Scientific Research Publishing

Neuroscience & Medicine, 2022, 13, 91-102
https://www.scirp.org/journal/nm
ISSN Online: 2158-2947
ISSN Print: 2158-2912

Ginkgo biloba Extract EGb 761® Improves Central Vestibular Vertigo in Patients Undergoing Vestibular Exercises: A Randomised Placebo-Controlled Trial

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How to cite this paper: Heide, W., Adlung, B., Körtke, C. and Hoerr, R. (2022) *Ginkgo biloba* Extract EGb 761® Improves Central Vestibular Vertigo in Patients Undergoing Vestibular Exercises: A Randomised Placebo-Controlled Trial. *Neuroscience & Medicine*, **13**, 91-102.
https://doi.org/10.4236/nm.2022.133008

Received: May 25, 2022
Accepted: July 12, 2022
Published: July 15, 2022

Abstract

Background: *Ginkgo biloba* extract EGb 761® is widely used to treat various types of vertigo. **Aims**: An exploratory trial was conducted to evaluate the efficacy of EGb 761® in addition to vestibular exercises in central vestibular vertigo caused by vertebro-basilar ischaemia. **Subjects and Methods:** In this randomised, placebo-controlled, double-blind trial, 40 patients were enrolled in the vertigo clinic of a neurological university hospital and treated with daily doses of 240 mg EGb 761® or placebo for a period of 180 days. All patients regularly performed vestibular exercises in addition. Efficacy was assessed using: a visual analogue scale for the patients to rate the overall intensity of vertigo; a numeric scale for physician-rated change; a vertigo score based on intensity, duration, and frequency of vertigo; and electronystagmography. **Results:** Until day 180, the mean patient-rated intensity of vertigo decreased by 46% during EGb 761® treatment and by 19% with placebo ($p < 0.05$ for between-group difference). The vertigo score decreased at a significantly greater rate in the EGb 761® group compared to the placebo group. Nystagmus or other eye movement disorders were present only in small subgroups of patients without sufficient statistical power to detect differences between treatment groups. **Conclusions**: EGb 761® alleviated vertigo caused by ischaemic lesions in the brainstem or cerebellum in patients undergoing vestibular exercises.

Keywords

Ginkgo biloba Extract, EGb 761®, Randomised Controlled Trial (RCT),

Vertigo, Dizziness, Vestibular Exercises

1. Introduction

Vertigo and dizziness are not disease entities unto themselves; instead, they are key symptoms of various diseases of differing etiologies, including dysfunction of the vestibular system, both peripheral and central. Cerebrovascular disease can lead to ischaemic lesions in the brainstem or cerebellum and thus cause central vestibular vertigo/dizziness. This form is one of the three most frequent types of vertigo observed in a large outpatient vertigo clinic [1]. Acute vertigo has a profound impact on patients' well-being and impairs the quality of life significantly [2].

Dizziness (used as a term that includes vertigo) ranks among the most common complaints in medicine, affecting 15% - 35% of the general population at some point in their lives [3]. In a nationally representative sample in Germany, the 12-month prevalence of dizziness or vertigo was 22.9% [3]. In the 2008 National Health Interview Survey in the USA, it was estimated that 11.5% of adult Americans had experienced dizziness in the past 12 months [4] and 14.8% had dizziness or balance problems [5]. The incidence increases by age; about one in three elderly persons (≥65 years old) suffer from dizziness or balance problems [3].

The quantified *Ginkgo biloba* extract EGb 761® has been used successfully since the mid-seventies for the treatment of dementia [6]. Furthermore, controlled clinical trials have confirmed symptomatic improvement including vertigo in patients with mild cognitive deficits [7] [8]. In three independent meta-analyses, the efficacy and safety of EGb 761® were demonstrated in patients with cognitive impairment and dementia. In addition, it was shown that dizziness had a significantly lower incidence in the EGb 761® group than in the placebo group [6] [9] [10].

Nonclinical investigations underlined that the drug has neuroprotective effects, attenuates age-related deficits in neurotransmitters, improves microcirculation and blood rheology, has free radical-scavenging effects, improves mitochondrial function, and enhances neurogenesis [11]. Furthermore, EGb 761® has been proven to accelerate vestibular compensation after unilateral labyrinthectomy or vestibular neurectomy in animal studies [12] [13] [14]. In particular, it improved the recovery of spontaneous nystagmus, postural asymmetry, and locomotor deficits, as well as the restoration of neuronal firing rates and synaptic reoccupation in the deafferented medial vestibular nucleus. In placebo-controlled clinical trials, EGb 761® alleviated vertigo [15] and postural sway amplitudes [16] after peripheral vestibular lesions, the latter in combination with vestibular exercises. Vestibular rehabilitation has been shown to improve balance, dizziness, and quality of life in central vestibular disorders [17].

The present monocentric, exploratory trial applied a vertigo score that had been developed by specialists at the University Hospital of Lübeck, Germany. It was conducted in a pilot manner to investigate the efficacy of EGb 761® in facilitating the effects of vestibular rehabilitation to alleviate vertigo and associated physiological measures in patients with central vestibular vertigo/dizziness due to ischaemic lesions of the brainstem or cerebellum.

2. Subjects and Methods

2.1. Patient Selection

In a double-blind, placebo-controlled clinical trial (ISRCTN14486389), we enrolled 40 patients aged 30 to 75 years presenting with permanent or recurrent central vestibular vertigo due to either transient ischaemic attacks or infarctions in areas supplied by the vertebro-basilar arteries; these incidents had to have occurred at least 3 months ago. The diagnosis was ascertained by extensive medical history, neurological examination, oculomotor testing, posturography, and computed tomography.

Vertigo was quantified by a score ranging from 0 to 35 (described in detail in Section 2.3) based on its intensity, frequency, and duration. A minimum score of 5 was required for inclusion. Exclusion criteria were: other causes of vertigo, dizziness, ataxia, or eye movement disorders, e.g. peripheral vestibular lesions, congenital nystagmus, drugs, low blood pressure, or cardiac arrhythmia; severe hemiparesis; aphasia; dementia; Parkinson's disease. Patients taking perfusion-enhancing drugs, haemorheologically active agents or drugs to treat vertigo were also not enrolled. Written informed consent was obtained from all patients prior to enrolment.

2.2. Procedures

The trial protocol was approved by the ethics committee of the university. The trial was performed in accordance with the applicable versions of the Declaration of Helsinki and the Guideline for Good Clinical Practice as well as national laws.

After a 14-day single-blind placebo run-in period, patients were randomly allocated to receive either *Ginkgo biloba* extract EGb 761® capsules (EGb 761® is a registered trademark of Dr. Willmar Schwabe GmbH & Co. KG), 120 mg twice a day for 180 days, or an equal number of placebo capsules of identical appearance and flavour. All patients had to perform standardised vestibular exercises once daily [15] [18]. Patient numbers and treatments were matched by a validated computer program. Drug and placebo packs were identical in appearance and were allocated to patients in ascending order of patient numbers.

The investigational product, EGb 761®, is a dry extract from *Ginkgo biloba* leaves (35 - 67:1), extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0% - 27.0% Ginkgo flavonoids calculated as Ginkgo flavone glycosides and 5.0% - 7.0% terpene lactones consisting of 2.8% - 3.4% ginkgolides A, B, C and

2.6% - 3.2% bilobalide. It contains less than 5 ppm ginkgolic acids.

2.3. Outcome Measures

The primary outcome measures were a visual analogue scale (VAS) ranging from 0 (no complaints) to 100 (very severe complaints), on which the patients indicated the global severity of their vertigo and ataxia complaints, and a numeric scale from 1 (returned to normal) to 6 (markedly deteriorated), on which the physician rated the global change of the patients' vertigo.

As a secondary outcome measure, multiple eye movement parameters quantified by DC electronystagmography were assessed. Furthermore, intensity (I), duration (D), and frequency (F) of vertigo were to be rated by the patients in a questionnaire along 5-point scales, from which the vertigo score (S), developed by the investigator, was calculated according to the formula:

$$S = I \times (D + F)$$

with intensity (I), duration (D) and frequency (F) all rated along 5-point scales (I: 0 = no vertigo, 5 = very severe vertigo; D: ≤1 minute = 1, >1 minute and ≤1 hour = 2, >1 hour and ≤1 day = 3, >1 day and ≤2 weeks = 4, >2 weeks or all the time = 5; F: <1 attack per month = 1, ≥1 attack per month and <1 attack per week = 2, ≥1 attack per week and <1 attack per day = 3, ≥1 attack per day and <1 attack per hour = 4, ≥1 attacks per hour = 5).

The vertigo score focusses on quantifying the intensity, duration, and frequency of vertigo symptoms, analogous to the vestibular-balance section of the Vertigo Symptom Scale [19], which has proved itself as a rather reliable measure and has been used frequently, also in recent studies of vertigo [20].

All the aforementioned tests and assessments, a complete neurological examination, safety assessments and drug dispensation were performed on days 0 (baseline), 60, 120 and 180. In addition, laboratory blood analyses (blood cell counts, haemoglobin, creatinine, blood glucose, alanine transaminase and gamma-glutamyltransferase) were carried out at enrolment and at study exit.

2.4. Sample Size and Statistical Analysis

The statistical analysis was planned on an intent-to-treat (ITT) basis. The sample size was calculated for a comparison of the change in patient-rated global severity of vertigo. The assumption of an advantage in favour of EGb 761® of at least 0.7, a significance level of 0.05 and a power of 80% resulted in an estimated sample size of 2 × 20 patients. The confirmatory analysis was based on a one-sided, exact U-test.

3. Results

Figure 1 shows a flowchart of the enrolment and intervention allocation, follow-up, and data analysis with number of subjects for each treatment. Of the 40 patients enrolled, 21 were randomly allocated to EGb 761® treatment and 19 to placebo. Five patients in the EGb 761® group discontinued the study prematurely.

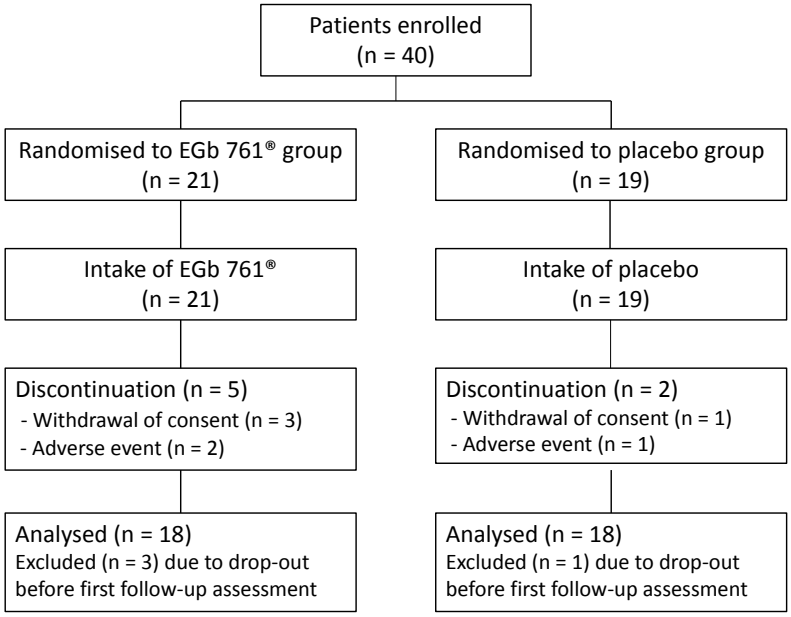

Figure 1. Flowchart presenting the recruitment and intervention allocation, and progress through the study.

Reasons were withdrawal of consent (n = 3) or adverse events (n = 2; pancreatitis, diarrhoea). In the placebo group, one patient withdrew consent and one dropped out due to an adverse event (haemorrhage in basal ganglia). Due to the discontinuation, no efficacy data was available for four of these patients after baseline (EGb 761®: n = 3; placebo: n = 1).

Data from the remaining 36 patients (18 per treatment group) were included in the ITT analysis. Demographics and baseline characteristics are shown in **Table 1**.

The patient-rated global severity of vertigo complaints (**Table 2**, **Figure 2**) showed a noticeable difference to placebo already at day 60, which further increased until day 180. The mean improvement was significantly greater (p = 0.012, Mann-Whitney U-test, two-sided) in the EGb 761® group (by 46%) than in the placebo group (by 19%).

For the physician's global rating, a slight improvement in both treatment groups was seen at day 120, which continued to increase in the EGb 761®-treated patients until day 180. However, the numeric difference in favour of EGb 761® was not statistically significant (**Table 2**).

Among the secondary outcome measures, the vertigo score indicated a statistically significant advantage (p = 0.04) for the EGb 761® group at day 180 (**Table 2**, **Figure 3**).

Most of the patients (n = 27) showed eye movement disorders due to brainstem-cerebellar dysfunction. Twenty-two of them had pathological nystagmus, as follows (multiple forms possible):

- spontaneous nystagmus (EGb 761®: n = 3; placebo: n = 2),
- downbeat nystagmus (EGb 761®: n = 1; placebo: n = 1),

Table 1. Demographics and baseline characteristics, absolute and (relative) numbers are shown if not stated otherwise.

	EGb 761® (N = 18)	Placebo (N = 18)	p-Value*
Gender male	11 (61)	15 (83)	0.079
Age (years) [median (range)]	63 (42 - 74)	55 (45 - 72)	0.066
Location of ischaemic lesion			
cerebellum	2	1	
brainstem	15	15	
multiple	1	2	
Nystagmus			
spontaneous	3	2	
downbeat	1	1	
gaze-evoked	7	5	
positional	5	2	
head-shaking	9	3	
Patient's global rating of severity (VAS) at baseline [points, median (95% CI)]	45.0 (30.0; 55.0)	27.5 (20.0; 40.0)	0.031
Vertigo score at baseline [points, median (95% CI)]	12.0 (8.0; 12.0)	10.0 (8.0; 15.0)	0.775

*two-sided p-values of U-test unless stated otherwise.

Table 2. Changes in clinical outcome measures* from baseline to day 120 and day 180, respectively.

	EGb 761® (N = 18)	Placebo (N = 18)	p-Value*
Patient's global rating of severity (VAS, 0 - 100)			
change at day 120	−17.8 (−26.7; −8.8)	−3.9 (−15.0; 7.2)	0.012**
change at day 180	−20.4 (−30.7; −10.1)	−6.8 (−18.0; 4.4)	0.04
Physician's global rating of change#			
at day 120	3.0 (2.5; 3.5)	3.2 (2.6; 3.8)	0.31#
at day 180	2.6 (2.1; 3.1)	3.2 (2.6; 3.7)	0.19
Vertigo score			
change at day 120	−7.3 (−11.5; −3.0)	−2.9 (−5.2; −0.6)	0.14
change at day 180	−7.8 (−12.4; −3.1)	−2.7 (−5.0; −0.4)	0.04

*means and 95% confidence intervals, two-sided p-values of U-test unless stated otherwise; **one-sided p-values; #1 = returned to normal, 2 = markedly improved, 3 = slightly improved, 4 = unchanged, 5 = slightly deteriorated, 6 = markedly deteriorated.

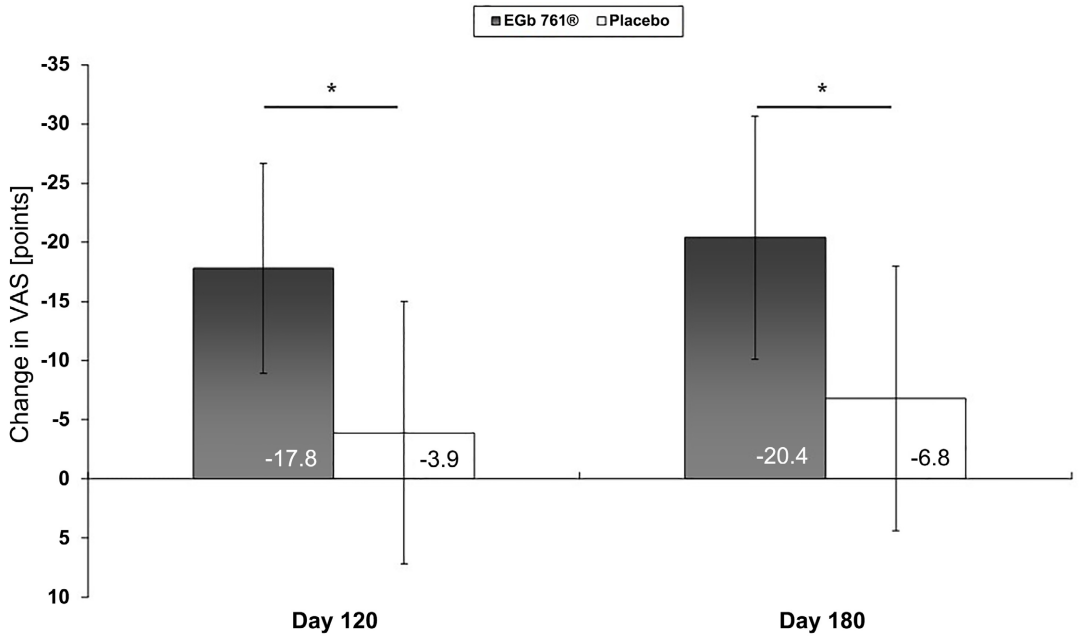

Figure 2. Decrease from baseline (day 0) in patient-rated global severity (VAS) of vertigo and ataxia during treatment (means and 95% confidence intervals; *p < 0.05, Mann-Whitney U-test).

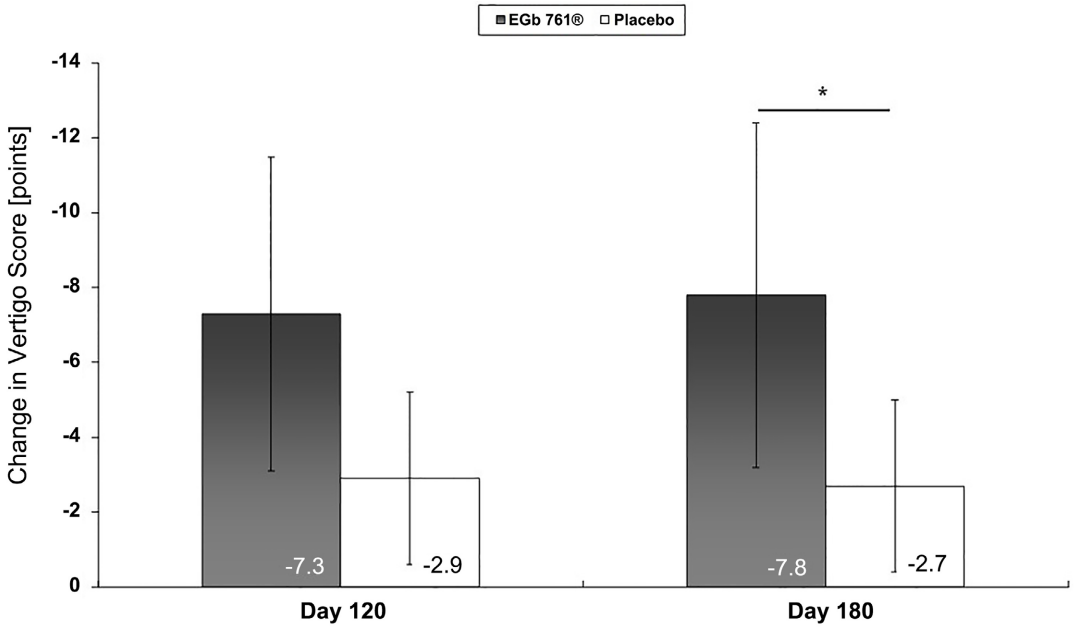

Figure 3. Decrease from baseline (day 0) in vertigo score during treatment (means and 95% confidence intervals; *p < 0.05, Mann-Whitney U-test).

- gaze-evoked nystagmus (EGb 761®: n = 7; placebo: n = 5),
- positional nystagmus (EGb 761®: n = 5; placebo: n = 2), or
- head-shaking nystagmus (EGb 761®: n = 9; placebo: n = 3).

The frequency of occurrence of each type of nystagmus decreased in both groups. After 120 days of treatment, head-shaking nystagmus was still present in one patient of each group. Due to the small numbers of patients affected with

each single type of nystagmus, differences between EGb 761® and placebo regarding remission of pathological nystagmus were not statistically significant (χ^2 test).

Furthermore, no significant effects were found on ocular motor disorders such as saccadic dysmetria (n = 8), low gain of smooth pursuit and optokinetic nystagmus (n = 17), impaired fixation suppression (n = 16), hyperexcitability (n = 4) or directional asymmetries (n = 10) of the vestibulo-ocular reflex, or impaired head tilt suppression of post-rotatory nystagmus (n = 12). The statistical power needed to achieve meaningful between-group comparisons was not reached due to the small numbers of patients who exhibited just one condition each. As each type of nystagmus was present in only a few patients, the study objective of finding neurophysiological correlates of subjective vertigo could not be attained.

EGb 761® was well tolerated. Laboratory tests did not reveal any clinically relevant deviations in either treatment group. One nonserious (infection with herpes zoster) and two serious (acute pancreatitis, vertebral fracture) adverse events occurred in the EGb 761® group, which were all not related to the study medication. For another nonserious adverse event (diarrhoea), a possible relationship with EGb 761® intake remained unclear albeit unlikely. From a patient of the placebo group, one serious adverse event (hypertensive haemorrhage in the left basal ganglia) was reported.

4. Discussion

Our exploratory, monocentric, randomised, controlled study, run in a pilot setting, demonstrates a significant therapeutic effect of EGb 761® on subjective vertigo and dizziness in patients with ischaemic lesions in the central vestibular system who were undergoing vestibular exercises. The patients' favourable global perception of improvement was supported by the results of the vertigo score, which takes the intensity, duration and frequency of vertigo into account.

The mechanism underlying this clinical effect is still a matter of scientific discussion. A combination of synergistic mechanisms is most likely. In addition to a general psychotropic effect, a specific effect on neuronal recovery in the central vestibular system might be considered in light of the experimental literature [12]. It remains to be elucidated to what extent, after ischaemia, improved microcirculation [21], energy metabolism [22], or enhanced neurogenesis and synaptogenesis [22] play a role. In rats with vestibular deafferentation, Lindner *et al.* [12] recently demonstrated experimental evidence that EGb 761® appears to modulate vestibulo-ocular motor, vestibulo-spinal, and cortico-striatal networks and improves spatial exploration indicating additional effects on vestibulo-hippocampal circuits.

We did not find any physiological correlate for the therapeutic effect in our patients, since a significant improvement of associated deficits such as nystagmus or other eye movement disorders could not be shown. This, however, may

be due to two reasons. First, the number of patients in each subgroup of oculomotor symptoms was too small for achieving meaningful between-group comparisons. Second, it is known that, in contrast to peripheral vestibular lesions, vertigo of central vestibular origin poorly correlates with the intensity of nystagmus [23]. It is important to note that many of these patients, as well as those with neurodegenerative cerebellar ataxias [24], are not necessarily disabled by their nystagmus, but more by their impaired balance and disequilibrium or vertigo, which could be improved by EGb 761® and vestibular exercises in our study.

Our findings support the results reported from other randomised, placebo-controlled trials. Enhanced vestibular compensation in patients with peripheral vestibular lesions was observed by Hamann [25] when a standardized exercise programme was combined with EGb 761® treatment. Others found improvements in patients' subjective ratings as well as in objective measures (e.g., electronystagmography, cranio-corpography) in patients with vestibular vertigo not specified by location [15] [26] [27]. From a study in patients with central or peripheral vertiginous syndromes, Sokolova *et al.* [28] reported improvements in clinical symptoms and balance tests that were comparable between EGb 761® and betahistine. Notably, EGb 761® treatment alleviated dizziness and vertigo associated with dementia (Alzheimer's disease, vascular dementia) in randomised controlled trials [29]. These findings indicate that EGb 761® has an effect on basic mechanisms related to the perception of balance.

Due to the monocentric setting, our trial was planned and conducted with a small sample size. This can be considered a limitation of our study. Nevertheless, the sample size estimate indicated a reasonable statistical power, and conducting the study at the one clinical site which had developed the vestibular training ensured a relatively uniform implementation of the exercise program.

Another limitation is that patients in the placebo group were slightly younger and more often male compared to those in the EGb 761® group. However, a bias in favour of EGb 761® is unlikely considering both the facts that previous trials with EGb 761® did not suggest different treatment effects in men and women and that it is not very likely that older patients respond more readily to the vestibular training than the younger ones.

At baseline, the VAS rating of the global vertigo score in the placebo group was significantly lower than in the EGb 761® group. Although we cannot rule out that this baseline difference might have influenced the differential improvement of VAS scores during treatment, this appears rather improbable, since the quantitative vertigo score did not show a significant difference in baseline measures and improved significantly more during EGb 761® treatment than under placebo as well.

The safety profile of EGb 761® seen in the present study is in line with results from earlier trials and long-standing clinical use. The drug is safe and tolerable and no indication for new drug-associated risks has become apparent.

5. Conclusion

Ginkgo biloba extract EGb 761® alleviated vertigo/dizziness in patients with ischaemic lesions in the central vestibular system that underwent vestibular and balance training. It may therefore be considered a valid treatment option to enhance and accelerate vestibular compensation after ischaemic events in vertebro-basilar circulation and may improve the quality of life in these patients [2] [17]. Thus, it might enrich the still rather limited spectrum of drugs that show potential for the symptomatic treatment of vertigo or other disequilibrium problems in patients with lesions of central vestibular structures [30]. However, this effect needs to be confirmed in a larger randomised, controlled trial on a more homogeneous population of vertigo patients with ischaemic brainstem or cerebellar lesions.

Acknowledgements

We thank Gunnar P.H. Dietz for his valuable suggestions on the manuscript.

Conflicts of Interest

WH received speaker honoraria from Dr. Willmar Schwabe GmbH & Co. KG; RH is a full-time employee of Dr. Willmar Schwabe GmbH & Co. KG receiving a fixed salary; BA and CK declare no conflict of interest.

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