

Effect of vitamin C supplementation on stroke recovery: A case-control study

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Background and purpose: Epidemiological studies have associated increased dietary intake of antioxidants (vitamin C, E, and β -carotene) in preventing and decreasing the extent of ischemic brain injury. The effect of vitamin C supplementation on functional recovery after stroke has not been studied.

Method: In this retrospective, case-control study of 23 patients with ischemic stroke taking vitamin C were identified and matched for age, sex, onset to admission, and admission total functional independence measure (TFIM) with 23 patients with ischemic stroke not taking Vitamin C supplementation. Vitamin C 1000 mg daily was prescribed on admission to our unit mainly to patients who were undernourished (defined as significant weight loss and/or 90% or less ideal body weight for age and sex) and those with pressure sores. The outcome measures were: change in the TFIM, FIM-Cognition (FIM-Cog), and FIM-Motor sub-scores, discharge disposition, and length of stay (LOS).

Results: The change in TFIM (20 ± 13 standard deviation [SD] vs. 26 ± 6 , $p = 0.20$), FIM-Cog (3 ± 3 SD vs. 4 ± 5 , $p = 0.41$), FIM-Motor (15 ± 11 SD vs. 20 ± 13 , $p = 0.21$) sub-scores were less in the vitamin C treated group, but these differences did not reach statistical significance. Similarly, no significant differences were found in LOS (21 ± 9 SD vs. 23 ± 9 , $p = 0.59$), and discharge disposition (home/institution) (9/10 vs. 13/9, $p = 0.60$) between the vitamin C and the control groups.

Conclusion: This study suggests vitamin C supplementation did not enhance functional recovery in undernourished ischemic stroke patients.

Keywords: vitamin C; ischemic stroke; functional recovery

Introduction

Epidemiological studies show that diets high in fruits and vegetables are associated with lower risk of cardiovascular disease, stroke, and cancer, and with increased longevity (Keli et al 1996; Joshupura et al 1999; Voko et al 2003; Fung et al 2004). Whether these protective effects are directly attributable to vitamins C or E or other food constituents is not known.

Cerebral ischemia results in vascular (endothelial) damage, and tissue injury (infarction). Tissue injury in the acute phase generates increase production of oxygen (O_2^-) radical, which in turn triggers necrosis in the acute phase, inflammatory responses in the subacute phase, and apoptosis in the chronic phase. This oxidative stress increases the permeability of the blood-brain barrier leading to edema, and tends to increase lesion volume and neurological impairment in stroke (Leinonen et al 2000).

Cherubini and colleagues (2000), Gariballa and colleagues (2002), and Sanchez-Moreno and colleagues (2004), in their respective studies have shown that the serum

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levels of most of the antioxidants (including vitamin C levels) are reduced immediately after an acute ischemic stroke compared with controls, presumably as a consequence of increased oxidative stress. Inflammatory markers (C-reactive protein, intercellular adhesion molecule-1, monocyte chemoattractant protein-1) are increased simultaneously. Intervention studies with vitamin C have shown no change in markers of oxidation or clinical benefit in chronic diseases particularly diabetes mellitus (Padayatty et al 2003). Schutte and colleagues (2004), studied the markers of vascular function in 31 young healthy male adults, who were administered a daily dosage of 1000 mg vitamin C, 800 mg vitamin E, and 10 mg folate. Beneficial decreases in diastolic blood pressure due to increase in arterial compliance after 12 weeks of vitamin supplementation was noted, while no statistically significant changes were observed with other cardiovascular variables such as systolic blood pressure, stroke volume, heart rate, cardiac output, vascular resistance, and arterial compliance.

In contrast to the epidemiological data on diet and stroke incidence and severity, and clinical intervention studies in the acute phase, no prior studies have addressed the effectiveness of vitamin C supplementation on functional recovery in patients undergoing rehabilitation after an ischemic stroke.

Method

Patients

Of the stroke patients admitted to our designated acute stroke rehabilitation unit over a 12-month period, 23 recovering ischemic stroke patients on vitamin C were matched to 23 recovering ischemic stroke patients not on vitamin C (control). The inclusion criteria were: first ischemic stroke event, and neuroimaging (computed tomography and/or magnetic resonance imaging) showing ischemic lesion corresponding to the clinical signs and symptoms. The exclusion criteria were: hemorrhagic stroke and recurrent ischemic stroke. Patients were matched for age; sex, onset-to-admission, and admission total functional independence measure (TFIM), which are factors known to influence functional motor recovery. The physician and the rehabilitation team members prospectively recorded the data in a computerized stroke database.

Intervention(s)

Ischemic stroke patients who were undernourished (defined as significant weight loss, and/or 90% or less ideal body weight for age and sex, and an admission serum albumin <3.4 gm/dl) and/or had the presence of pressure sores were

administered 1000 mg of vitamin C daily as part of its treatment protocol. Our institution's Institutional Review Board approval was not obtained because administration of vitamin C for undernourished patients and/or presence of pressure sore are considered a part of the standard of care at our institution.

Quantifiable outcome measures

The primary outcome measures were: change in the TFIM score, FIM-Cognition (FIM-Cog), and FIM-Motor sub-scores. The secondary outcome measures were: discharge disposition (home discharge vs. long-term care facility) and length of stay (LOS).

The Functional Independence Measure (FIM™) tool was used to measure the degree of disability as well as the progress the patients made through medical rehabilitation programs (Granger 1998). The FIM scale is a reliable (Stineman et al 1996) and a valid functional independence measure (Stineman and Maislin 2000). The FIM has become the standard functional assessment measures of self-care and mobility in rehabilitation medicine in the United States. The FIM is an 18-item ordinal scale scored from 1 to 7. A FIM item score of seven is categorized as "complete independence", while a score of one is "total assist". The possible total score ranges from 18 (maximum level of dependence) to 126 (highest level of independence). Stroke rehabilitation team members who are FIM-certified scored the admission and discharge total FIM score.

Data analysis

Groups were compared for demographic data and outcome measures. Continuous and nominal variables between the two groups were analyzed using Student's t-test and Chi-square analyses.

A $p < 0.05$ significance level was used for all analyses. The statistical analysis was carried out by commercial statistical software package Stat View (version 5.0.1 SAS Institute Inc. Cary, NC 27513; 1992 to 1998). Subgroup analysis was done by paired t-test in Excel.

Results

Table 1 presents the demographics of our study sample ($n = 46$) for the 2 groups based on presence or absence of vitamin C supplementation intake. The mean age ($\pm$ SD) of our patients was 76 ± 11 years (range 49–89 years). The male/female ratio was 26/20. The onset of stroke to admission to our unit was 11 ± 6 days. The admission TFIM score was 41 ± 18 . The average LOS in our study population was

Table 1 Baseline variables between the two patient groups based on the presence or absence of vitamin C intake (Mean $\pm$ SD)

Grouping variables	Total population (n = 46)	Vitamin C (n = 23)	Control (n = 23)	P-value
Age in years ^a	76 $\pm$ 11	76 $\pm$ 11	77 $\pm$ 11	0.84
Sex (M:F) ^a	26:20	13:10	13:10	1.0
Onset to admission in days ^a	11 $\pm$ 6	12 $\pm$ 7	11 $\pm$ 5	0.38
Stroke type: ^a				0.14
Ischemic				
Thrombotic	33 (71%)	19 (82%)	14 (61%)	
Embolic	10 (22%)	02 (9%)	08 (35%)	
Carotid occlusion with stroke	03 (7%)	02 (9%)	01 (4%)	
Risk factors ^a				
Hypertension	35 (76%)	16 (70%)	19 (83%)	0.29
Diabetes mellitus	17 (37%)	11 (48%)	06 (26%)	0.12
Hyperlipidemia	11 (24%)	06 (26%)	05 (22%)	0.72
Myocardial infarction	06 (13%)	01 (4%)	05 (22%)	0.06
Congestive cardiac failure	10 (22%)	02 (9%)	08 (35%)	0.47
Atrial fibrillation	09 (20%)	02 (9%)	07 (30%)	0.03
Osteoarthritis	08 (17%)	05 (22%)	03 (13%)	0.43
Prior level of independence				1.0
Independent	36 (78%)	18 (78%)	18 (78%)	
Independent with assistive device	08 (17%)	04 (17%)	04 (17%)	
Need physical assistance	02 (4%)	01 (4%)	01 (4%)	
Pressure sore ^a	16 (35%)	15 (65%)	01 (4%)	0.0001
Stroke severity:				
MMSE ^m	15 $\pm$ 11	16 $\pm$ 10	14 $\pm$ 12	0.70
Visual field: ^a				0.12
Normal	28 (61%)	12 (52%)	16 (70%)	
Left homonymous hemianopsia	04 (9%)	04 (17%)	00 (%)	
Right homonymous hemianopsia	07 (15%)	02 (9%)	05 (22%)	
Left visual neglect	04 (9%)	03 (13%)	01 (4%)	
Right visual neglect	03 (6%)	02 (9%)	01 (4%)	
UE MSS ^a (n = 16, n = 17) (range: 0–66)	29 $\pm$ 26	25 $\pm$ 27	33 $\pm$ 25	0.37
LE MSS ^a (range: 0–34)	14 $\pm$ 10	14 $\pm$ 11	14 $\pm$ 9	0.95
Limb placement ^a	6 $\pm$ 4	6 $\pm$ 4	6 $\pm$ 3	0.71
TFIM Score—Admission ^a	41 $\pm$ 18	41 $\pm$ 18	41 $\pm$ 18	0.99

Note: ^a Student's t-test; ^c Chi-square; ^m Mann–Whitney U test.

Abbreviations: LE, lower extremity; MMSE, Mini-Mental State Examination; MSS, Motor Status Score; SD, standard deviation; TFIM, total functional independence measure; UE, upper extremity.

19 $\pm$ 11 days. The vitamin C treated (n = 23) versus control (n = 23) group were well matched for: age (p = 0.84), M/F ratio (p = 1.0), onset-to-admission (p = 0.38), prior level of physical independence (p = 1.0), and admission TFIM (p = 0.99) (Table 1). There were 15 patients in the vitamin C group and only 1 patient in the control group (p = 0.0001) who had pressure sores.

The changes in TFIM (p = 0.20), FIM-Cog (p = 0.41), and FIM-Motor (p = 0.21) sub-scores were consistently less in the Vitamin C treated group compared with the controls but the differences did not reach statistical significance (Table 2). Similarly, no significant differences were found between the 2 groups for LOS (p = 0.59), and discharge disposition to home/or institution (p = 0.60). In view of the

lack of difference between the primary and secondary outcome measures between the 2 groups, a post-hoc analysis between the two groups for the primary outcome variables in the undernourished ischemic stroke patients (n = 8) versus their cognate controls (n = 8) was undertaken. The p value (0.07, but power <0.8) failed to reach pre-set levels for statistical significance (p < 0.05), but possibly suggested that individual displaying evidence of malnourishment had worse outcomes.

Discussion

In this retrospective, case-study, administration of vitamin C supplementation did not improve functional recovery in ischemic stroke patients. However, ischemic stroke patients

Table 2 Secondary outcome measures between the two patient groups based on presence or absence of vitamin C intake (Mean $\pm$ SD)

Grouping variables	Vitamin C (n = 23)	Control (n = 23)	p-value
Change in UDS TFIM Score ^a	20 $\pm$ 13	26 $\pm$ 6	0.20
Change in UDS Cog-FIM Score ^a	3 $\pm$ 3	4 $\pm$ 5	0.41
Change in UDS Motor-FIM Score ^a	15 $\pm$ 11	20 $\pm$ 13	0.21
Length of Stay (LOS in days) ^a	21 $\pm$ 9	23 $\pm$ 9	0.59
Healed pressure sore ^c	05 (33%)	00 (%)	0.48
Discharge disposition: ^c			0.60
Home	09 (39%)	13 (57%)	
Skilled nursing facility	10 (43%)	09 (39%)	
Acute hospital	03 (13%)	01 (4%)	

Note: ^a Student's t-test; ^c Chi-square.

Abbreviations: FIM, Functional Independence Measure; LOS, length of stay; UDS, unified data set.

who had pressure sores and were assigned to the vitamin C group had a much lesser change in the functional outcome scores compared with those assigned to the control group. We are unable to explain the results of these findings. Moreover, the finding of this study is in agreement with the result of other randomized control trials of vitamin C, E, and β -carotene supplementations in high-risk patients with occlusive arterial disease or diabetes. In these cases vitamin C supplementation had no effect on the incidence of any type of vascular disease (fatal and nonfatal myocardial infarction and stroke), nor did it produce any significant reductions in the 5-year mortality. This result was found despite significant increases in the plasma concentrations of these vitamins (HPSCG 2002).

Confounding factors which may have been responsible for this lack of difference between the 2 groups associated with our study include: 1) Inappropriate timing of the vitamin C administration. Most of the oxidative stress damage is said to occur in the initial 24–48 hours post-stroke (Keli et al 1996), when one would expect a better response to antioxidants administration. Our patients were admitted 11 $\pm$ 6 days post-stroke. 2) Inappropriate dosing of vitamin C. It is possible that the dose of vitamin C was not high enough to exert its desired effect (Hathcock et al 2005). 3) Vitamin C may be a weak antioxidant *in vivo*, and its antioxidant effect may be more effective when given together with other antioxidant vitamins, as typically occurs in the diet (Willett and Stampfer 2001), rather than when taken by itself alone. 4) The pro-oxidant effect of vitamin C could be a mitigating factor. *In vitro* studies have shown that vitamin C has the ability to act as a pro-oxidant by chemically catalyzing hydroxyl-radical formation in the presence of metal, such as iron (Guo et al 2002; Bailey et al 2006). Recent double-blind placebo controlled *in vivo* study of 22 patients undergoing

vascular surgery for elective abdominal aortic aneurysm, and by-pass repair found vitamin C prophylaxis to promote oxidative lipid damage during surgical ischemia-reperfusion (Podmore et al 1998). 5) Though our groups were (demographically and entry FIM) case-control, the vitamin C group was predominantly undernourished compared with the nonvitamin C group.

This study is limited by three considerations: i) the retrospective analysis of computerized stroke patient data, which inherently constrains the ability to randomize the patient population; ii) the small sample size, which limits the types of conclusions that can be tested statistically, eg, because of the potential for Type II statistical errors, and; iii) the subjects though matched for variables known to influence functional outcomes, they could not be matched for nutritional status or for pressure sores without changing the standard of care at our hospital. While this does place some constraints on the potential to draw conclusions from our data, it is possible that the observed trend toward worse outcomes for vitamin C-treated patients might be at least partially independent of the pre-entrance status of these individual. This is consistent with the recently published study showing a detrimental effect of vitamin C in surgical patients noted above (Podmore et al 1998). Finally, our data suggest consideration, such as matching for nutritional status should be considered for future prospective, randomized trials.

Conclusion

This study suggests that vitamin C supplementation in 1 gm dosage has no impact on motor recovery after ischemic stroke. Retrospective subgroup analysis of a small sub-population (n = 8) suggests a possible negative association between undernourished ischemic stroke patients, vitamin C

treatment, or the combination of these factors in a rehabilitation population.

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