REVIEW ARTICLE

Impact of Vitamin B_{12} and folic acid supplementation in adults with stroke: A systematic review

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Abstract

Role of B vitamin supplementation in reducing the elevated homocysteine level in preventing ischemic stroke risk is conflicting. This systematic review was conducted to evaluate the impact of vitamin B_{12} and folic acid supplementation in adults with stroke. Literature search included Randomized Controlled Trials (RCT). The outcome of the study was assessing the homocysteine-lowering effect with supplementation of B vitamins to prevent the risk of ischemic stroke. Of 321 citations, 10 eligible RCTs were identified. The findings were inadequate to determine whether vitamin B_{12} or folic acid supplementation, alone or in combination, help in preventing the risk of ischemic stroke among people with history of stroke.

Keywords: Folic acid, Homocysteine, Stroke, Vitamin B_{12}

Introduction

Stroke, a leading health concern causing significant mortality and morbidity, is the second largest cause of death worldwide [1]. The estimated age-adjusted prevalence rate for stroke is between 84/100,000 and 262/100,000 in rural regions and between 334/100,000 and 424/100,000 in urban areas, according to the updated India stroke factsheet from 2012 [2]. It is also known that stroke can have psychosocial effect on patients in terms of poor quality of life. It is also hypothesized that increasing physical function may aid to improve quality of life for stroke patients, however it needs further evaluation. As many as 70% of strokes occur in low-income countries and the subsequent disease burden is greater than that of high-income countries [3]. Life expectancy in India has recently increased to over 60 years of age [4]. Stroke is India's fourth leading cause of death and fifth leading cause of disability [5]. There is need for more research on treatment and rehabilitation to improve the quality of life so that structured and focused interventions may be developed by policy makers [6].

Factors such as hypertension, dyslipidemia, smoking, diabetes mellitus, obesity, and positive family history are known to increase the risk of stroke. Consequently, raised plasma concentration of total homocysteine (tHcy) has also been proposed as a causal risk factor for cardiovascular disease [7]. Homocysteine is a sulfur-containing amino acid produced by the demethylation of the essential amino acid methionine, and the Methylene Tetra Hydro Folate Reductase (MTHFR) C677T polymorphism is a major determinant of blood homocysteine level [8]. This deleterious effect is also mediated by an increase in vascular

inflammation, endothelial dysfunction, and/or hyper coagulability. Poor dietary factors including low intake of folate, vitamin B_6, and B_{12} or genetic defects or renal failure also elevates homocysteine levels [8].

It has been found that plasma homocysteine levels have less or no predictive validity for cardiovascular disease. Instead, elevated homocysteine level may be an acute-phase reactant that is predominantly a marker of atherogenesis, or a consequence of other factors more closely linked to risks of cardiovascular disease [9]. Hence, elevated tHcy levels and the recurrence of vascular events and the associated patient morbidity and mortality still remains inconclusive. B vitamins such as folate, vitamin B_{12}, and vitamin B_6 that can be supplemented via nutrient intake play a key role in the metabolism of tHcy among patients with previous history of ischemic stroke [8, 10-12]. However, it remains uncertain whether lowering the tHcy slows down the progression of atherosclerosis and prevent atherothrombotic events. Furthermore, systematic reviews evaluating the Randomized Controlled Trials (RCT) on B vitamin supplementation and ischemic stroke are scarce [9]. This review thus aimed to investigate the association of Hcy and B vitamins (folate, vitamin B_{12}), and whether the supplementation of these B vitamins can reduce the risk of stroke in adults.

Methods

Search strategy and study selection

Relevant studies were identified through a systematic literature search of PubMed, EMBASE, and Google Scholar. Articles were identified from databases using MeSH terms with boolean operators such as: ((("Folic Acid"[Mesh]) AND "vitamin B_{12}"[Mesh]) AND "Stroke"[Mesh]"). Only articles written in English, RCTs, published studies, and studies with abstracts were included in the review. Other forms of studies such as case reports, laboratory studies, and uncontrolled trials were excluded. The studies of non-RCT clinical trials, animal experiments, comments, reviews, and real-world studies were also excluded from the study. The publication time of the retrieved articles were from the available date of inception until the latest issue. Reference lists from relevant articles selected were hand-searched to filter potentially eligible studies (Figure 1).

Type of studies, participants, and outcome

Only RCTs were included in the study. The research subjects were diagnosed with any type of stroke using internationally recognized diagnostic criteria. The treatment group took vitamin B and folic acid. The following comparisons were considered: placebo and any supplementation except intervention. Primary outcome was assessing the homocysteine-lowering effect with supplementation of vitamins to prevent the recurrence of ischemic stroke.

Quality assessment

Quality assessment tool based on Cochrane risk-of-bias criteria was used to evaluate the methodological quality of the included studies involving the data of RCTs [13]. This tool contains 7 items used to assess bias in each trial that included the randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, and each paper was described as low risk, high risk, or unclear risk.

Data extraction and collection

Two reviewers independently extracted relevant

data from the included studies using a pre-designed data collection form, and any discrepancies were resolved through discussion between the reviewers. The main contents of data collection form included basic information of studies (title, authors, year, and country); reporting quality; interventions; outcomes (changes of the above outcomes before and after treatment, adverse events).

Results

Description of eligible studies

The literature search retrieved 321 articles, of which 48 duplicates were removed. The remaining 273 records were screened manually for suitability based on title/abstract level, with 230 articles being excluded. A total of 43 full-text articles were then reviewed for eligibility based on the inclusion criteria. Ten RCTs meeting the study inclusion criteria were included for systemic review. The studies assessed herein were published between the year 2004 and 2010. The study population included both genders from various geographical locations. The reported sample size ranged from 13 to 1853 participants.

Assessment of study risk of bias

Summary of assessment of the ten studies based on Cochrane Collaboration's tool for assessing the risk of bias is summarized in Table 1. It was observed that there is a significant certainty regarding the quality of studies as important details about the study designs were described in all publications. In terms of selection bias, most of the studies provided a complete description of sequence generation process. The allocation posed a potential problem in only one study which might be due to the recruitment of small sample size. However, none of the studies described the bias in blinding. Selective reporting and other important sources of bias were absent in all the studies included. Table 2 summarizes the outcomes of included studies in this review article. Patients with history of ischemic stroke were treated either with single folic acid or methylcobalamin; combination of folic acid and methylcobalamin; and combination of folic acid and methylcobalamin with other vitamins, to lower total homocysteine levels to prevent recurrent stroke.

Effect of vitamin treatment on total homocysteine

All the studies reviewed in this study agreed that vitamin administration significantly reduced the tHcy irrespective of long- or short-term administration. However, the lowering of tHcy was not necessarily associated with biomarkers of inflammation or endothelial function. Further, the change in tHcy levels (participants vs controls) varied between studies reflecting on the vitamin dosage and measurement duration. Homocysteine is predicted to be an influencer of inflammation and possibly promotes vascular inflammation and endothelial dysfunction. However, we could not find conclusive evidence to indicate that lowering tHcy leads to reduced vascular inflammation. For example, Dusitanond *et al.* (2005) [10] observed that lowering tHcy was not associated with equivalent reduction of other inflammatory markers. Similar conclusions were also derived by Viswanathan *et al.* (2009) [14]. By additionally adding other antioxidants and vitamin B_{12}, Ullegaddi *et al.* (2006) [15] reported significantly higher improvement in inflammatory markers compared to supplementation with vitamin B

group only. These findings suggest that reduction in tHcy is independent of inflammatory pathways.

Total homocysteine levels and clinical outcome

All the studies have addressed that there is an increased baseline level of tHcy in patients presenting with stroke. Further, there is conclusive evidence to report that vitamin B group supplementation reduces the tHcy levels. However, their impact on secondary clinical outcomes or protection against strokes in future is not clear. Based on the findings reported in the quoted studies we gather that the reduced tHcy levels following supplementation with vitamins conferred a protection against stroke in short term. However, the long-term impact was not evident. For instance, Potter *et al.* (2009) [16] showed an improved outcome in arterial wall inflammation in patients with history of stroke for short term. The same team subsequently showed that a long-term reduction of tHcy did not have any significant impact. These findings collectively suggest that vitamin B_{12}, folate and vitamin B_6 intervention lowers the tHcy levels and reduce the risk of stroke albeit for a short term only.

Alternative or novel markers

Historically, it has been suggested that tHcy levels independently measure the risk of stroke. However, during the systematic analysis, we found that CF6 and Aβ40 in plasma were also found to be significantly associated with stroke. Interestingly, increased Aβ40 found in ischaemic stroke cases did not drop with reduction in tHcy.

Table 1: Cochrane collaboration's tool for assessing the risk of bias

Studies	Selection bias		Reporting bias	Performance bias	Detection bias	Attrition bias	Other bias
	Random sequence generation	Allocation concealment	Selective reporting	Blinding	Blinding	Incomplete source data	Other source bias
Sato [24]	Low	Low	Low	Low	Low	Unclear	Low
Dusitanond [10]	Unclear	Low	Low	Low	Unclear	Low	Low
Potter [29]	Low	Low	Unclear	Low	Low	Low	high
Viswanathan [14]	Low	Low	Low	Low	Low	Low	Low
Ho [25]	Unclear	High	Low	Low	Low	Unclear	Low
Hankey [11]	Low	Low	Low	Unclear	Low	Low	Low
Toole [12]	Low	Low	Low	low	Low	unclear	Low
Potter [16]	Low	Low	Unclear	low	Low	Low	Low
Osanai [30]	Low	unclear	Low	low	Low	unclear	Low
Ullegaddi [15]	Low	Low	Low	Unclear	Low	Low	Low

Table 2: Summary of articles included in the review

Study design	Patient cohort description (N)	Intervention groups and dosage (n)	Control group/ comparator (n)	Outcomes
Sato [24]	RCT, (N = 263)	Folic acid (5 mg), (n = 63/d); mecobalamin (1500 μ/d) (n = 64), folic acid (5 mg/d) + methylcobalamin (1500 μ/d)(n = 64)	Control (n = 72)	Vitamin B_{12} synergizes with folic acid in reducing plasma homocysteine in Japanese patients with ischemic stroke and the combined therapy may be particularly effective in the secondary prevention.
Dusitanond [10]	RCT, (N = 285)	Folic acid (2 mg/d) + methylcobalamin (0.5 mg/d) + pyridoxine (25 mg/d) (n = 143)	Placebo, (n = 142)	Lowering tHcy by 3.7 - micro mol/L with folic acid-based multivitamin therapy does not significantly reduce blood concentrations of the biomarkers of inflammation, endothelial dysfunction, or hypercoagulability. Therefore, elevated tHcy causing cardiovascular disease is by mechanisms other than the biomarkers measured.
Potter [29]	Randomised, double-blind, placebo-controlled intervention trial (N = 532)	Single daily tablet containing folic acid (2 mg) + pyridoxine (25 mg), + vitamin B12 (500 μg) (n = 268)	Placebo, (n = 264)	Although short-term treatment with B-vitamins is associated with increased flow-mediated dilation, long-term homocysteine-lowering did not significantly improve flow-mediated dilation or carotid intima-medial thickness in people with a history of stroke
Viswanathan [14]		High dose folic acid + vit B_{12} + pyrodoxine	low dose folic acid + vit B_{12} + pyrodoxine	Vitamin therapy demonstrates a strong correlation between serum tHcy and plasma Aβ40 concentrations in subjects with ischemic stroke. Treatment with high dose vitamins does not, however, influence plasma levels of Aβ, despite their effect on lowering tHcy. Although tHcy is associated with plasma Aβ40, they may be regulated by independent mechanisms

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Study design	Patient cohort description (N)	Intervention groups and dosage (n)	Control group/ comparator (n)	Outcomes
Ho [25]	RCT (N = 443)	Folic acid (2.5 mg) + vitamin B_{12} + (0.5 mg) + pyridoxine (25 mg) (n = 169)	Placebo (n = 167)	Vitamin therapy reduced mean tHcy levels by 3.8 micro mol/L in the Singaporean stroke population one year after treatment. MTHFR C677T but not A1298C is independently associated with tHcy levels at baseline, and neither impacts the tHcy-lowering effect of vitamins used in this study
Hankey [11]	Randomized , double-blind, placebo-controlled study (N = 285)	Folic acid (2.0 mg/d) + pyridoxine (25 mg/d) + methylcobalamin (0.5 mg/ d) (n = 143)	Placebo (n = 142)	The homocysteine- lowering effect of the active VITATOPS trial medication has not attenuated significantly in the past 5 years despite increasing voluntary fortification of foods with folic acid as reflected by a progressive rise in baseline folate status
Toole [12]	Double-blind randomized controlled trial (N = 3680)	High dose folic acid + vitamin B_{12} + (0.5 mg) + pyridoxine (n = 1827)	low dose folic acid + vitamin B_{12} + pyridoxine (n = 1853)	Mean reduction of tHcy was 2 µmol/L greater in the high-dose group than in the low-dose group, but there was no treatment effect on any end point. Overall, moderate reduction of tHcy after non disabling cerebral infarction had no effect on vascular outcomes during the 2 years of follow-up.
Potter [16]	Randomized Double-Blind, Placebo-Controlled Trial (N = 30)	Folic acid (2 mg) + pyridoxine (25 mg) + vitamin B_{12} (0.5 mg) (n = 15)	Placebo, (n = 13)	Long-term Hcy reduction with B vitamins does not affect arterial wall inflammation assessed by F-FDG PET.
Osanai [30]	RCT (N = 59)	Folic acid (5 mg/d) + vitamin B_{12} (1500 µg/day) for two months (n = 30)	Without vitamins (n = 29)	The plasma level of CF6 was increased in patients with stroke and was positively and weakly correlated with that of tHcy in a multiple regression model. Vitamin treatment decreased the plasma level of CF6 as well as tHcy after the treatment. CF6 thus appears to be a novel molecule for the pathogenesis and treatment of stroke.

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Study design	Patient cohort description (N)	Intervention groups and dosage (n)	Control group/ comparator (n)	Outcomes
Ullegaddi [15]		Folic acid+vitamin B_2+ pyridoxine + vitamin B_{12}	No supplementation or vitamin E&C	Antioxidants supplementation with or without B-group vitamins enhances antioxidant capacity, mitigates oxidative damage, and may have an anti-inflammatory effect immediately post infarct in stroke disease.

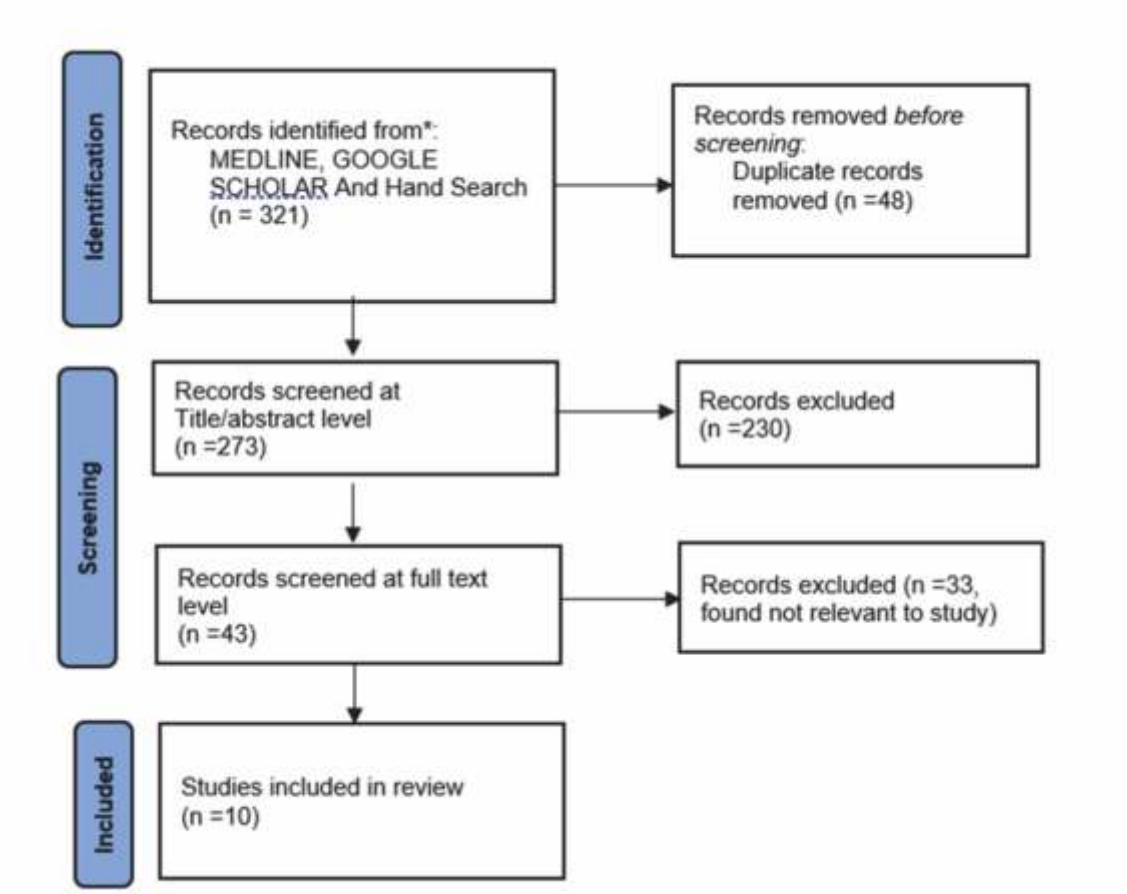

Figure 1: PRISMA flow diagram for the systematic review which included searches of databases

Discussion

Adequate nutrition reduces the risk of ischemic stroke. Elevated levels of homocysteine increase the risk for vascular diseases, such as stroke. Hence, a decline in homocysteine levels reduces the risk of stroke. Previous studies reporting reduced plasma homocysteine concentrations with B-vitamin supplements have produced conflicting results [17, 18]. In contrast, B-vitamin treatment did not reduce vascular mortality or morbidity, apart from ischemic stroke [19, 20]. Hence, the underlying reason for this mixed data warrants further exploration. Therefore, this review was performed to investigate this inconsistency by systematically assessing the association of tHcy, folate, vitamin B_{12} with incidence of stroke and whether B vitamin supplementation reduced the risk of recurrent stroke.

Based on the existing results in this systematic review, B_{12} supplementation along with folic acid or other B vitamins in lowering tHcy levels did not demonstrate a major benefit in terms of reducing stroke risk. The metabolism of tHcy has been explored by various researchers to identify possible preventive measures to decrease the serum level of tHcy [21]. Among them, folate, vitamin B_{12}, and vitamin B_6, the three critical vitamins involved in the metabolism of tHcy are promising candidates to lessen the incidence of stroke [21]. Homocysteine is metabolized either through remethylation or trans-sulfuration. Homocysteine remethylation to methionine synthesis is catalyzed by vitamin B_{12}-dependent enzyme methionine synthase [22].

Homocysteine trans-sulfuration pathway to form cystathionine, is catalyzed by the vitamin B_6-dependent enzyme cystathionine h-synthase [22, 23]. Therefore, there are close relations between plasma homocysteine and cobalamin, folic acid, or vitamin B_6. Evidence has shown that daily folic acid supplementation reduces the plasma tHcy in patients with coronary heart disease, and the combined administration of folic acid along and mecobalamin is highly effective in lowering tHcy levels [24]. Hence, reduction in plasma tHcy in stroke patients, may be beneficial for secondary prevention. Furthermore, tHcy has not attenuated significantly despite increase in fortification of foods with folic acid in the past 5 years [11]. All the studies in this systematic review did not provide exact data regarding the extent of lowering of tHcy with B vitamin supplementation. Two studies reported a mean reduction of 3.8 micro mol/L and 3.7 micro mol/L after intervention with folic acid, vitamin B_{12} and B_6 [15, 25]. Furthermore, reduction of tHcy was greater in the high-dose group than in the low-dose group [12]. Another similar study showed that tHcy decreased from 10.50 ± 3.93 to 6.56 ± 1.53 micromol/l after a 1-year intervention with folate and vitamin B_{12} and reduced the carotid intima-media thickness in patients at risk of cerebral ischemia [26].

The Vitamin Intervention for Stroke Prevention trial in the US conducted in 3680 participants with administration of 25 mg of folic acid, 25 mg pyridoxine (B_6), and 400 µg cyanocobalamin (B_{12}) showed no reduction in recurrent stroke or in secondary outcomes, including coronary heart disease and cardiovascular disease [12]. In a similar prospective population-based study, intake and plasma levels of vitamin B_{12} did not reduce the risk of either ischemic or hemorrhagic stroke [17]. In another meta-analysis study, folic acid supplementation did not find a major role in

reducing the risk of stroke (RR = 0.93; 95% CI, 0.85-1.03; $p = 0.16$). Whereas combination therapy of folic acid and vitamins B_6 and B_{12} (RR = 0.83; 95% CI, 0.71-0.97; $p = 0.02$) has shown a mild benefit [27]. In another study by Huo *et al*. (2012) [28] supplementation of folic acid reduced the risk of stroke by 8% (n = 55,764; RR: 0.92; 95% CI: 0.86-1.00, $p = 0.038$). While partial folic acid fortification (n = 43,426), reduced the risk of stroke by 11% (0.89; 0.82-0.97, $p = 0.010$).

Literature report that MTHFR polymorphisms limit the amount of folate available for methylation of homocysteine to form methionine and might thus affect associations between folate and risk of stroke [17]. Ho *et al*. [25] (2006) reported that MTHFR C677T is independently associated with tHcy levels at baseline, and did not impact the tHcy-lowering effect of vitamins. Similar prospective case-reference study has shown MTHFR polymorphisms were possible reason for 334 ischemic and 62 hemorrhagic stroke cases. However, the plasma folate concentrations did not differ by MTHFR genotype [17]. Previous studies reported B vitamin supplementation significantly lowered tHcy and improved the vascular outcomes of carotid intima-media thickness and flow-mediated dilation [26-28].

The present study has a few potential limitations that need consideration when contemplating the results. Although systematic reviews are of the gold standard and preferred technique for conducting clinical research reviews, they are not exclusive. Scoping reviews need to be carried out to uncover knowledge gaps. Number of studies included was lacking as compared to that of general topic. Literature search in only a few databases might have overlooked other publications that are in other archive. Furthermore, although we did not assign a time frame to the publications obtained; the earliest article on vitamin supplementation on stroke published was in the year 2002 in the included studies. Hence, there might be a chance to miss older articles that did not use the searched term in the titles or abstracts. Another limitation is that non-English papers and grey literature were excluded. Furthermore, publication bias might still exist as we only searched published RCTs; hence validity of the review depends on the quality of data retrieved. Nevertheless, the low risk of bias identified in the included studies is the main strength of this review. Further, the review study found the mild effects of vitamin B_{12}, folate and vitamin B6 intervention in lowering the tHcy levels to reduce the stroke risk. However, the study provided an insight into the role of CF6 in the pathogenesis and treatment of stroke. Hence, CF6 can be targeted in future studies in the pathogenesis and treatment of stroke.

Conclusion

Our systematic review concluded that high-dose vitamin B_{12} and folic acid supplementation is beneficial in reducing the elevated homocysteine levels to some extent in few patients with ischemic stroke risk. However, the evidence found is inadequate to determine whether vitamin B_6 or B_{12} or folic acid supplementation, alone or in combination help in preventing the risk of ischemic stroke among people with history of stroke. Hence, further research is warranted in these settings to generalize the present point of view.

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