The Efficacy and Safety of Add-on Ginko TD (Ginkgo Biloba) Treatment for PTSD: Results of a 12-Week Double-Blind Placebo-Controlled Study

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Objective: Exposure to traumatic stressors lead to activation of arousal responses mediated by serotonergic and noradrenergic systems and it may cause a change in numerous neurotransmitters and neuroendocrine systems. There is ample experimental and clinical evidence to suggest that Ginkgo biloba extract is neuroprotective and has antioxidant properties and can restore stress-induced elevation in brain levels of catecholamines, 5-HT and plasma corticosterone to normal level.
Method: In a 12-week, double-blind, placebo-controlled study, the efficacy and safety of adding-on a fixed-dose (200mg) of Ginkgo TD to the previous treatment regime of adults with PTSD were examined. Subjects were forty male and female outpatients from a public-owned psychiatric clinic who met criteria for PTSD seven month after a 6.3 Richter earthquake in Bam city on December 26, 2003. The changes in five symptom domains including posttraumatic stress, anxiety and affective symptoms, general health and subjective stress after trauma were assessed at weeks 0, 12 and 16 to examine effectiveness of the added-on Ginkgo TD and stability of its effects.
Results: Ginkgo TD was associated with a significantly greater improvement than placebo in PTSD patients as measured by five symptom domain scales including: GHQ-28; Watson PTSD Scale; HAM-D; HAM-A and IES (p= 0.02, 0.01, 0.001, 0.01, 0.02 respectively) Four weeks after the discontinuation of intervention, no significant difference was determined between the two groups in the five outcome measures (p= 0.005, 0.01, 0.004, 0.005, 0.01 respectively). No significant difference was observed between the two groups in terms of side effects.
Conclusions: We found Ginkgo TD to be superior to placebo as an adding-on in the treatment of PTSD. Although we did not examine the comparative efficacy of Ginkgo TD on the three main elements of PTSD, beneficial effects both on specific PTSD symptomatology and general conditions including anxiety, depression, general health and perceived stress were indicated.

Keywords:
Controlled clinical trial, Ginkgo biloba,, Post traumatic stress disorder

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Disasters are events that collectively have been distinguished from other types pf potentially traumatic events by applying a definition of “mass collective stress” or “violent encounters with nature, technology or humankind”(1). They are regular occurrences with one estimate placing their frequency at an average of 1 per day somehow throughout the world (2) .

Disasters yield at specific and nonspecific psychological distress. Of the specific psychological problems reported among survivors of a disaster, PTSD is typically the most commonly identified condition (2). Kessler et al found that the risk of developing PTSD after a traumatic event is 8.1% for men and 20.4% for women. For young urban population, higher risks have been reported (3). Breslau and colleagues found an overall risk of 23.6% (4) and a risk of 13% for men and 30.2% for women(5). Studies show that a majority of people will experience at least one traumatic event in their lifetime (3) .

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PTSD is common; in a large representative sample in the US, a lifetime prevalence of PTSD was estimated 7.8% (women 10.4%, men 5.0%), using DSM-III-R criteria (4). Estimates for 12-month prevalence range between 1.3% (6) and 3.6%(7). Estimates for 1-month prevalence range between 1.5-1.8% using DSM-IV criteria and 3.4% using the less district ICD-10 criteria (8) .

Although PTSD shows substantial natural recovery in the initial month and years after traumatic event, with a steep decline in PTSD rates occurring in the first year (3-5), at least a third of the individuals who initially develop PTSD remain symptomatic for 3 years or

longer, and are at risk of secondary problems such as substance misuse (3).

Symptoms of PTSD cause considerable distress and can significantly interfere with social, educational and occupational functioning. Sufferers may also develop further secondary psychological disorders as complications of the PTSD. The most common complications are substance use disorders and depression as well as the risk of suicide and other anxiety disorders. Other possible complications of PTSD include somatisation, chronic pain and poor health (9). Sufferers from PTSD are at greater risk of medical problems such as circulatory and musculoskeletal disorders, and have a greater number of medical conditions compared to people without PTSD (10) .

Post-traumatic stress disorder presents an excessive health and economic burden on patients, families, healthcare workers, hospitals and society as a whole. Its effects extend far beyond the healthcare sector and affect the quality of life as well as the ability to function socially and occupationally. The economic and social impact of PTSD is felt not only by those who experience the disorder but also by families, co-workers, employers and the broader part of the society (11).

The psychobiology of traumatic memory and PTSD has been the subject of increasing research interest (12). The hypothalamic-pituitary-adrenal axis plays an important role in the acute response to stress. During the acute phase, glucocorticosteroid release has a number of beneficial effects for short-term survival (13-14); however, prolonged stress results in a sustained elevation of circulating glucocorticosteroids, which can produce structural and functional changes in areas of the brain involved in learning and memory processing (13). The HPA axis in PTSD is characterized by enhanced negative feedback (15). Due to chronic increases in corticotrophin-releasing factor (14), a down regulation of corticotrophin-releasing factor receptors at the anterior pituitary may happen. Overall, the pattern of finding suggests that HPA axis in PTSD is set to produce large responses to further stressors .

The hippocampus is a major target organ for glucocoticosteroids in the brain (16) and is particularly vulnerable to neurotoxicity resulting from high levels of glucocoticosteroids following stress (14). Studies using imaging techniques such as functional MRI (fMRI) and Positron Emission Tomography (PET) have provided data on changes in hippocampal volume in patients with PTSD compared to healthy controls (17-19) .

Exposures to traumatic stressors lead to activation of arousal responses mediated by the serotonergic and noradrenergic systems and it may cause a change in numerous other neurotransmitters and neuroendocrine systems (20-21). In animal studies, serotonergic mechanisms have been shown to be involved in conditioned fear responses which are mediated by the amygdale, and they involve corticotropine releasing factor (CRF) release in symptoms such as intrusions, depression, depersonalization and avoidance behaviour (22-23) .

The Ginkgo biloba tree has been a part of traditional Chinese medicine for several thousand of years (24). Ginkgo biloba extract is most widely used for the treatment of non-specific age-related deterioration of mental function (25), as well as for degenerative dementias of the Alzheimer and multi-infarct type (26-28) .

Ginkgo biloba extract (GBE) has numerous constituents. The antioxidant and free-radical scavenging properties of GBE are primarily attributable to the flavonoid fraction29-30. The trepenoid fraction comprising two classes of compounds, ginkgolides and bilobalides, contains antagonists of platelet-activating factor. Several studies have shown that the trepenoid components of GBE can reduce ischemia-induced neurotoxicity and inhibit glutamate-induced excitotoxicity (31-33).

In addition to general neuroprotective effects, GBE has properties that are directly relevant to psychobiology of PTSD. Several behavioural studies indicated that GBE restored stress-induced elevation in whole brain levels of catecholamines (NE, DA) (34-35), 5-HT (34, 36) and plasma corticosterone to near normal level (34, 37-39). Behavioural investigations show that GBE counters stress-induced desensitization of 5-HT1A receptors (40) and age-related decrease in the density of this serotonin receptor subtype (41). There is also a line of evidence which indicate a specific neuroprotective effect of GBE on neurons of hippocampal origin (33, 42) .

There is ample experimental and clinical evidence to suggest that GBE causes no adverse effects even on long-term usage (43). These observations indicate that Ginkgo biloba extract could be considered a potential therapeutic utility in the treatment of posttraumatic stress disorder. In the present study, we examined the effect of Ginkgo TD tablets which include GBE on each of three main elements of PTSD (re-experiencing, avoidance and hyperarousal), as well as its tolerability.

Materials and Methods

Study design

This study was a 12-week, double-blind, placebo-controlled experimentation in which a fixed-dose (200mg) of Ginkgo TD was added-on to the previous treatment regime of adults with PTSD. Subjects were randomly assigned to treatment and control groups. All the included patients had not experienced any changes in their medications during one mouth prior to beginning of the study. Ginkgo TD and placebo were administrated in two divided dose. Assessments were conducted at weeks 1, 12 and 16 to examine effectiveness of added-on Ginkgo TD and its effects profile. The available form of Ginkgo biloba in the Iranian market is a -40 mg tablet. The manufacturer company of Ginkgo biloba provided 100 mg tablets for

this study as well as the same exact shape and colour tablets without pharmacologically active components as placebo.

Patient selection

On December 26, 2003, a powerful earthquake struck the city of Bam in Iran. The earthquake, measuring 6.3 on the Richter scale, killed over 40,000 people, destroyed approximately 45,000 homes and leaved over 45,000 homeless people. The profound tragedy of thousands killed has caused emotional and psychological trauma for tens of thousands of people who have survived. The study was started at 7th month after the earthquake.

Subjects were male and female outpatients from a public-owned psychiatric clinic who met criteria for PTSD as measured by trained psychiatrist using PTSD-section of Structured Clinical Interview for DSM-IV-TR44 that has been standardized in Farsi by Sharifi et al (45). Ethically, we were not allowed to apply Ginko to treatment-resistant PTSD patients because its effectiveness was not indicated as an augmentation or adjunctive treatment for PTSD. Therefore, in this preliminary study, symptomatic PTSD patients were assigned in treatment and placebo groups randomly. Concurrent affective and anxiety disorders were allowed in study patients provided that PTSD was considered the principal diagnosis (i.e., the main focus of attention or need for treatment) and the onset of PTSD preceded that of concurrent disorders. Furthermore, patients could not have had another axis I disorder as a principal diagnosis within 12 months of screening, serious medical disorder, head trauma, neurological disorder and mental disorders due to general medical conditions.

All subjects provided informed written consent to participate in this study, which was approved by the Neuroscience Research Centre of Shaheed Beheshti Medical University. Demographic data, history of drug use, hospitalization for medical and psychiatric reasons, psychiatric and psychological treatments and injuries resulting from the earthquake were obtained using an author's made questionnaire.

Table 1. Socio-demographic and other characteristics of case and control subjects[†]

Variables	Case (n=20)	Controls (n=20)	P
Gender			ns
Male	15%(3)	15%(3)	
Male	85%(17)	80%(16)	
Age, Mean (SD)	38.15 (11.17)	38.5 (13.67)	ns
Education Status			ns
Illiterate	30%(6)	20%(4)	
Primary school	50%(10)	55%(11)	
Secondary school	5%(1)	10%(2)	
High school	15%(3)	15%(3)	
University	0%(0)	0%(0)	
Marital status			ns
Single	35%(7)	70%(14)	
Married	65%(13)	30%(6)	
Occupational status			ns
Employed	20%(4)	5%(1)	
Unemployed	5%(1)	5%(1)	ns
Retired	5%(1)	0%(0)	
Student	5%(1)	0%(0)	
Housekeeper	65%(13)	80% (16)	
Participation in war	10%(2)	5%(1)	ns
Existence of Life event			ns
In past 6 month, other than earthquake	40%(8)	45%(9)	
Current tobacco use	15%(3)	20%(4)	ns
Past substance abuse	0	0	ns

[†]The number in parentheses indicates raw number of the variable.

Outcome measures

Primary outcome measures were chosen to portray change in five symptom domains: posttraumatic stress: using a 17-item self-report questionnaire derived from the PTSD interview by Watson et al (46); depressive: using Farsi version of Hamilton Depression Rating Scale (HAM-D) (47-49); anxiety: using Farsi version of Hamilton Anxiety Rating Scale (HAM-A) (49); mental health: using Farsi version of General Health Questionnaire-28 (GHQ-28)) (50) and subjective stress after trauma: using Farsi version of the Impact of Event Scale (IES) (51). All of these questionnaires have reviously been used for the Iranian population. A previous study showed that GHQ-28 could be administered for measuring mental health following exposure to earthquake and is sensitive to changes in PTSD symptoms (52). Patients were visited by the clinic's psychiatrists every two weeks in the first month after commencing of trial; after that, they were visited at least monthly. During each visit adverse events were obtained by open-ended questions.

Data analysis

The data for intervention and placebo groups were compared using t-test and chi-square test. A paired t-test was used to assess the effects of Ginkgo TD on severity of PTSD, depression, anxiety, mental health and perceived stress, with $p<0.05$ deemed statistically significant.

Results

Forty patients, who continued to take their previous medications, were randomly assigned to take either Ginkgo TD or placebo in two divided doses for 12 weeks. Each group consisted of 20 male and female patients. All patients completed the study and there were no drop-outs. The zero rate of drop-out could be attributed to active follow-up of patients by a clinical psychologist, high tolerability of intervention and offering medication and services free of charge in the public-owned clinic .

The two groups were matched by age, gender, marital and occupation status and other conditions such as current smoking status, history of substance abuse,

Table 2. Drugs† used by case and control group

Drug	Mean (SD) Case (n=20)	Mean (SD) Control (n=20)	P
(Floxetine) SSRIs	25(11)	31(12.09)	ns
(Amitriptyline) TCAs	23.5(19.14)	12.25(23.3)	ns
(Lorazepam) Benzodiazepine	1.55(1.31)	1.95(1.46)	ns
(Sodium valproate) Antikindlings	80(198.94)	10(44.72)	ns
(Trifluoperazin) Antipsychotics	0.1(0.44)	0	ns
Propranolol	4(12.31)	10(17.77)	ns

† dose of a prototypical drug from relevant category was Indicated

history of participation in war and life event in past 6 month. Table 1 demonstrates the sociodemographic characteristics of the sample.

The medications used by subjects are shown in table 2. Drugs were divided to five main groups and equivalent dose of each group was used for evaluation. As shown in table 2, case and placebo groups did not show significant differences in the previously prescribed drugs. The patients did not have any changes in their medication regime during the previous month.

Table 3 demonstrates that at the beginning of the study, there was not a significant difference between the two groups in GHQ, Watson's PTSD, HAM-D, HAM-A and IES scores. Ginkgo TD was associated with a significantly greater improvement than placebo in PTSD patients as measured by five symptom domain scales including: GHQ-28, Watson PTSD Scale, HAM-D, HAM-A and IES (Table 3). Four weeks after the discontinuation of adding-on psychopharmacological intervention, no significant difference was determined between the two groups in the five outcome measures (Table 3).

Some patients reported side effects such as restlessness; headache and vertigo, but the side effects were mild and did not result in dropping-out of the trial. There was not any significant difference between the two groups in terms of side effects (Table 4).

Discussion

Since one third of the individuals who initially developed PTSD remained symptomatic for 3 years or longer, and were at risk of secondary problems such as substance misuse (3), there thus remains a clear need for interventions that can potentiate the effects of usual treatment regimes for PTSD. Pharmacological (including Ginkgo TD) and psychological therapies should be tested systematically and under controlled conditions for this purpose .

We found that Ginkgo TD is superior to placebo as an adding-on in the treatment of PTSD. Although we did not examine comparative efficacy of Ginkgo TD on three main elements of PTSD, beneficial effects both on specific PTSD symptomatology, and general conditions including anxiety, depression, general health and perceived stress were indicated.

Striking concordance of findings in all outcome measures supports the notion that Ginkgo TD could alleviate symptoms of PTSD as well as anxiety and depression in PTSD patients .

These findings were consistent with results of a study that reported Ginkgo biloba, extract EGb 761 attenuate anxiety, tension and aggression in generalized anxiety disorder (GAD) and adjustment disorder with anxious mood (53).

Further studies for determination of Ginkgo TD effectiveness on PTSD (and/or other anxiety disorders) as monotherapy, combination therapy or adjunctive therapy is suggested. According to improvement of PTSD symptoms in the case group compare with the control, it is hypothesized that Ginkgo TD (like Olanzapine) (54) may be effective as an adjunctive

Table 3. Assessments at baseline, week 12 and week 16 (four week after discontinuation of added-on Ginkgo TD) and percent of response rate as compared to baseline, mean (SD)

Assessment	Baseline [a]		P value	Post-treatment-1 [b]		Response rate-1 [b] (%)		P value (1 tailed)	Post-treatment-2 [c]		Response rate-2 [c] (%)		P value (1 tailed)
	Case	Placebo		Case	Placebo	Case	Placebo		Case	Placebo	Case	Placebo	
General Health Questionnaire	17.4 (6.77)	18.89 (3.74)	ns	4.5 (5.52)	11.6 (8.2)	12.9 (8.1)	7.47 (8.31)	0.02	2.94 (3.4)	11.8 (7.45)	14.42 (7.03)	7.15 (9.7)	0.005
Watson's PTSD Scale	82.1 (15.78)	85.5 (11.56)	ns	60.3 (11.77)	74.7 (17.66)	21.8 (12.58)	10.8 (16.84)	0.01	58.5 (10.46)	73.15 (17.34)	23.6 (12.65)	12.35 (16.5)	0.01
Hamilton Depression Scale	43.35 (8.37)	38.4 (12.83)	ns	28.9 (9.18)	34.1 (11.74)	14.45 (11.2)	4.3 (8.46)	0.001	27.45 (9.36)	32.85 (13.19)	15.9 (12.4)	5.55 (10.89)	0.004
Hamilton Anxiety Scale	40.1 (8.15)	39.5 (10.85)	ns	24.3 (8.7)	29.85 (11.83)	15.8 (7.93)	9.65 (8.17)	0.01	22.3 (8.44)	28 (10.38)	17.8 (8.4)	11.5 (7)	0.005
Impact of Event Scale	31.25 (7.12)	29.3 (9.07)	ns	22.85 (8.17)	25.8 (6.9)	8.4 (5.4)	3.5 (9.6)	0.02	31.25 (7.12)	29.3 (9.07)	10.8 (4.68)	5.45 (9.96)	0.001

[a] **Before treatment**
[b] **12 weeks adding-on treatment**
[c] Week 16. Four weeks after discontinuation of 12 week treatment with Ginkgo biloba.

Table 4. Comparison of adverse events(AE) between case and control group†

Side effect	Case (n=20)	Control (n=20)	P‡
Headache	15%(3)	15%(3)	ns
Vomiting	15%(3)	10%(2)	ns
Insomnia	15%(3)	5%(1)	ns
Restlessness (transient)	25%(5)	5%(1)	ns
Vertigo	5%(1)	5%(1)	ns
Anorexia	5%(1)	5%(1)	ns

† Number in parentheses indicates the raw number of adverse event (AE) in each group
‡ Fisher's exact test

pharmacological treatment in cases that are resistant to usual medication regimes. This hypothesis remains to be investigated in future studies .

During the course of the treatment period, 25 adverse events (AE) were reported, 25 for the case group and 9 for the control group. No serious adverse events occurred. The study indicated adding-on Ginkgo TD to previous medication regime tolerated well. These appear to be in line with previous clinical studies of Ginkgo that found good tolerability of Ginkgo (53, 55-56).

In contrast to benzodiazepines which are commonly used for alleviating anxiety symptoms, Ginkgo TD does not impair vigilance and cognitive functioning. Studies in healthy volunteers and in cognitively impaired subjects found that it has vigilance-enhancing and cognitively activating effects (55-57). It may ,therefore, be particularly suitable for the treatment of patients who wish to continue driving or who need to operate dangerous machines, as well as for patients undergoing cognition-based psychotherapy. Moreover, neither clinical studies nor extensive long-term use of marketed products have revealed a potential in EGb 761 to cause dependence .

Considering the lack of wide-scale availability of psychosocial treatment and modest efficacy of usual treatment regimes (58) and a good tolerability of Ginkgo TD and the absence of a risk for dependence, the results of this study recommends Ginkgo TD as an added treatment in case of inadequate response to previous medical regimes. In addition, it would allow individuals with PTSD to choose the approach they favour.

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