, with drug therapy or pacing being initiated at the treating physician's discretion.

Yoga intervention was performed at the Centre for Integrative Medicine and Research (CIMR) at AIIMS, New Delhi, India. Patients assigned to the yoga group underwent yoga training according to a specialized yoga module designed for this trial by yoga physicians and therapists at the CIMR. The module was further validated by 5 yoga experts of national repute. The module comprised preliminary stretching and loosening exercises followed by breathing exercises and then isotonic physical postures (asanas) in 4 categories, pranayama (controlled breathing), and meditation (dhyana) (Supplemental Table S3). Each of the 4 categories of asanas was followed by a guided yogic relaxation. The supervised yoga intervention was given under the guidance of an institutionally certified yoga therapist.

There were 8 supervised sessions in the first 2 weeks after which patients had to continue practicing yoga at home for at least 5 daily sessions in a week. There were 2 supervised follow-up sessions in the second month and then 1 guided session per month till the sixth month (conducted by yoga therapists at the CIMR, AIIMS or via videoconference) (Supplemental Table S4). A booklet containing the details of the practice with a pictorial representation of the yoga module was given to the participants. All patients were encouraged to clarify their doubts through phone, by using an audiovisual internet facility, or by visiting the CIMR. Compliance was ensured by a twice-monthly telephone call from the yoga center to the patient and by a daily self-reported

FIGURE 1 Trial Flow Chart



HUTT = head up tilt test.

yoga log maintained by the patient. Besides twice-monthly telephone calls, patients were followed-up at 6 weeks, 6 months, and 12 months. A syncope logbook was given to all patients to report the frequency and duration of presyncope and syncope episodes. Data collection was at baseline, 6 weeks, 6 months, and 12 months. The follow-up matrix is provided in **Figure 1** and Supplemental Table S5. The HUTT protocol is provided in Supplemental Table S6.

OUTCOMES. The primary outcome was a composite of the number of episodes of syncope and presyncope over a follow-up period of 12 months. Secondary outcomes included QoL assessment by World Health Organization Quality of Life Brief Field questionnaire (WHOQoL-BREF) scores and syncope functional status questionnaire (SFSQ) scores at 12 months, HUTT-negative response, and heart rate variability (HRV) at 6 weeks.

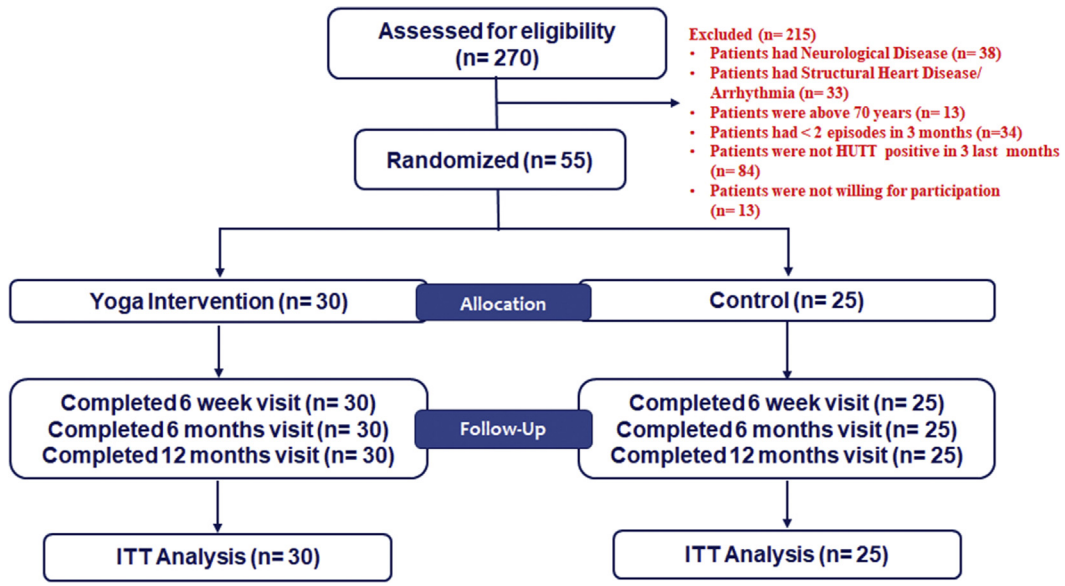
STATISTICAL ANALYSIS. To calculate the sample size of the present study, a trial conducted by Gunda et al (14) was taken into account, which was a single-center pilot study that had similar outcomes on VVS (syncope, presyncope, and QoL scores). Sample size of 6 (3 in each group) was calculated by taking the mean ± SD of the number of episodes as 1.3 ± 0.7 and 3.3 ± 0.5 in intervention and control groups, respectively.

Because the calculated sample size was small for a phase II clinical trial, by considering a moderate to high standardized effect size of 0.65, 2-sided $\alpha = 0.05$, and $\beta = 0.2$, a sample size of 78 (39 in each group) was determined. It was decided that 100 (50 in each group) participants would be recruited by considering a dropout rate of 20%. Continuous variables were reported as mean ± SD or median as appropriate and categorical variables as number (percentages). Two sample Student's *t*-test or Wilcoxon rank-sum test as appropriate, was used to ascertain the statistically significant difference in case of continuous variables, and the chi-square test was used in case of categorical outcomes. A value of $P < 0.05$ was considered statistically significant throughout the statistical analysis. Stata version 14.2 was used in statistical analysis.

RESULTS

BASELINE CHARACTERISTICS. A total of 270 patients were screened, of which 55 were enrolled (30 in the intervention group, 25 in the control group) (**Figure 2**). Both arms were well matched with respect to baseline characteristics (**Table 1**). The mean age of patients, comprising 36 (65.4%) females, was 39.3 ± 15.0 years. Mean body mass index (BMI) was 23.6 ± 3.2 kg/m^2. The mean systolic blood pressure was 122.0 ± 10.5 mm Hg and the mean diastolic blood

FIGURE 2 Consort Diagram



ITT = intention to treat; other abbreviation as in Figure 1.

pressure was 76.9 ± 9.6 mm Hg, respectively. No patients were on pharmacological therapy or pacing for VVS in either arm before enrollment. The preceding mean composite of VVS or presyncope episodes was 2.6 ± 1.3.

OUTCOMES AND FOLLOW-UP. Data collection began in May 2018 and ended in February 2021. Fifty-five patients were recruited from the Out-Patient Department of the Cardiothoracic Sciences Center, AIIMS. Thirty patients were randomized to intervention and 25 were randomized to control groups, respectively (Figure 2). All patients were followed-up for the duration of 12 months.

In the intention-to-treat analysis, the mean composite number of syncopal or presyncopal episodes at 12 months was 0.7 ± 0.7 (95% confidence interval: 0.43 to 0.96) in the intervention arm compared to 2.52 ± 1.93 (95% confidence interval: 1.71 to 3.32) in the control arm with a difference of 1.82 which was statistically significant ($P < 0.01$) (Central Illustration). The reduction in events began early (Supplemental Table S7) starting at 6 weeks (0.16 ± 0.46 vs 0.48 ± 0.71 events, $P = 0.05$) with a trend towards statistical significance and was significant at 6 months (0.33 ± 0.60 vs 1.52 ± 1.73 events, $P < 0.01$), and continued to separate till the end of the 12 months of follow-up (0.7± 0.7 vs 2.52 ± 1.93 events, $P < 0.01$).

In event-free survival analysis (Supplemental Table S8), more patients remained symptom-free in the intervention arm than in the control arm. At 6 weeks, 26 of 30 (86.7%) patients and 16 of 25 (64.0%) patients remained event-free, respectively ($P = 0.04$), and at 6 months 22 of 30 (73.3%) and 10 of 25 (40.0%) patients remained event-free, respectively, which was statistically significant ($P = 0.01$). At 12 months, 13 of 30 (43.3%) yoga intervention patients and 4 of 25 (16.0%) controls remained event-free with a statistically significant difference ($P = 0.02$) (Supplemental Table S8). Median (interquartile range) events between both arms were also statistically significant at 6 months and 12 months. The median number of events were 0 (0 to 1) versus 1 (0 to 2) respectively at 6 months ($P < 0.01$) and 1 (0 to 1) versus 2 (1 to 4) at 12 months, respectively ($P < 0.01$) (Supplemental Table S9).

Comparison of VVS frequency by Poisson regression between the groups also showed statistically significant improvement in the intervention arm at 6 weeks, 6 months, and 12 months (Supplemental Table S10). Analysis of the secondary outcome of QoL scores revealed positive results, with all but 2 scores showing significant improvement in QoL scores at 12 months (Table 2).

Of the patients who underwent repeat HUTT at 6 weeks, 8 of 20 showed HUTT-negative responses in

the intervention arm versus 6 of 18 in the control arm, which was not statistically significant ($P = 0.67$). HRV at 6 weeks revealed no significant difference (Table 3). All patients adhered to their yoga regimen of 5 sessions per week for more than 80% of the study duration. No adverse events due to yoga were reported. No patient was initiated on a pharmacological agent or advised pacing during the study period.

TABLE 1 Baseline Characteristics

	Overall (N = 55)	Group	
		Yoga (n = 30)	Control (n = 25)
Demographics			
Age, yrs	39.34 ± 15.04	38.30 ±16.01	40.60 ± 14.00
BMI, kg/m^2	23.61 ± 3.28	23.83 ± 03.63	23.36 ± 2.85
SBP, mm Hg	122.07 ± 10.56	122.43 ± 09.44	121.64 ± 11.95
DBP, mm Hg	76.94 ± 09.66	76.16 ± 08.41	77.88 ± 11.08
WHOQoL-BREF scores[a]			
Domain 1	56.58 ± 13.53	57.36 ± 15.68	55.64 ± 10.64
Domain 2	57.43 ± 15.64	57.93 ± 16.70	56.84 ± 14.59
Domain 3	65.54 ± 20.81	67.00 ± 20.48	63.80 ± 21.48
Domain 4	63.10 ± 13.42	63.70 ± 13.87	62.40 ± 13.12
SFSQ scores			
Impairment	41.49 ± 26.06	39.20 ± 27.01	44.24 ± 25.14
Fear/worry	60.85 ± 31.65	60.80 ± 31.92	60.92 ± 31.98
Control	43.83 ± 23.29	42.93 ± 20.82	44.92 ± 26.35
Hope	19.01 ± 25.02	19.80 ± 28.07	18.08 ± 21.33
Syncope dysfunction	51.14 ± 25.10	49.90 ± 25.90	52.64 ± 24.55
Patients on prior therapy[b]	0	0	0
VVS frequency			
Mean ± SD	2.60 ± 1.31	2.66 ± 1.60	2.52 ± 0.87
Median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)

Values are mean ± SD unless otherwise indicated. [a]Transformed 100 scores are taken. [b]Includes beta-blockers, alpha agonists, fludrocortisone, selective serotonin reuptake inhibitors, and pacing.

BMI = body mass index; DBP = diastolic blood pressure; IQR = interquartile range; SBP = systolic blood pressure; SFSQ = Syncope Functional Status Questionnaire; WHOQoL-BREF = World Health Organization Quality of Life Brief Field Questionnaire.

DISCUSSION

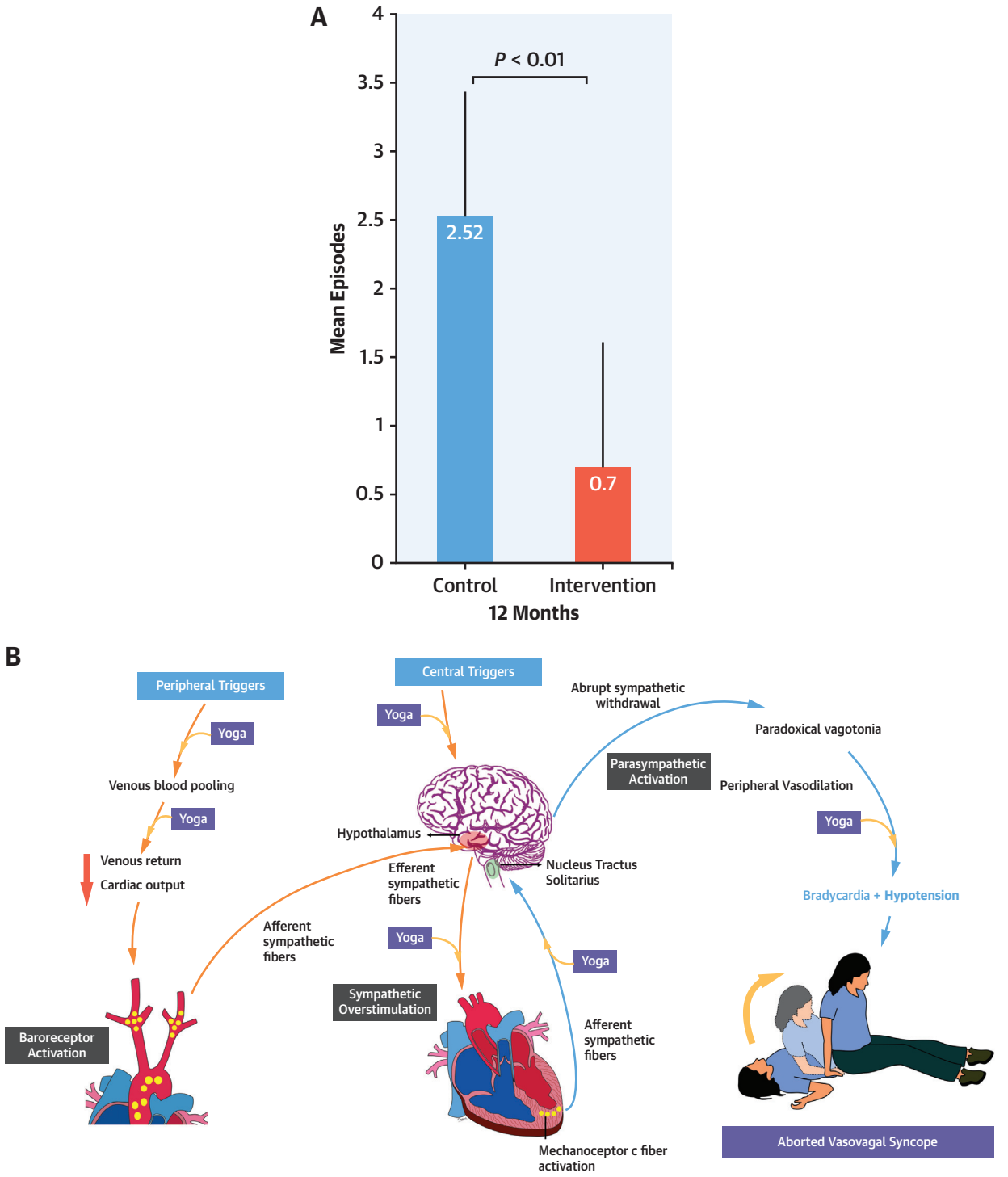
This trial studied the effect of yoga on patients with VVS. To the best of our knowledge, this study represents the first RCT comparing yoga, over a period of 12 months, as an adjunct to routine care, in patients with recurrent VVS. The trial showed a significantly lower incidence of the primary outcome of syncope or presyncope episodes in patients in the intervention group during the follow-up period. The difference in benefit was apparent from 6 weeks, with a trend towards statistical significance, and reached significance on subsequent follow-up. The margin of benefit was sizeable, with a mean episode reduction of 1.82 events at 12 months. Patients practicing yoga also had significantly improved QoL at 12 months as shown by all SFSQ scores and the WHOQoL-BREF domain A and B scores, with numerical improvement in domain C and D scores. We believe these findings may make yoga a suitable adjunctive treatment modality for VVS.

There was no difference in the outcomes of HUTT and HRV at 6 weeks. This could be explained because the assessment at 6 weeks was perhaps premature and because of the small number of patients who underwent the repeat tests. In the study by Gunda et al (14), there was a decrease in the number of positive HUTT responses in the yoga intervention arm. The difference could be attributed to a later assessment at 3 months. Perhaps a similar later assessment could have allowed adequate time for the overall effect of yoga to mature and mitigate the VVS-related adverse physiology. HUTT has also been recognized to be unreliable, inconclusively adjudicating positive treatment response in VVS (16).

Treatment of VVS patients has hitherto proven to be difficult, with various treatment modalities showing a modest benefit if any. Pharmacological options including beta blockers, autonomic modulators, and mineralocorticoids have yielded mixed results (17–22). Among postural treatment options, PCMs (which attempts to increase venous return through increased muscular tone) have been useful. Results from a RCT showed a 39% relative risk reduction, providing a risk-free and inexpensive method to abort or reduce syncopal episodes (23). Tilt training, comprising repeated tilt table testing or standing against support for prolonged lengths of time daily, has been evaluated. Several RCTs have shown no added benefit in reducing recurrences, although smaller observational studies have shown some reduction (24–27). The inadequacies of currently available treatment options have led to the exploration of traditional forms of medicine, including yoga (14,28). In the study by Gunda et al (14), yoga reduced syncopal burden in VVS patients. However, it was a small nonrandomized pilot study that included predominantly young women and the results cannot be generalized. A recent RCT has also shown a reduction in syncope burden in patients with recurrent VVS (15). However, our trial includes presyncope in addition to syncope episodes as the primary endpoint, which we believe is a more clinically relevant reflection of the symptomatic burden in patients with recurrent VVS.

The specially designed yoga module for this trial included postures, breathing, and relaxation techniques that were chosen keeping in view the pathophysiology of VVS. Yoga was taught by qualified therapists under the guidance of yoga physicians. Patients in both groups were similarly followed-up

CENTRAL ILLUSTRATION Yoga as Adjunctive Therapy in Vasovagal Syncope



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(A) Primary outcome event frequency. **(B)** Pathophysiology of vasovagal syncope indicating the potential sites **(orange arrows)** of yoga-mediated modulation.

TABLE 2 Secondary Outcomes — QoL Scores

QoL Scores at 12 mo	Group		*P* Value
	Intervention (n = 30)	Control (n =25)	
Syncope impairment	13.93 ± 20.25	26.36 ± 22.40	0.03
Syncope fear-worry	22.5 ± 21.8	38.2 ± 30.91	0.03
Syncope control	19.36 ± 19.23	31.16 ± 21.68	0.04
Syncope hope	8.03 ± 14.8	22.72 ± 26.96	0.01
Syncope dysfunction[a]	22.06 ± 22.74	35.96 ± 27.57	0.04
WHOQoL-BREF			
Domain A	74.06 ± 16.13	59.36 ± 20.02	<0.01
Domain B	70.93 ± 13.07	57.52 ± 20.68	<0.01
Domain C	70.53 ± 14.04	69.64 ± 13.71	0.81
Domain D	69.13 ± 17.52	64.16 ± 12.50	0.24

Values are mean ± SD. [a]Mean ± SD of Syncope Impairment Score and Syncope Fear-Worry Score. Higher SFSQ scores represent greater QoL impairment. Higher WHOQoL-BREF scores represent better QoL.

QoL = quality of life; other abbreviation as in Table 1.

TABLE 3 Heart Rate Variability

Time Point	Yoga (n = 19)	Control (n = 19)	*P* Value
Mean HR, beats/min			
Baseline	71 (60-77)	68 (63-77)	0.82
6 w	77 (69.0-83.97)	76.69 (70-80)	0.81
Mean SSDN, ms			
Baseline	57.2 (42.9-71.5)	53.7 (46.4-65.8)	0.69
6 w	56.1 (44.6-69.9)	51 (43.7-65.0)	0.45
Mean RMSSD, ms			
Baseline	29.3 (16.5-36.4)	25.5 (17.6-34.7)	0.75
6 w	25.9 (18.2-37.2)	22.5 (17.1-31.52)	0.30
Mean pNN_{50}, %			
Baseline	9 (2.7-17.1)	6.86 (2.9-13.7)	0.81
6 w	6.8 (3.12-17.1)	4.8 (2.0-12.2)	0.37
Mean ULF, ms^2			
Baseline	550.2 (301.9-774.9)	428.3 (299.7-664.9)	0.38
6w	383.5 (292.0-898.1)	440.9 (300.7-765.9)	0.59
Mean VLF, ms^2			
Baseline	2,259.2 (1,280.3-2,966.2)	1,577.4 (889.0-2,392.9)	0.23
6w	1,345.7 (958.2-3,326.3)	1,560.6 (952.3-2,458.6)	0.83
Mean LF, ms^2			
Baseline	985.5 (344.5-1.293.9)	776.4 (356.5-1,108.7)	0.31
6w	709.2 (334.9-1,685.9)	699 (340.1-1,047.0)	0.64
Mean HF, ms^2			
Baseline	261.6 (79.7-841.6)	289.1 (128.9-479.9)	0.75
6w	235.9 (65.8-554.7)	261.6 (120.1-390.8)	0.93
Log LF/HF			
Baseline	0.57 (0.27-0.67)	0.47 (0.392-0.598)	0.91
6w	0.526 (0.339-0.612)	0.558 (0.374-0.623)	0.77
ULF, %			
Baseline	11.5 (10.1-12.6)	11.1 (10.8-12.6)	0.84
6w	11.78 (9.2-13.02)	12.2 (10.9-14.8)	0.16
VLF, %			
Baseline	48.5 (44.1-53.2)	48 (45.1-52.2)	0.84
6w	46.6 (43.9-53.4)	50.1 (46.54-53.60)	0.37
LF, %			
Baseline	26.8 (25.0-30.3)	28.5 (24.2-31.5)	0.49
6w	27.1 (25.0-31.5)	26.3 (22.8-30.3)	0.49
HF, %			
Baseline	9.2 (7.9-17.8)	11.2 (8.0-15.6)	0.90
6w	10.2 (6.6-15.6)	9.5 (6.8-13.56)	0.78

Values are median (IQR).

HF = high frequency; HR = heart rate; LF = low frequency; log = logarithmic; pNN_{50} = percentage of successive RR intervals that differ by more than 50 ms; RMSSD= root mean square of successive RR interval differences; SSDN = standard deviation of NN intervals; ULF = ultra-low frequency; VLF= very low frequency; other abbreviation as in Table 1.

through regular telephone and video calls. Regular contact ensured adequate follow-up of patients at 12 months with all patients completing the daily regimen 5 times a week for 12 months for more than 80% of the study period. Guided practice ensured safety and no adverse events were reported for the duration of the study.

The pathophysiology behind VVS has been postulated to be a cascade set off by a trigger and/or intrinsic and extrinsic stressors, causing an initial venodilation phase leading to decreased cardiac output (29). This is followed by a sympathetic overdrive phase leading to increased force of contraction and tachycardia which stimulates the c-mechanoreceptors in the myocardium ultimately leading to a bradycardia and/or hypotensive phase and subsequently, syncope (29,30).

We postulate that positive effects of yoga in this study could be related to a multidimensional effect of this intervention acting through both central and peripheral mechanisms, including physical, psychological, and autonomic pathways (**Central Illustration**). Regular practice of asanas which comprise various isotonic postures involving different muscle groups leads to enhanced muscle and vascular tone in addition to building muscle strength. Enhanced vascular and muscular tone, especially in lower limbs, not only blunts the venodilation phase of a syncope episode but may also accelerate the venous return. Yoga breathing and relaxation techniques have been shown to increase vagal tone and improve autonomic balance which could potentially curtail the sympathetic overdrive phase and interrupt the activation of the c-mechanoreceptors, which is a critical step in the syncope cascade (10,31). Additionally, mindfulness may help allay anxiety and alleviate stress which may help truncate the VVS cascade by inhibiting the central sympathetic drive thereby preventing or decreasing the intensity of clinical events. Meditation and mindfulness components of yoga have a positive influence on mental health and general wellbeing (32). Yoga has also proven beneficial in improving the QoL in atrial fibrillation and postmyocardial infarction rehabilitation (8,9). Yoga has also recently been shown to be useful in reducing migraine attack frequency and headache intensity (33).

The economic burden of VVS is also a matter of concern. In an earlier study from the United States, up to 740,000 emergency visits and 460,000 hospital admissions annually were attributed to VVS (34). There is a significant financial cost involving the diagnostic evaluation and management of syncope. Furthermore, there exist the indirect costs of loss of productivity and reduced performance (35,36). A low-cost intervention in the form of yoga, which essentially requires only a mat, can reduce both direct and indirect costs significantly.

STUDY LIMITATIONS. It was an open-label trial. We did not have a sham yoga group, although the standard patient advice including PCMs was emphasized. Assessment of precise compliance was limited by self-reporting. The sample size recruited was less than the initially calculated number because of the current pandemic.

CONCLUSIONS

Yoga as add-on therapy in VVS is superior to medical therapy in reducing syncopal and presyncopal events and in improving the QoL. It may be useful to integrate a cost-effective and safe intervention such as yoga into the management of VVS.

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ADDRESS FOR CORRESPONDENCE: Dr Gautam Sharma, Department of Cardiology, Centre for Integrative Medicine and Research, All India Institute of Medical Sciences, New Delhi, India. E-mail: drgautamsharma12@gmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Yoga represents a safe, efficacious, and inexpensive adjunctive treatment option for patients with VVS.

TRANSLATIONAL OUTLOOK: Larger studies may further delineate the effect of yoga on clinical outcomes and QoL facilitating the incorporation of yoga into management guidelines of VVS.

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KEY WORDS arrhythmia, cardiovascular disease, integrative medicine, vasovagal syncope, yoga

APPENDIX For supplemental tables, please see the online version of this paper.