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Randomized Controlled Trial Assessing Vitamin D's Role in Reducing BPPV Recurrence in Older Adults

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Abstract

Objective. To determine if the recurrence rates of BPPV in older adults were lower in the vitamin D-treated group as compared to placebo groups.

Study Design. Double-blinded randomized control placebo trial.

Setting. A single-centre study.

Methods. Double-blinded randomized controlled trial design with 12 months follow-up. Vitamin D3 deplete participants were randomized into treatment (Group A) or placebo groups (Group B). Treatment group received 13 weeks of 2000 IU vitamin D3 followed by 1000 IU for the next 13 weeks. Patients who were replete were allocated to a control group (Group C) for observation and follow up. All groups had dietary interventions for vitamin D3 and calcium.

Results. Results showed an 87% reduction in recurrence rates of BPPV in the treatment group (Group A), with 0.75 fewer clinical episodes per 1 person-year as compared to placebo (Group B). Time to first recurrence was also significantly longer in Group A. There was no statistically significant difference between Group A and C in both recurrence rates and dizziness handicap scores.

Conclusions. This clinical trial has laid the foundation to expand the investigation of vitamin D as standard of care treatment in BPPV patients in future phase IIb and III studies.

Summary. A reduction in BPPV episodes in older adults has implications on fall risk, as dizziness from BPPV may cause falls. With fewer BPPV episodes and longer time to recurrence, seniors may have better postural stability and hence reduced risk of falls.

Level of Evidence. 2.

Keywords

BPPV, dizziness, randomized controlled trial, recurrence, vitamin D deficiency

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Benign Paroxysmal Positional Vertigo (BPPV) is the most common cause of vertigo in older adults.[1] It is caused by dislodged otoconia, which fall from the utricular macula into the semicircular canals causing them to move through the canals with the effect of gravity.[2] Treatment of BPPV is primarily with Canalith Repositioning Procedure (CRP) with more than 80% success rates. However, BPPV can recur in 10%–20% of the time and in some long-term follow-up studies reporting up to 50% recurrence rates.[3] Despite BPPV being considered a benign self-limiting condition, it has far-reaching physical and psychosocial consequences for the geriatric population such as injuries from falls precipitated by vertiginous attacks and fear of unexpected vertigo leading to restriction of daily activities and functional decline.[4,5] Studies have shown that the 1-year prevalence of individuals with BPPV attacks rises steeply with age, with the cumulative (lifetime) incidence of BPPV reaching almost 10% by the age of 80.[1] Aging has also been shown to be a primary risk factor for idiopathic BPPV, with events

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such as prolonged bed rest postulated for being a trigger for BPPV.[1] BPPV is also noted to be underreported in the elderly mainly due to the different manifestations such as less rotatory vertigo and more nonspecific dizziness and instability, with consecutive examinations in geriatric population revealing that 9% of older adults have unrecognized BPPV.[6] Given the increased prevalence and severe implications of BPPV on there is a strong impetus for this study to lower the recurrence of BPPV in this vulnerable older population.

To date there are no local studies on the relationship between deplete Vitamin D levels and occurrence or recurrence of BPPV among the geriatric population. International studies have shown that there is an association between deplete Vitamin D levels and recurrence of BPPV,[7,8] however not specifically for the geriatric population. Other studies have also shown that the geriatric population has a higher percentage of deplete Vitamin D levels compared to the general population.[9] Currently patients with BPPV in our country are not routinely investigated for serum Vitamin D3 levels. This study will inform clinicians managing BPPV patients to investigate and treat any potential deficiencies in Vitamin D3 in addition to performing standard CRP, which might help lower the recurrence of BPPV episodes potentially leading to falls.[10] Although prior studies have established a connection between vitamin D insufficiency or deficiency with BPPV,[11-14] a recent systematic review and meta-analyses[15] have suggested conflicting evidence on the association between BPPV incidence and vitamin D deficiency, with some reporting lower vitamin D levels in patients with recurrent BPPV, while others observe no significant difference.[16] The studies reviewed were heterogenous in the patient selection, canal involvement (single vs multiple/mixed), BPPV type (cupula versus canal variant) and were not well-controlled. Among several independent risk factors[16] identified such as advanced age, sex (female), hypertension, hyperlipidaemia, diabetes, migraine, and osteoporosis, the association of hypovitaminosis D3 and BPPV as an independent risk factor has been extensively studied over the last decade. However, no clear relationship has been established[17] and there is still a scarcity and need of well-designed randomized controlled trials to elucidate the treatment effect of vitamin D supplementation,[18] especially in the context of older adults. Despite inconclusive evidence, patients are still treated with vitamin D regardless of its role in BPPV recurrence. Hence, our study aims to add to the evidence in the literature to better inform clinicians on managing such a common otologic condition.

A recent meta-analysis[19] on supplementation, suggested a reduction in BPPV recurrence with treatment of Vitamin D. However, most studies were of a nonrandomized design with unstandardised dosing of vitamin D. Of the 6 studies identified, only 1 was a randomized controlled pragmatic trial,[19] but without placebo and not specifically looking at older adults. In our study, we looked at older patients aged 50 and above, which is a population group that may benefit from Vitamin D replacement even without BPPV as a diagnosis.

Primary and Secondary Objectives of the Study

The primary objective was to determine if replacement of vitamin D combined with dietary intervention "group A" was superior to a placebo with dietary intervention "group B" in reducing the incidence rate of BPPV over 12 months following randomization, among patients with history suggestive of idiopathic BPPV and vitamin D < 30 ng/mL at randomization. The primary endpoint was defined as a difference in incidence rates of BPPV at 12 months follow-up between groups. Recurrence of clinical BPPV was defined by a positive geotropic nystagmus, with corresponding subjective vertigo in a gold-standard Dix-Hallpike assessment.

The secondary objective was to look at total BPPV episodes (clinical and subclinical) to determine if patients had a lower incidence rate over 12 months from baseline (between groups randomized A&B) and compared to vitamin D replete patients who had ≥30 ng/mL vitamin D at baseline and received only dietary intervention, "group C." We also looked at time-to-first recurrence of BPPV and the difference in Dizziness Handicap Index-Short (DHI-S) total score at 12 months since randomization between groups A and B. Subclinical BPPV was defined as the presence of subjective vertigo without corresponding nystagmus patterns. We hypothesized that Vitamin D replacement will be more effective than diet-alone in the placebo and control groups at achieving both endpoints at 12 months with lower incidence rates of clinical and subclinical BPPV episodes and/or longer time to recurrence.

Methods

This was a single-centre Phase IIa double-blinded randomised control trial (RCT) with 1:1 randomization investigating the effectiveness of Vitamin D versus placebo and control at reducing recurrence rates of BPPV in older adults, over a 12-month follow-up period. All patients 50 years of age and above, who were referred to the Department of Otorhinolaryngology-Head and Neck Surgery Specialist Outpatient Clinic (SOC) between September 2021 and December 2022, who met inclusion and exclusion criteria for study were recruited. This study was approved by Singhealth Centralized Institute Research Board (CIRB); approval number 2020/2654 and clinical trial was registered in clinicaltrial.gov database #NCT04578470. Patients' sources of referral were mainly from outpatient government polyclinics and private general practitioners. As patients may also be referred for non-otologic complains at the SOC, the study team reviewed the patients' chart

for keywords "BPPV"; "Vertigo"; "Dizziness"; and "Giddiness" on the day of their appointment, to further screen patients for otologic complains, that may be BPPV for potential recruitment.

Inclusion/Exclusion Criteria

Both male and female participants aged 50 and above with history suggestive of idiopathic BPPV, supported by positive Dix Hallpike test were recruited. Participants must be cognisant or with not more than a mild neurocognitive impairment (AMT ≥ 7) to ensure that informed consent can be taken. Participants with any identified neurological cause of giddiness or with significant cervical-spinal radiculopathy impeding successful canalith repositioning maneuver for treatment of BPPV were excluded. Bedside examination was performed to exclude any focal neurological deficits nor vestibular-cerebellar signs or suspicion of underlying peripheral vestibular disorders and/or central vestibular signs. Please refer to supplementary file for study protocol with a complete list of inclusion and exclusion criteria.

Recruitment Process

On the same day of the consult with the ENT doctor, patients with history of giddiness suggestive of idiopathic BPPV and a positive Dix Hallpike test, were recruited either at the ENT clinic or in the Emergency Department (ED) when they first presented. If the diagnosis is confirmed by an ENT team member, the patient may be recruited in the ED, but it was anticipated that most patients will be reviewed at the ENT clinic. After being seen at the ENT clinic for treatment of BPPV, all patients attended same day audiology as per standard care. The study team collected informed consent from the patients who had an AMT score of ≥7. When all inclusion and exclusion criteria were met and consent obtained, the patient undertook a vitamin D and corrected calcium test. Based on the blood test results, the randomisation process and administration of Vitamin D treatment or placebo was administered by the unblinded team leaving all others blinded to the study.

Randomisation, blinding, and study design

Patients that were Vitamin D deplete were blinded and randomised into 2 groups (Group A or Group B), with 1 group who received vitamin D supplementation (2000 IU a day for 13 weeks followed by 1000 IU per day for 13 weeks) and the other, a placebo (with similar dosing regimen). Patients that were Vitamin D replete was assigned to Group C and only received dietary advice on maintaining their levels of vitamin D. Please refer to supplementary file for the clinical trial protocol and **Figure 1** for the study design and participant flow.

Power Calculation and Statistical Analysis

This study aimed to recruit 20 patients in each group. Recruitment of a total of 60 patients would provide a minimal clinical important difference (MCID) of 1 BPPV episode, standard deviation of 1 with a power of 85%.′ The reporting of trial results was in accordance with CONSORT guidelines.[20] Descriptive statistics of patient demographic and clinical characteristics were reported as number and percent for categorical data, mean ± standard deviation (SD) for normally distributed data, and median and interquartile range (IQR) for nonnormally distributed data.

The primary endpoint was examined via the incidence rate difference (IRD) and the incidence rate ratio (IRR), with corresponding 95% confidence intervals (CIs). Plots of the Kaplan-Meier estimator for the first recurrent BPPV-free probability against time were also generated. Differences in survival distributions were assessed using the log-rank test, while differences in DHIS-total score were assessed using the Wilcoxon rank-sum test. To examine if there were differences in BPPV recurrence rate and DHI-S total score over/at 12 months from baseline between group A and C, similar statistics and tests were used. Statistical tests were 2-sided with a 0.05 significance level. All statistical analyses were conducted using Stata 18 (StataCorp LLC).

Results

Of the 228 BPPV patients identified, 76% (174/228) were resolved or subclinical BPPV, leaving a small number of acute BPPV patients who had subjective vertigo and corresponding nystagmus on the gold standard Dix-Hallpike examination. The 54-remaining acute BPPV patients met eligibility criteria for inclusion into our clinical trial and 53 were eventually recruited (1 patient refused consent). All 53 patients had diagnostic confirmation of primary idiopathic BPPV of the posterior canal only and had no prior treatment or history of BPPV, when they presented to the ENT department and patients all note a history of short-lasting vertigo provoked by changes in vertical head pitching. A detailed breakdown of the diagnoses of patients screened is shown in **Table 1**.

Fourteen participants were assigned to group C (replete vitamin D), while 39 participants were randomized in a 1:1 ratio to groups A (n = 19) and B (n = 20). The median overall follow-up time was 12.3 months (374.5 days) in group A and 12.7 months (385.2 days) in group B. 10.5% (2/19) of participants in group A were lost to follow-up before 6 months postrandomization, while 5% (1/20) in group B were lost to follow-up before 12 months postrandomization. In group B, all participants were followed up to approximately 12 months postrandomization.

The mean age at randomization in groups 1 and 2 were 66.5 ± 9.4 and 66.5 ± 8.1 years, respectively. 79.0% (15/19) of participants in group A were female, compared to 60%

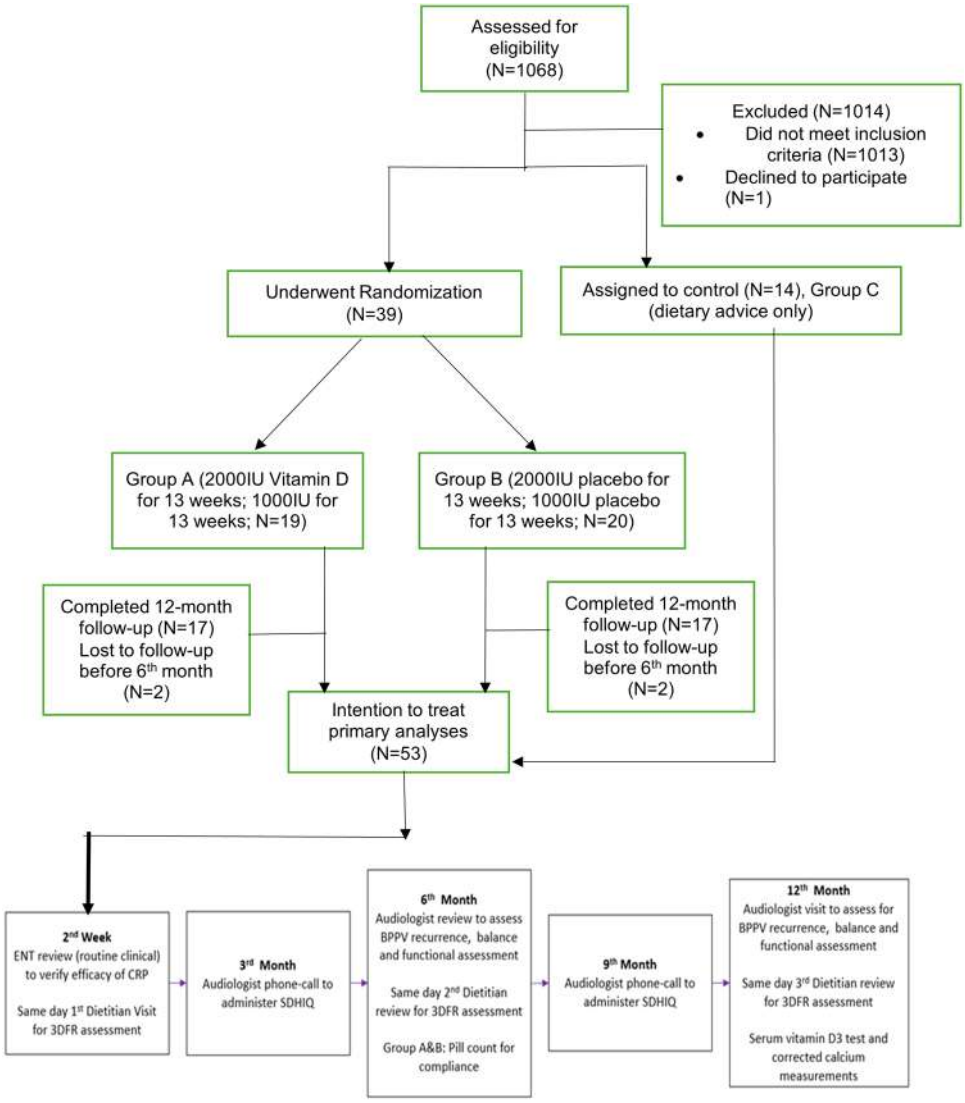

Figure 1. Study design and participant flow chart.

(12/20) of participants in group B. The baseline demographic and clinical characteristics overall and by group, are shown in **Table 2**.

Group A Versus Group B

All participants were included in the primary analysis based on the original group assignment. Participants in Group A has 2 clinical BPPV recurrences over 17.5 person-years at risk (6373 days) as compared to 18 clinical episodes in Group B over 20.8 person-years at risk (7605 days). Comparatively, that is an incidence rate difference of 0.75 (fewer clinical BPPV recurrences per 1 person-year; IRD −0.75, 95% CI −1.18 to −0.32, $P = .035$; **Table 3**. The corresponding IRR was 0.13 (95% CI 0.01-0.55, $P = .016$; **Table 3**). Similar results were obtained when including subclinical cases in the definition of BPPV recurrence, where there were significantly fewer recurrences (1.26 fewer total subclinical BPPV episodes per person-year; IRD −1.26, 95% CI −1.83 to −0.69, $P < .001$; **Table 3**). The corresponding IRR was 0.16 (95% CI 0.05-0.51, $P = 0.002$; **Table 3**).

Time to first recurrence was also significantly longer in Group A as compared to Group B in both clinical (**Figure 2**) episodes of recurrent BPPV and subclinical cases (**Figure 3**). The Wilcoxon rank-sum test did not show evidence of a difference in DHI-S total score between the 2 groups ($P = .908$).

Group A Versus Group C

We also explored if there were differences in the total BPPV recurrence rates (clinical and subclinical) and the DHI-S total score at 12 months between groups A and C. There was no evidence of a difference in BPPV recurrence rate per person-year (**Table 4**) or the DHI-S total score at 12 months (Wilcoxon rank-sum test $P = .313$; **Table 4**).

Table 1. Clinical Diagnoses of Patients Screened

Clinical diagnosis (ENT related)	Count	Total
Benign paroxysmal positional vertigo (BPPV)	54	54
Resolved/resolving benign paroxysmal positional vertigo (BPPV)	174	174
Meniere's disease/hydrops of the inner ear	70	70
Central issues		
Migraine	16	46
Neurological signs	8	
Vascular conflict (anterior or posterior circulation)	4	
Trigeminal neuralgia	2	
History of stroke	6	
Disequilibrium	10	
Nonspecific dizziness	230	230
Outer/middle ear issues		
Otitis externa	12	40
Chronic suppurative otitis media (CSOM)	12	
Eustachian tube dysfunction (ETD)	2	
Otomastoiditis	2	
Ossicular chain adhesion	2	
Ossiculoplasty	2	
Cholesteatoma	8	
Nasal/airway/head-neck/throat issues		
Nasal polyps	6	48
Nasal pus	2	
Allergic rhinitis	2	
Obstructive sleep apnoea	10	
Dysphagia	2	
Multi-nodular goitre (MNG)	6	
Chronic rhino sinusitis (CRS)	2	
Laryngo-pharyngeal reflux (LPR)	6	
Rhinoplasty	6	
Thyroidectomy	2	
Acute sinusitis	2	
Temporal mandibular joint (TMJ) pain	2	
Hearing loss (HL; Asymmetrical, Sudden, Presbycusis)		46
Asymmetrical sensorineural HL	24	
Sudden HL	4	
Presbycusis	18	
ENT-Head and neck lesions		10
Parotid gland adenoma	2	
Basal cell carcinoma	2	
Temporalis liposarcoma	2	
Warthin tumour	2	
Maxillary alveolar tumour	2	
Other otologic causes		54
Vestibular neuronitis	26	
Vestibular schwannoma	12	
Labyrinthitis	4	
Superior semi-circular canal dehiscence (SSCD)	2	
Bilateral vestibulopathy	2	
Tinnitus	8	
Postural dizziness/pre-syncope/persistent postural perceptual dizziness		20
Persistent perceptual postural dizziness (P3D)	10	
Pre-Syncope	2	
Postural hypotension	8	
Others		18
Multifactorial dizziness	6	
Cardia sarcoidosis	2	
Hypoglycaemia	2	
Cardiovascular disease	2	
Cervical lymphadenopathy	2	
Cervical myelopathy	2	
Pineal gland cyst	2	
No show	258	258
Total		1068

Adverse Events

Table 5 shows the list of adverse events, by group. 73.7% (14/19), 95% (19/20), and 78.6% (11/14) of participants had follow-up adverse event data in groups A, B, and C, respectively. There was a total of 4 nonserious and 1 serious adverse event: 3 in group A, 1 in group B, and 1 in group C. One patient in group C was hospitalized for 3 days for headache and blurring of vision at 3 months from baseline. This was classified as a serious adverse event. However, we believe that these events were unrelated to BPPV and neither a side-effect of vitamin D nor placebo as group C received dietary interventions only.

Discussion

Despite the higher prevalence of BPPV in females,[21] this trial had a nearly balanced sex distribution across both groups and the loss to follow-up was relatively low, which strengthens the validity of the study finding. Despite the slightly higher loss to follow-up in Group A before 6 months, this did not significantly affect our primary endpoint.

The significant reduction in clinical BPPV recurrence rate in group A (vitamin D) compared to group B (placebo) suggests a potential protective effect of vitamin D supplementation against BPPV recurrences. When we looked at total BPPV episodes whether clinical or subclinical, findings were aligned with primary outcome, further supporting the potential benefit of vitamin D. An incidence rate ratio of 0.13 suggests that participants in group A had an 87% lower rate of clinical BPPV recurrence compared to group B. This is a substantial reduction and is clinically relevant, especially when looking at older adults whose risk of falls may be increased with

Table 2. Baseline Demographic and Clinical Characteristics of Participants

Characteristic	All participants (n = 53)	Participants randomized to group A (n = 19)	Participants randomized to group B (n = 20)	Non-randomized participants in group C (n = 14)
Age in years, mean ± SD	66.2 ± 8.1	66.5 ± 9.4	66.5 ± 8.1	65.6 ± 6.4
Age group in years, n (%)				
<50	12 (22.6)	5 (26.3)	4 (20)	3 (21.4)
50-59	23 (43.4)	6 (31.6)	10 (50)	7 (50)
60-69	16 (30.2)	7 (36.8)	5 (25)	4 (28.6)
70-79	2 (3.8)	1 (5.3)	1 (5)	0 (0)
≥80				
Female gender, n (%)	35 (66.0)	15 (79.0)	12 (60)	8 (57.1)
BMI in kg/m^2	22.4 ± 9.6	21.3 ± 11.3	24.0 ± 9.6	21.7 ± 7.4
Fear of falling, n (%)	22 (47.8)	3 (21.4)	10 (55.6)	9 (64.3)
Fell in the past year, n (%)	2 (4.4)	0 (0)	2 (11.1)	0 (0)
History of fall, n (%)	2 (3.8)	0 (0)	2 (10)	0 (0)
DHI-S, median (IQR)				
Physical sub-score	6 (4-9)	4 (2-10)	6 (4-8)	8 (6-10)
Functional sub-score	2 (0-4)	2 (0-4)	2 (0-4)	2 (2-2)
Total score	8 (5-12)	6 (2-14)	8 (6-10)	10 (8-12)
Biochemical marker, mean ± SD				
Calcium in mmol/L	2.23 ± 0.10	2.25 ± 0.12	2.20 ± 0.08	2.23 ± 0.08
Albumin in g/L	46.0 ± 3.1	46.1 ± 2.5	44.6 ± 3.4	47.9 ± 2.5
25-hydroxyvitamin D_3 in ng/mL	24.1 ± 8.8	20.7 ± 5.5	19.5 ± 7.1	35.2 ± 3.5

Table 3. Group A Versus Group B (Primary and Secondary Outcomes)

Outcome	Group A (n = 19)	Group B (n = 20)	IRR (95% CI), group A vs group B	*P* value	IRD (95% CI), group A vs group B	*P* value
Primary						
No. of clinical BPPV recurrences over 12 months (total person-years at risk)	2 (17.5)	18 (20.8)	–	–	–	–
Clinical BPPV recurrence rate per person-year over 12 months (95% CI)	0.11 (0.03-0.46)	0.86 (0.54-1.37)	0.13 (0.03-0.69)	.016	−0.75 (−1.18-−0.32)	.002
Secondary						
No. of subclinical or clinical BPPV recurrences over 12 months (total person-years at risk)	4 (17.5)	31 (20.8)	–	–	–	–
Subclinical or clinical BPPV recurrence rate per person-year over 12 months (95% CI)	0.23 (0.09-0.61)	1.49 (1.05-2.12)	0.16 (0.05-0.51)	.002	−1.26 (−1.83-−0.69)	<.001
Median DHI-S total score at 12 months* (95% CI)	0 (0-2.33)	0 (0-2.97)	–	–	–	.908†

*14 and 8 participants had available DHI-S total score data at 12 months from randomization in group A and C, respectively.
†P value for the difference in DHI-S total score between group A and C, using the Wilxocon rank-sum test.
Abbreviation: BPPV, benign paroxysmal positional vertigo; CI, confidence interval; DHI-S, dizziness handicap inventory, short version; IRD, incidence rate difference. IRR, incidence rate ratio.

BPPV recurrence due to dizziness symptoms. When we look at the survival-curves and log-rank test, there was statistically significant difference in the time to first recurrence of clinical and total BPPV between treatment and placebo groups, with group A showing a longer recurrence-free duration. Although seniors may not always present themselves even when they have vertigo and may avoid BPPV-triggering positions, this limitation is ubiquitous in all studies of BPPV. Seniors were told to report to the study team whenever they are symptomatic, to facilitate an in-person assessment as mitigation. The findings, however, are consistent with the lower recurrence

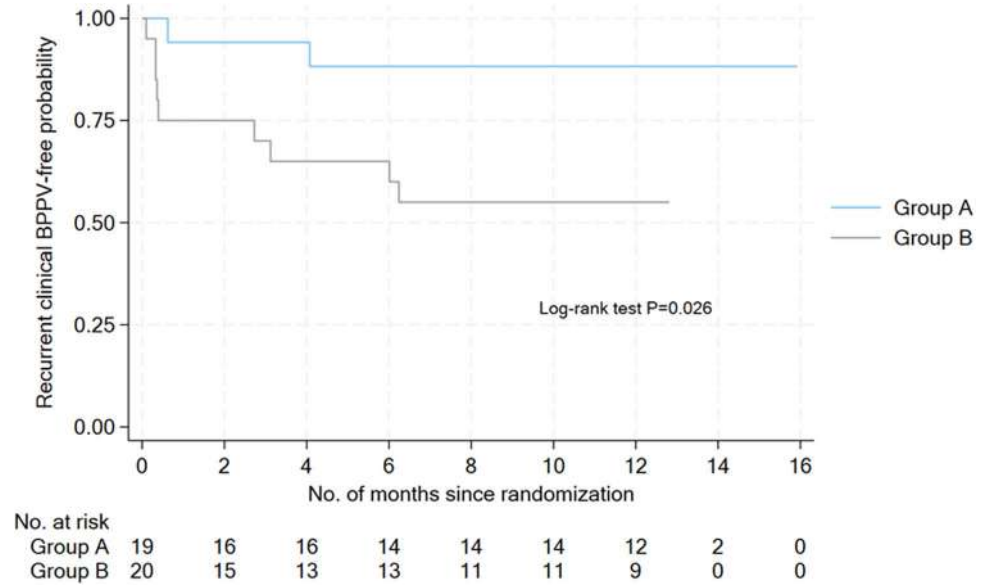

Figure 2. Kaplan-Meier curves for the first recurrent clinical BPPV against time. BPPV, Benign paroxysmal positional vertigo.

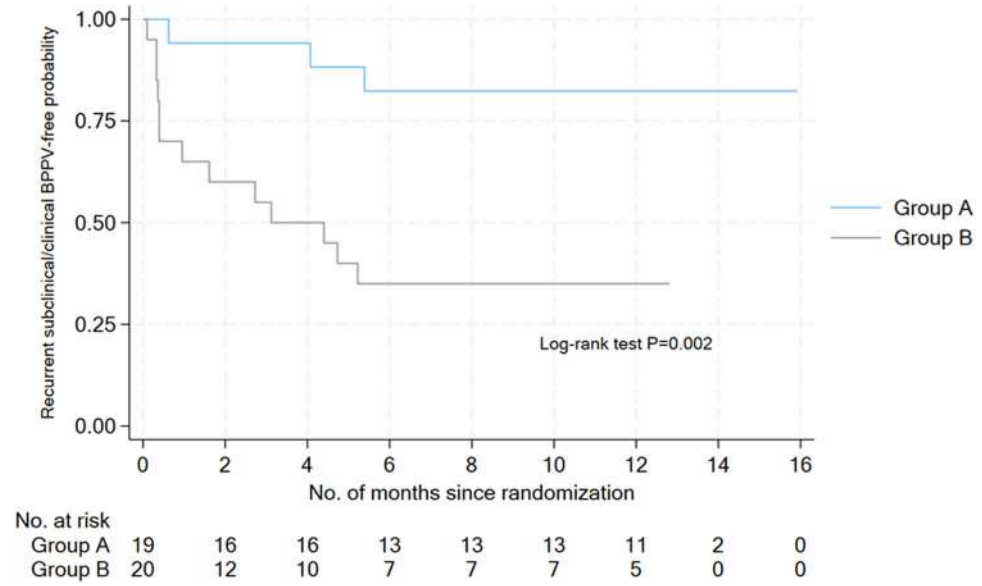

Figure 3. Kaplan-Meier curves for the first recurrent subclinical or clinical BPPV against time. BPPV, Benign paroxysmal positional vertigo.

rates observed in the primary and secondary outcomes. Although it has been suggested in the literature that BPPV in general has a high recurrence rate of approximately 22% to 28% in the first year,[22] ageing does not appear to increase the risk of recurrence as compared to other independent risk factors such as, Meniere's disease, and vascular risk factors.[22] BPPV recurrence rates can also be affected by confounding factors such as prior head trauma,[23] which predisposes a bilateral, mixed, or multiple canal involvement that is usually more refractory and known to recur more than idiopathic cases. Although some studies[23,24] may show no significant difference in the recurrence rates between primary idiopathic BPPV and secondary BPPV (trauma), there is a clinically minimum important difference in the number of recurring episodes and a systematic review[25] has showed clear evidence of an almost 3 times higher recurrence rates of traumatic BPPV as compared to idiopathic.

Our trial was hence, focused on a homogenous group of older adults with primary idiopathic BPPV of the posterior canal only. Both treatment and placebo group also had similar follow-up time frames and were properly blinded and randomized. Given these considerations, we believe that the treatment effect observed is less likely due to common chance of recurrence of the disease in general. However, we acknowledge that the sample size can be

Table 4. Group A Versus Group C (Secondary Outcomes)

Outcome	Group A (n = 19)	Group C (n = 14)	IRR (95% CI), group A vs group C	*P* value	IRD (95% CI), group A vs. group C	*P* value
No. of clinical BPPV recurrences over 12 months (total person-years at risk)	2 (17.5)	4 (15.0)	–	–	–	–
Clinical BPPV recurrence rate per person-year over 12 months (95% CI)	0.11 (0.03-0.46)	0.27 (0.10-0.71)	0.43 (0.08-2.34)	.328	−0.15 (−0.46-0.15)	.352
No. of subclinical or clinical BPPV recurrences over 12 months (total person-years at risk)	4 (17.5)	8 (15.0)	–	–	–	–
Subclinical or clinical BPPV recurrence rate per person-year over 12 months (95% CI)	0.23 (0.09-0.61)	0.53 (0.27-1.07)	0.43 (0.12-1.55)	.198	−0.31 (−0.74-0.13)	.170
Median DHI-S total score at 12 months[a] (95% CI)	0 (0-2.33)	2 (0-8)	–	–	–	.313[b]

Abbreviations: BPPV, Benign paroxysmal positional vertigo; CI, confidence interval; DHI-S, Dizziness handicap inventory, short version; IRD, incidence rate difference; IRR, incidence rate ratio.
[a]14 and 8 participants had available DHI-S total score data at 12 months from randomization in groups A and C, respectively.
[b]*P* value for the difference in DHI-S total score between groups A and C, using the Wilxocon rank-sum test.

further expanded in Phase IIb and III trials to corroborate such findings.

Past studies were mostly with high bias and non-randomized except for a large multicentered trial conducted in 2020 by Jeong et al. However, this pragmatic trial did not use a placebo. Although the trial results were conclusive and suggested a significantly lower recurrence rate of BPPV, there were a few confounding factors such as recruiting atypical types of BPPV including mixed canal, including patients with sufficient vitamin D3 in the intervention group, not measuring vitamin D3 levels in their controls and taking subclinical BPPV as a positive recurrence. Our study is well designed as a placebo trial, focused on older adults, and only looked only at participants with idiopathic posterior canalithiasis, as recurrence rates have been reported to be significantly higher in atypical cases.[26,27]

Of note, the lack of significant difference in the Dizziness Handicap Inventory-Short (DHI-S) total scores between the 2 groups at 12 months, suggest that while vitamin D may reduce the recurrence rate of BPPV, it does not appear to impact the perceived handicap associated with dizziness in those who do experience recurrences. This is expected as the subjective perception of dizziness is often dissociated with objective findings.[28] The limitation, however, is that DHI-S should have been assessed at more regular intervals instead of at 12-month only. At 12-month, most of our patients were negative for BPPV of any variant in either ear and hence DHI-S is expected to be close to 0 and back to baseline in both groups. Although our study protocol did plan for regular DHI-S to be administered at 3, 6, and 9 months, this data was unfortunately missing. DHI-S has also been used to predict the recurrence of BPPV,[29] but as patients with BPPV may be avoiding triggering positions and reporting absence of symptoms, we find less relevance in interpreting DHI-S.

Vitamin D is believed to affect BPPV in several ways, through its role in calcium metabolism,[30] high bone turnover rates in the temporal bone,[31] otoconia biomineralization,[31] and in inflammatory response[32] where vitamin D has immunomodulatory functions that may be protective.

While the exact mechanisms of vitamin D and BPPV is not clear, treatment of vitamin D should be strongly considered as standard of care in BPPV for a few salient reasons. First, even if we are not treating BPPV, vitamin D deficiency should be treated and in the context of older adults will be additionally beneficial for bone and muscle health. Improving or maintaining bone and muscle health in seniors can improve postural stability and minimize fall risks. When BPPV is a comorbidity and dizziness from BPPV increases fall risk, treating vitamin D deficiency becomes equally important, if not for reducing BPPV recurrence. We specifically also treated participants with vitamin D only without calcium, to minimize risk of hypercalcemia and constipation. Our study team decided with this approach as our local study[33] in older adults showed that while hypovitaminosis D3 is common, hypocalcemia is rare. Furthermore, international

Table 5. Adverse Events Over 12 Months

	Group A (n = 14)		Group B (n = 19)		Group C (n = 11)	
Event	No. of patients (%)	No. of events	No. of patients (%)	No. of events	No. of patients (%)	No. of events
Dizziness	1 (7.1)	1	1 (5.3)	1	0 (0)	0
Headache and blurring of vision	0 (0)	0	0 (0)	0	1 (9.1)	1
COVID-19 positive	1 (7.1)	1	0 (0)	0	0 (0)	0
Insomnia	1 (7.1)	1	0 (0)	0	0 (0)	0

14, 19, and 11 participants had follow-up adverse event data in groups A, B, and C, respectively. One patient in group C was hospitalized for 3 days for headache and blurring of vision at 3 months from baseline. This was classified as a serious adverse event.

consensus[34] only advocated for the additional supplementation of calcium in high-risk patient and supplementation must be well considered with the potential risk of renal stones and gastrointestinal symptoms. Our study has shown that vitamin D3 can significantly reduce the incidence rates when looking at clinical and subclinical BPPV. In the context of older adults, this has implications on reducing fall risk. Furthermore, residual dizziness after resolution of BPPV is also not uncommon and has also been associated with hypovitaminosis D3.[35] Hence, treating BPPV patients with vitamin D supplementation may not only reduce recurrence rates, but also improve post-BPPV dizziness, muscle, and muscle health in our older adults.

In conclusion, our well-designed phase IIa randomized control trial adds value to the literature as there is a paucity of evidence in the use of vitamin D in the treatment of BPPV. Despite a smaller sample size, we have demonstrated good efficacy in the use of vitamin D at managing older patients with BPPV. This lays the groundwork to expand the study further with an increased sample size and a multi-site trial to enhance the robustness and repeatability of the trial results.

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Author Contributions

Kenneth W. De Chua, study design, data collection, manuscript creation and revision; **Xiaoting Huang**, contributed to the data interpretation and result discussion; **Koh X. Han**, statistical analysis and data interpretation; **Joshua F. S. J. Yi**, literature review, study design and concept; **Vivian C. Barrera** and **Poongkulali Anaikatti**, study design and data collection; **Deng Jing**, **Shirlene Moh**, and **Miko Yeo**, data collection and interpretation of the result; **Yuen H. Wai** and **David Low**, study design and concept while **Barbara H. Rosario** is the corresponding author and contributed to conceptualization, review, data collection and interpretation, results analyses and revision of manuscript. All authors agree to be accountable for all aspects of the work.

Disclosures

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