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Reviews

Neuroprotective Properties of Vitamin C: A Scoping Review of Pre-Clinical and Clinical Studies

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Abstract

There is a need for novel neuroprotective therapies. We aimed to review the evidence for exogenous vitamin C as a neuroprotective agent. MEDLINE, Embase, and Cochrane library databases were searched from inception to May 2020. Pre-clinical and clinical reports evaluating vitamin C for acute neurological injury were included. Twenty-two pre-clinical and 11 clinical studies were eligible for inclusion. Pre-clinical studies included models of traumatic and hypoxic brain injury, subarachnoid and intracerebral hemorrhage, and ischemic stroke. The median [IQR] maximum daily dose of vitamin C in animal studies was 120 [50–500] mg/kg. Twenty-one animal studies reported improvements in biomarkers, functional outcome, or both. Clinical studies included single reports in neonatal hypoxic encephalopathy, traumatic brain injury, and subarachnoid hemorrhage and eight studies in ischemic stroke. The median maximum daily dose of vitamin C was 750 [500–1000] mg, or $\sim$10 mg/kg for an average-size adult male. Apart from one case series of intracisternal vitamin C administration in subarachnoid hemorrhage, clinical studies reported no patient-centered benefit. Although pre-clinical trials suggest that exogenous vitamin C improves biomarkers of neuroprotection, functional outcome, and mortality, these results have not translated to humans. However, clinical trials used approximately one tenth of the vitamin C dose of animal studies.

Keywords: ascorbic acid; neuroprotection; stroke; subarachnoid hemorrhage; traumatic brain injury; vitamin C

Introduction

Vitamin C, or ascorbic acid, is an essential micronutrient with a normal plasma concentration of 30–80 μmol/L.[1] Approximately 90% of vitamin C is present in the plasma as ascorbic acid and 10% as dehydroascorbic acid (DHA), the reduced form of vitamin C.[2] Vitamin C is a necessary cofactor in >60 enzyme reactions that control a broad range of vital biochemical reactions.[1] Importantly, vitamin C is the primary circulatory antioxidant depleted during oxidative stress and is the only antioxidant capable of preventing lipoprotein peroxidation.[3] Brain tissue is highly susceptible to oxidative lipid damage because of its large oxygen demand and high content of polyunsaturated fatty acid.[1] In health, vitamin C concentrations are 80 times greater in brain cells and 4 times greater in cerebrospinal fluid compared to plasma, driven by active transport.[4] This active concentration of vitamin C in the central nervous system is thought to be an evolutionary adaptation to protect against neuronal oxidative stress.[5]

Humans do not synthesize vitamin C, and, in health, maintenance of total body stores is dependent on dietary intake.[6] Rapid and substantial vitamin C deficiency is reported from blood samples obtained after a multitude of neurological insults, including traumatic brain injury, ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.[7–10] Further, the nadir in vitamin C concentration correlates with worse functional outcome.[7,8] This fall in antioxidant capacity parallels an overwhelming increase in free radicals and reactive oxygen species, which is thought to be central to the pathogenesis of these neurological insults.[11]

Systematic reviews have focused on the possible efficacy of supplementing vitamin C during excessive oxidative stress in sepsis, cancer, and post-cardiac arrest.[12–14] However, there has been no comprehensive review of the possible neuroprotective properties of vitamin C. Accordingly, we aimed to systematically review all currently available reports of the therapeutic properties of exogenous vitamin C after acute neurological insults.

Methods

Study design

We conducted a systematically structured scoping review using the guidelines from the Cochrane Collaboration and Centre for Reviews and Dissemination and reported the results according to

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the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline and its extension for scoping reviews.[15]

Inclusion and exclusion criteria

Eligible studies met the following criteria: 1) randomized controlled trials, non-randomized controlled trials (case control or controlled cohort), observational studies, and case series; 2) study population was divided into pre-clinical animal models and clinical studies of adult and pediatric populations; 3) exposure to traumatic brain injury, hypoxic brain injury, ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage; and 4) outcomes of neuroprotection were reported after the administration of exogenous vitamin C by any route. Studies that reported the effect of vitamin C in combination with other interventions were included. Studies reporting only *in vitro* data were excluded. We included only studies reported in English. No data or publication status restrictions were imposed.

Definition of neuroprotection

Neuroprotection in this systematic review was defined as any outcome measure that was proposed by the original authors to be favorable to brain function or neurological performance. This included studies reporting post-mortem pathology, neuroimaging, plasma and cerebrospinal fluid biomarkers, vasospasm, blood–brain barrier integrity, functional outcome scores (both animal and human), and mortality.

Data sources and search strategy

A librarian and two reviewers (L.K. and E.T.) searched MEDLINE (Ovid), EMBASE (Ovid), and Cochrane Library databases from their inception to May 2020. Searches included synonyms and combinations of the following terms: subarachnoid hemorrhage, stroke, traumatic brain injury, and vitamin C. Terms were truncated in order to capture variable terminology. The full search strategies are provided in Supplementary Materials Additional File S1. We applied no language restrictions during the searches. We also reviewed reference lists of retrieved articles to identify studies not captured in the primary search.

Study selection and data extraction

Two reviewers independently screened titles and abstracts of all identified studies. Relevant studies were independently evaluated in full text for eligibility. Disagreements were resolved by consensus or by consultation with a third reviewer (M.P.). Two reviewers independently extracted data from included studies using a standardized data collection form. Extracted information included study characteristics (author, publication year, design, and sample size), participant characteristics (species [for pre-clinical studies]), diagnosis of injury model, dose and route of vitamin C, other interventions in each arm, and metric of neuroprotection. The supplementary files of all included studies were also examined for the purposes of data extraction. A meta-analysis of randomized, placebo-controlled, clinical trials of vitamin C monotherapy was planned if including at least three studies.

Bias and quality assessment

The methodological quality of the pre-clinical studies was assessed using the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) checklist.[16] Risk of bias in human randomized controlled trials was assessed using the Cochrane risk-of-bias tool.[17] Risk of bias in human non-randomized trials was assessed using the ''Risk Of Bias In Non-randomized Studies – of Interventions'' (ROBINS-I) tool.[18]

Results

Our search retrieved 1520 citations with 251 full-text articles assessed for eligibility. After full text extraction, 33 studies (22 pre-clinical and 11 clinical) met the eligibility criteria (Fig. 1). Characteristics of the included studies are summarized in Tables 1 and 2. In studies reporting multiple interventions, only the vitamin C (or vitamin C combination therapy) arm is presented.

Pre-clinical studies

In 21 of the 22 trials, vitamin C therapy improved secondary markers of brain injury, functional outcome, or both (Table 1). Animal studies included models of hypoxic brain injury,[19,20] intracranial hemorrhage,[21] ischemic stroke,[22–33] subarachnoid hemorrhage,[34–36] and traumatic brain injury.[37–40] All of the studies were sham intervention or placebo-controlled trials. Dosing regimens are outlined in Table 1. The median [interquartile range; IQR] daily dose in pre-clinical studies was 120 [50–500] mg/kg. Six studies administered vitamin C pre-insult,[19,20,23,25,26,28] two at the time of the insult,[27,35] nine post-insult,[22,24,29–31,34,36,38,40] and five pre- and post-insult.[21,32,33,37,39] The summary of the risk of bias assessment is displayed in Figure 2.

Hypoxic brain injury

In neonatal rat models of global hypoxic brain injury, Miura and colleagues demonstrated that intracisternal vitamin C (up to 5 mg/kg) and intraperitoneal vitamin C (750 mg/kg) decreased neuronal cell death[19,20] (Table 1).

Intracranial hemorrhage.

In the only pre-clinical trial reporting no improvement with vitamin C, Peeling and colleagues demonstrated no effect of oral vitamin C (up to 120 mg/kg) and E supplementation on functional outcome, brain edema, or hematoma size in a murine model of intracranial hemorrhage[21] (Table 1).

Ischemic stroke.

All twelve studies utilizing animal models of ischemic stroke reported significant neuroprotective properties of vitamin C (or its analogues) when given as monotherapy,[23,25,27,29–31] as part of a therapeutic cocktail,[24] or both[22,26,28,32,33] (Table 1). The median [IQR] maximum daily dose was 150 [88–500] mg/kg.

Subarachnoid hemorrhage.

Three studies describe vitamin C attenuating vasospasm post–subarachnoid hemorrhage at an intracisternal dose of 1.2 mg/kg and intramuscular dose of 120 mg/kg/d[34–36] (Table 1).

Traumatic brain injury.

There have been four studies of vitamin C administration using rat models of traumatic brain injury, all of which demonstrated improvements in functional outcome (Table 1).[37–40] Interpretation of results from the study by Ishaq and colleagues is limited given that the route of vitamin C is not presented nor is any statistical analysis of survival[37] (Table 1). The mean (standard deviation) maximum daily dose of vitamin C in the remaining three studies was 333 (144) mg/kg.

Clinical studies

In 5 of 11 clinical studies,[41–45] vitamin C improved secondary markers of brain injury, including perilesional edema in traumatic brain injury, and markers of oxidative stress after ischemic stroke. However, these effects did not translate to an improvement in any patient-centered outcomes. Clinical studies included one randomized controlled trial in neonates after hypoxic ischemic

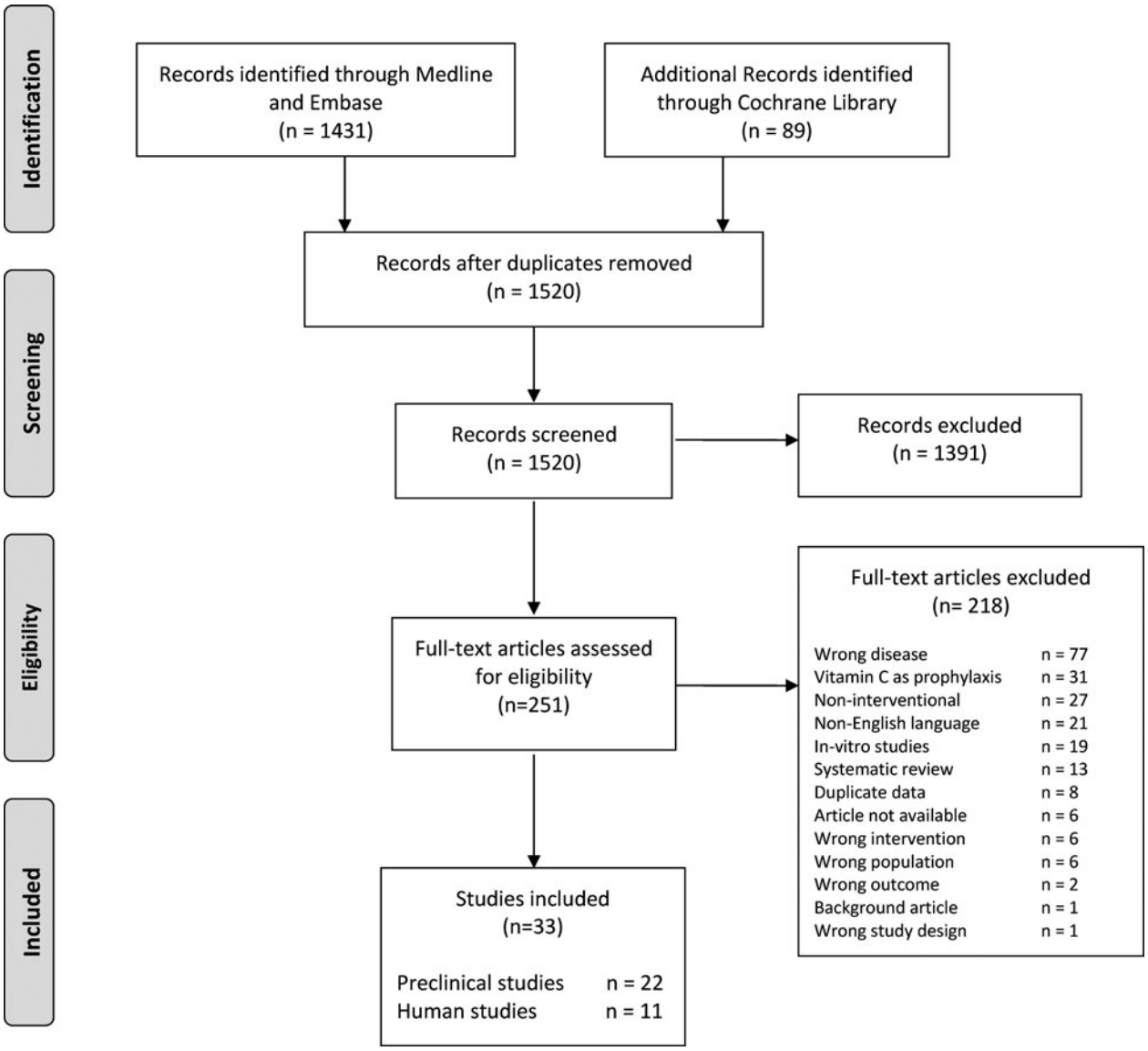


FIG. 1. PRISMA flow diagram.

encephalopathy,[46] one case series in adult patients after subarachnoid hemorrhage,[47] one randomized controlled trial in traumatic brain injury,[45] and eight studies in ischemic stroke; which included one observational study, one case-control study, and six randomized controlled trials.[41–44,48–51] Vitamin C as ascorbic acid was the only analogue studied, both as monotherapy[45,49–51] or as part of a combination treatment arm.[41–44,46–48,50] Oral doses ranged from 200[41] to 1000 mg/d,[50] and intravenous doses ranged from 500 mg/d[45,49] to 10 g/d.[45] One case series in patients with subarachnoid hemorrhage infused vitamin C, in combination with the thrombolytic urokinase, directly into the subarachnoid space by an intracisternal catheter at a dose of 120 mg/h (2.88 g/d) for 2–18 days.[52] The median [IQR] maximum daily dose of vitamin C in adult trials was 750 [500–1000] mg or ~10 mg/kg in an average-size adult male.

The clinical heterogeneity of these studies failed to meet the predefined threshold for meta-analysis. The summary of the risk of bias for the eight randomized controlled trials and two nonrandomized trials are displayed in Figures 3 and 4, respectively. The case series was not subjected to bias assessment.[47]

Neonatal hypoxic ischemic encephalopathy. In a prospective, double-blind, placebo-controlled trial of 60 neonates with hypoxic ischemic encephalopathy, intravenous vitamin C (100 mg/kg/d) in combination with ibuprofen had no effect on inflammatory markers, hospital mortality, or functional outcome.[46]

Ischemic stroke. No human trials have demonstrated any patient-centered benefit from oral or intravenous vitamin C in the management of ischemic stroke. Four randomized controlled trials utilizing disparate regimens of vitamin C have demonstrated an improvement in plasma markers of oxidative stress.[41–44] In three randomized controlled trials with low risk of bias, vitamin C failed to improve neurological or functional outcome both in the acute setting[41,51] and when administered for up to 1 year post-insult.[48] Only one trial administered vitamin C parenterally (500 mg/d).[49] The median maximum daily dose in trials of oral vitamin C was 500 (305–500) mg.

Table 1. Characteristics of Pre-Clinical Studies

					Vitamin C regimen			
	Design	*Design detail*	*Target condition*	*Sample size*	*Dose*	*Route*	*Duration*	*Results*
Miura et al., 2006[19]	Placebo controlled	Vit C (variable dose) vs. placebo	Hypoxic brain injury	50 rats	0.04, 0.2, 1, or 5 mg/kg	IC	Once pre-insult	↓ Neuronal cell death
Miura et al., 2009[20]	Placebo controlled	Vit C vs. placebo	Hypoxic brain injury	32 rats	750 mg/kg	IP	Once pre-insult	↓ Neuronal cell death
Peeling et al., 1998[21]	Placebo controlled	Vit C + Vit E vs. placebo	ICH	16 rats	40 mg/kg BD pre-ICH 60 mg/kg BD post-ICH	PO	2/52 pre-insult 1/52 post-insult	No difference in brain edema or functional outcome
Allahtavakoli et al., 2015[22]	Controlled study	No Tx vs. Vit C vs. r-tPA vs. Vit C + r-tPA	Ischemic stroke	60 rats	500 mg/kg	PO	Once post-insult	↓ Infarct size, improved functional outcome
Bemeur et al., 2005[23]	Placebo controlled	Sham + hyperglycemia + DHA vs.Ischemic + hyperglycemia + DHA vs. Ischemic + hyperglycemia	Ischemic stroke	43 rats	50 mg/kg	IP	Once pre-insult	↓ Brain edema during hyperglycemia
Corbett et al., 2015[24]	Placebo controlled	Vit C + simvastatin vs. fluoxetine vs. Vit C + simvastatin + fluoxetine	Ischemic stroke	57 rats	20 mg/kg/d	PO	1/52 post-insult	Improved functional outcome (Vit C + simvastatin + fluoxetine)
De Sales et al., 2019[25]	Placebo controlled	Vit C vs. placebo vs. sham	Ischemic stroke	12 rats	750 mg/kg	IP	Once pre-insult	Improved functional outcome
Ekici et al., 2009[26]	Controlled study	Sham vs. No Tx vs. DHA vs. DHA + Vit D	Ischemic stroke	35 rats	250 mg/kg	IV	Once pre-insult	↓ Lipid peroxidation (DHA + Vit D)
Henry et al., 1998[27]	Placebo controlled	Vit C vs. placebo	Ischemic stroke	15 monkeys	500 mg/kg	IV	Once peri-insult	↓ Infarct size
Sinha et al., 2001[28]	Placebo controlled	Sham vs. placebo vs. Vit C liposomes vs. Vit E liposomes vs. Vit C+E liposomes vs.empty liposomes	Ischemic stroke	1089 rats	8 mg/kg	IV	Once pre-insult	↓ Cerebral edema (Vit C and combination therapy)
Song et al., 2015[29]	Placebo controlled	DHA vs. placebo	Ischemic stroke	Not stated, rats	100 mg/kg	IP	Once post-insult	↓ BBB disruption, ↓ brain edema
Huang et al., 2001[30]	Placebo controlled	Vit C vs. DHA vs. placebo	Ischemic stroke	111 mice	DHA: 40 mg/kg, 250 mg/kg +500 mg/kg Vit C: 250 mg/kg, 500 mg/kg	IV	Once post-insult	DHA: ↓ infarct size and improved functional outcomes VC: no effect
Mack et al., 2006[31]	Placebo controlled	DHA vs. placebo	Ischemic stroke	57 mice	50 mg/kg, 100 mg/kg, 200 mg/kg	IV	Once post-insult	↓ Infarct size, ↓ lipid peroxidation

(*continued*)

Table 1. (Continued)

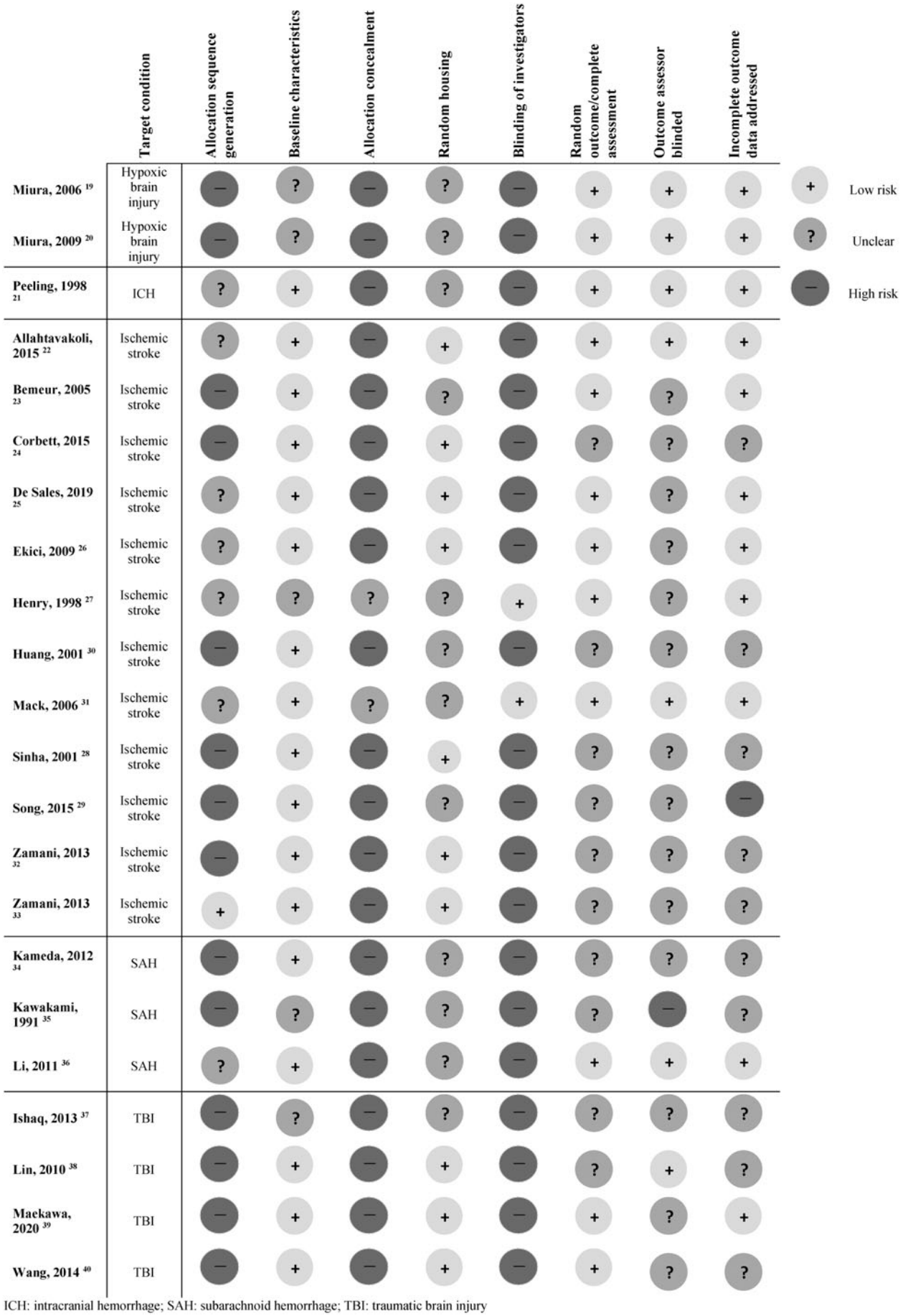
	Design	Design detail	Target condition	Sample size	Vitamin C regimen			Results
					Dose	Route	Duration	
Zamani et al., 2013[32]	Placebo controlled	Intact control vs. No Tx vs. placebo vs.Vit C vs. A1 agonist vs. A1 antagonist vs. Vit C + A1 agonist vs. Vit C + A1 antagonist	Ischemic stroke	56 mice	100 mg/kg	IP	1/52 pre-insult (Vit C only) 1/52 post-insult (other)	Improved functional outcome, ↓ neuronal cell death
Zamani et al., 2013[33]	Controlled study	No Tx vs. sham vs. Vit C vs. A1 agonist vs. Vit C + A1 agonist vs. Vit C + A1 antagonist Vit C post-insult vs. Vit C pre- + post-insult	Ischemic stroke	63 mice	100 mg/kg	IP	2/52 pre-insult 1/52 post-insult	Improved functional outcome, ↓ neuronal cell death
Kameda et al., 2012[34]	Controlled study	Intact control vs. No Tx vs. thrombin inhibitor vs. Vit C vs. Vit C + thrombin inhibitor	SAH	Not stated, rabbits	1.2 mg/kg	IC	Day 0 and day 2 post-insult	Improved vascular reactivity (Vit C + thrombin inhibitor)
Kawakami et al., 1991[35]	Controlled study	Oxy-Hb vs. Vit C–treated Oxy-Hb	SAH	Not stated, dogs	N/A	IC	Once	↓ Vasoconstriction no.
Li et al., 2011[36]	Controlled study	Intact control vs. No Tx vs. Vit C vs. Insulin vs. Vit C + insulin	SAH	65 rabbits	40 mg/kg TDS	IM	5 days post-insult	↓ Vasospasm (Vit C + insulin)
Ishaq et al., 2013[37]	Placebo controlled	Intact control vs. placebo vs. Vit C vs. Vit E vs. Vit C+E	TBI	72 rats	45 mg/kg, 60 mg/kg	Unclear	2/52 pre- and post-insult	↑ Survival (synergistic with Vit E)
Lin et al., 2010[38]	Placebo controlled	Intact control vs. placebo vs. Vit C vs. Vit E vs. NOS inhibitor vs. apocynin vs. allopurinol	TBI	72 rats	500 mg/kg daily	IP	Up to 3 months	Improved functional outcome, ↓ BBB disruption
Maekawa et al., 2020[39]	Controlled study	Stabilized Vit C pre- and post-insult vs. Stabilized Vit C post-insult vs. control	TBI	30 rats	250 mg/kg/d	PO	3 days pre- + 7 days post-insult 7 days post-insult	Improved functional outcome (prophylactic arm only)
Wang et al., 2014[40]	Placebo controlled	Sham vs. No Tx vs. Vit C vs. statin vs. Vit C + statin	TBI	30 rats	20 mg/kg/d	PO	3 days post-insult	Improved functional outcome

BBB, blood–brain barrier; DHA, dehydroascorbic acid; IC, intracisternal; ICH, intracranial hemorrhage; IM, intramuscular; IP, intraperitoneal; IV, intravenous; N/A, not applicable; NOS, nitric oxide synthase; PO, per oral; r-tPA, reverse tissue plasminogen activator; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; Tx, treatment; VC, vitamin C.

Table 2. Characteristics of Clinical Studies

	Design	Design details	Target condition	Sample size	Vitamin C regimen				Results
					Dose	Route	Frequency	Duration	
Aly et al., 2009[46]	Randomized, double-blind, placebo-controlled trial	Vit C + ibuprofen vs. placebo	Neonatal HIE	60	100 mg/kg/d	IV	Daily	3 days	No difference in neurological outcome
Garbagnati et al., 2009[48]	Randomized, double-blind, placebo-controlled trial	Antioxidant[a] vs. fatty acid vs. fatty acid, antioxidant[a] vs. placebo	Ischemic stroke	72	240 mg/d	PO	Daily	12 months	No effect in neurological or functional outcome
Lagowska-Lenard et al., 2010[49]	Controlled clinical trial	Vit C vs. no supplementation	Ischemic stroke	60	500 mg/d	IV	Daily	10 days	No effect on functional outcome at 3 months
Polidori et al., 2005[41]	Randomized, open-label clinical trial	Vit C + aspirin vs. aspirin only	Ischemic stroke	59	200 mg/d	PO	Daily	90 days	↓ Lipid peroxidation No difference in functional outcome
Rabadi et al., 2007[50]	Retrospective case-control study	Vit C vs. no supplementation	Ischemic stroke	46	1000 mg/d	PO	Daily	Not reported	No difference in functional outcome or disposition
Rabl et al., 1996[44]	Randomized, placebo-controlled study	Omnibionta[c] vs. placebo	Carotid artery surgery	57	1000 mg	IV	Once	Once	↓ Markers of oxidative stress and headache
Rumyantseva et al., 2017[51]	Randomized controlled trial	Vit C vs. Cytoflavin for 10/20 days	Ischemic stroke	373	1000 mg/d	IV	Daily	Not reported	Cytoflavin ↓ infarct size and improved functional outcome
Ullegaddi et al., 2005[42]	Randomized controlled trial	Vit C + Vit E vs. no supplementation	Ischemic stroke	48	500 mg/d	PO	Daily	14 days	↓ Markers of oxidative stress and inflammation
Ullegaddi et al., 2006[43]	Randomized controlled trial	Vit C + Vit E vs. Vit C + Vit E + Vit B group[b] vs. Vit B group[b] vs. no supplementation	Ischemic stroke	92	500 mg/d	PO	Daily	14 days	↓ Markers of oxidative stress and inflammation
Kodama et al., 2000[47]	Observational study	Vit C + urokinase	SAH	217	4 mg/mL at 30 mL/h	CI	Continuous	2–18 days	Vasospasm incidence 3%, mortality 3%
Razmkon et al., 2011[45]	Randomized, double-blind, placebo-controlled trial	Vit C (low dose) vs. Vit C (high dose) vs. Vit E vs. placebo	TBI	100	500 mg/d vs. 4–10 g/d	IV	Daily	7 days	High-dose Vit C ↓ perilesional edema

[a]Vit C (240 mg) + Vit E (290 mg) + polyphenols (150 mg) + β-carotene (19 mg) + n-3 polyunsaturated fatty acid (500 mg).
[b]Vit B9 (5 mg) + Vit B2 (5 mg) + Vit 6 (50 mg) + Vit B12 (0.4 mg).
[c]Multi-vitamin: Vit B groups, C, and E.
CI, cisternal irrigation; HIE, hypoxic ischemic encephalopathy; IV, intravenous; PO, per oral; SAH, subarachnoid haemorrhage; TBI, traumatic brain injury.



ICH: intracranial hemorrhage; SAH: subarachnoid hemorrhage; TBI: traumatic brain injury

FIG. 2. Risk of bias in pre-clinical studies. Risk of bias was assessed using the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) checklist.[16]

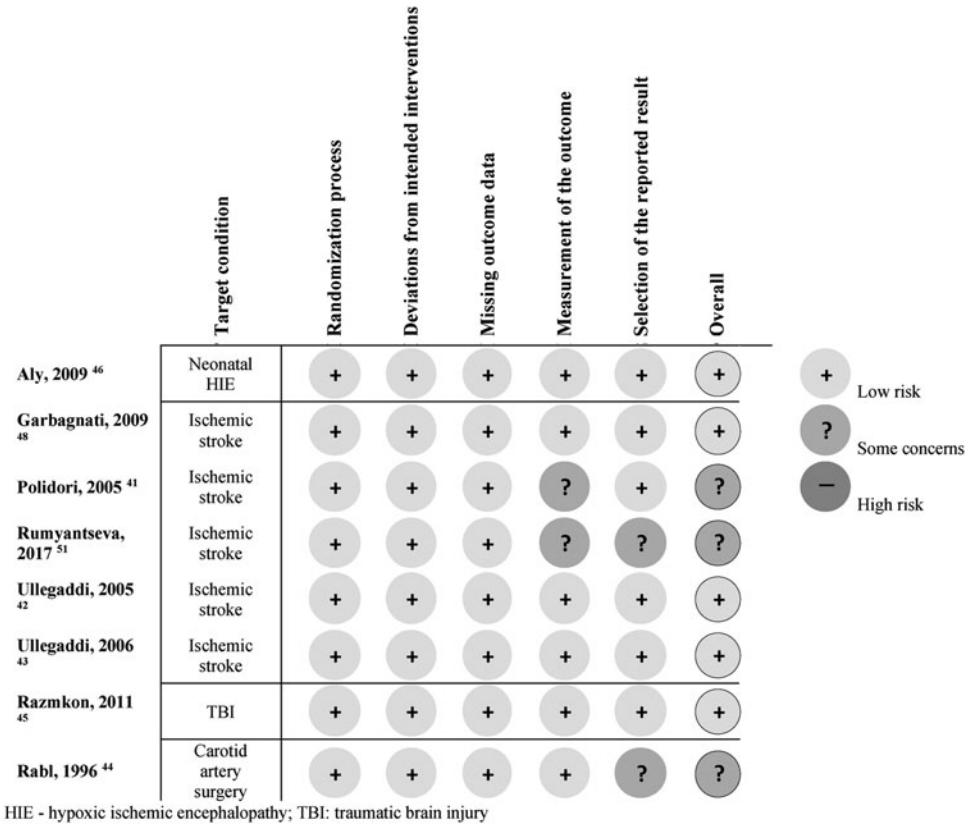


FIG. 3. Risk of bias in human randomized controlled trials. Risk of bias in human randomized controlled trials was assessed using the Cochrane risk-of-bias tool.[17]

Subarachnoid hemorrhage. The only human data on therapeutic vitamin C in subarachnoid hemorrhage comes from a single-center (Fukushima, Japan) case series of 217 patients with subarachnoid hemorrhage over a 14-year period from 1984 to 1998.[47] The authors describe their local practice of routine use of cisternal irrigation therapy to prevent vasospasm after clipping of ruptured aneurysms. The local technique involved an irrigation catheter inserted into the Sylvian fissure and a solution of Ringer's lactate with urokinase (120 IU/mL) and vitamin C (4 mg/mL) infused at 30 mL/h for 2–18 days (mean, 9.9).[47] The contemporaneous incidence of symptomatic vasospasm after subarachnoid hemorrhage in the late 1980s was 32.5%, of which 34% developed permanent neurological deficits and 30% died.[53] The authors reported a low rate of vasospasm (2.8%), with 1 patient (0.4%) developing a permanent neurological deficit and no patients dying from complications of vasospasm.[47]

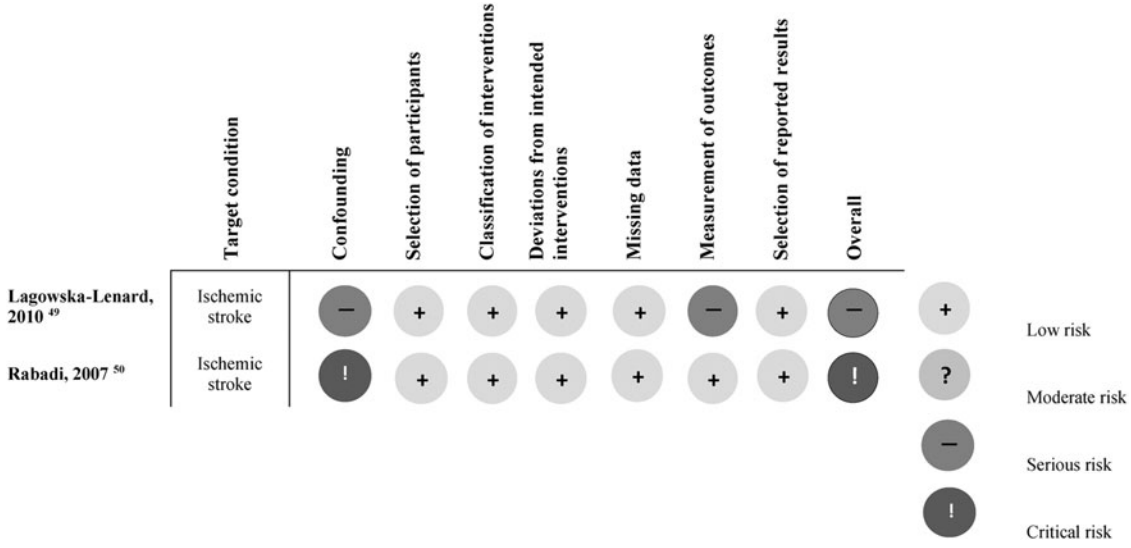


FIG. 4. Risk of bias in human non-randomized trials. Risk of bias in human non-randomized trials was assessed using the ''Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I)'' tool.[18]

Traumatic brain injury. In the only trial of vitamin C in traumatic brain injury, investigators randomized 100 patients with severe traumatic brain injury to a 7-day regimen of ''high-dose'' intravenous vitamin C, low-dose vitamin C, vitamin E, or placebo.[45] High-dose intravenous vitamin C (maximum daily dose, 10 g) decreased perilesional oedema on computed tomography (CT) imaging, but this did not translate to an improvement in functional outcome.[45]

Discussion

Key findings

We conducted a systematically structured scoping review to evaluate whether vitamin C therapy has neuroprotective benefit after acute neurological insults. Using an assessment of methodology, we evaluated both animal model (pre-clinical) and human studies of exogenous vitamin C in the setting of acute neurological injury. We identified 22 relevant pre-clinical studies and 11 clinical studies. We describe a pattern of promising observations using pre-clinical studies of high-dose vitamin C (median dose, 120 mg/kg) that have not translated to human trials utilizing substantially lesser doses (median dose, $\sim$10 mg/kg).

The neutral results from human studies may represent a true lack of efficacy of vitamin C. However, it may also represent inadequate dosing, particularly given the dosing regimens tested and the known pharmacokinetic profile of vitamin C in the critically ill. Ten of the 11 clinical studies evaluated a daily dose of vitamin C of $\leq$1000 mg/d, which would appear to be insufficient to achieve even physiological plasma concentrations during acute illness. In a single-center observational study of 44 critically ill patients, Carr and colleagues reported that 70% of patients had hypovitaminosis C despite receiving recommended vitamin C supplementation (mean daily intake, 125 ± 88 mg/d).[54] In a study of 57 elective post-operative patients in intensive care, up to 8 g of intravenous vitamin C over 12 h was required to normalize plasma vitamin C levels in the most severely deficient patients.[55] In a feasibility study of 24 patients, Fowler and collegaues reported that 50 mg/kg/24 h restored plasma levels to normal within 6 h of infusion commencement.[56]

Similarly, in a nested cohort study of 21 patients with septic shock, nearly half of the study cohort had either vitamin C deficiency or hypovitaminosis C at baseline, and 1.5 g of intravenous vitamin C every 6 h was required to maintain normal or supranormal vitamin C levels.[57] Finally, in a study of vitamin C pharmacokinetics in the critically ill, De Grooth and colleagues described that plasma vitamin C levels could be restored to just above the lower normal threshold with 2 g of intravenous vitamin C every 12 h (4 g/d) and that this regimen needs to be sustained for at least 48 h.[58] Based on these pharmacokinetic data, the 11 human studies that evaluated potential neuroprotective properties of vitamin C have used substantially lesser doses of vitamin C than are required to reach physiological or supraphysiological concentrations in other critically ill populations.

Five human trials in ischemic stroke utilized the oral route for vitamin C delivery.[41–43,48,50] It is now recognized that bolus oral supplementation is inadequate to achieve normal or supraphysiological plasma levels of vitamin C in a critically ill population.[59,60] In health, vitamin C absorption from the gut is determined by the saturable sodium vitamin C transport type 1 protein on the luminal surface of the enterocyte, such that bioavailability reaches a ceiling effect above an oral dose of $\sim$200 mg.[61] This limited uptake is further compromised in neurocritical illness where disturbances of intestinal function (ileus, malabsorption, constipation, and diarrhea) occur frequently.[62] Accordingly, trials using the oral route were unlikely to have achieved plasma concentrations to elicit any potential benefit (or harm).

The only study utilizing intravenous vitamin C at a dose that is known to achieve appropriate plasma concentrations in the critically ill was the randomized, blinded, placebo-controlled trial by Razmkon and colleagues whereby 100 patients with severe traumatic brain injury were randomized to receive low-dose vitamin C, high-dose vitamin C, vitamin E, or placebo.[45] Patients in the high-dose arm were administered 10,000 mg of vitamin C intravenously on days 1 and 4 and 4000 mg on days 5 through 7. The intervention decreased perilesional edema on CT, but there was no statistically significant effect on patient-centered outcomes.

Five of the pre-clinical trials of ischemic stroke administered DHA, the oxidized form of vitamin C.[23,26,29–31] Huang and colleagues demonstrated the superiority of DHA compared to equipotent doses of vitamin C in reducing infarct volume and improving functional outcome in a rat model of ischemic stroke.[30] The mechanism whereby vitamin C enters the brain is incompletely understood; however, DHA is thought to cross the blood barrier whereas the reduced form, ascorbic acid, does not.[63] This unique permeability property offers mechanistic plausibility that DHA may be superior to ascorbic acid in acute neurological injury.[30] Given these animal data, the potential for therapeutic use of DHA in human trials merits further investigation.

A final key difference between the pre-clinical and clinical studies is the timing of vitamin C delivery. In 13 of the pre-clinical trials, vitamin C was administered before, or at the time of, the neurological insult. Though not explicitly stated, by virtue of the animal model study design, trials delivering vitamin C post-insult would have had a shorter lag time to initiation of therapy than in clinical trials where resuscitation and consent hamper early therapy.[64] Oxidative stress commences within minutes of an inciting neurological insult and there is face validity that earlier initiation of antioxidant treatment may be preferable.[65]

The single-center case series after subarachnoid hemorrhage reported a low incidence of vasospasm and mortality when vitamin C was infused into the subarachnoid space in patients who had undergone clipping of ruptured intracranial aneurysms.[47] However, because of the substantive issues with internal validity of these data, it should not influence clinical practice. Interestingly, despite the magnitude of effect reported by the investigators, the use of vitamin C in this cohort has not been subjected to subsequent evaluation.

Implications

Our scoping review implies that there is a signal from pre-clinical trials that vitamin C may be neuroprotective in acute neurological injury and improve functional outcome. Moreover, it implies that clinical trials to date have used dosing strategies, which, based on current understanding of pharmacokinetics, would not achieve physiological plasma concentrations in health, let alone pharmacological concentrations. The recent publication of four large, randomized controlled trials of vitamin C in septic shock (ACTS, ATESS, CITRUS-ALI, and VITAMINS) supports the rationale for higher parenteral doses.[66–69] These trials compared intravenous vitamin C, at doses ranging from 6 g/d up to 200 mg/kg/d, to placebo for primary outcomes of time alive and free of vasopressor support[66] and the change in Sequential Organ Failure Assessment score at 72 or 96 h.[67–69] Recent experimental work in a sheep model of septic shock suggests that much greater doses of vitamin C (4 g/kg) has a more pronounced physiological effect.[70] Taken together, these observations imply that prospective clinical trials of high-dose, early vitamin C therapy after acute neurological insults are warranted.

Strengths and limitations

To our knowledge, this is the first systematic review of the neuroprotective properties of vitamin C therapy. Our review provides a comprehensive assessment of the efficacy of vitamin C as a neuroprotective therapy in both pre-clinical *in vivo* studies and clinical trials.

Our review has some limitations. We conducted a scoping review without formal meta-analysis. This was because we expected considerable heterogeneity in the dosing regimens and outcome measures across both pre-clinical and clinical trials. This concern was confirmed by our review. To increase the breadth of the review, we included case series and observational studies acknowledging that these yield a lower level of evidence and these studies had a higher risk of bias. We assessed both pre-clinical and clinical studies, and the lack of external validity in translating pre-clinical research to the bedside is a well-recognized limitation of animal models of neurological injury.[71,72] Rodents have vastly different brain size and structure, higher function deficits such as language and emotion cannot be assessed, brain injury models represent mild-moderate injury without prolonged periods of coma, and, as outlined above, the time window for therapeutic intervention is often hyperacute (or prophylactic).[65,71] Moreover, none of the pre-clinical studies had a low risk of bias. Finally, we only included studies in the English language and excluded 18 articles written in other languages. However, there is no evidence of a systematic bias when non-English articles are excluded.[73]

Conclusion

There is a dissociation in the efficacy of vitamin C as a neuroprotective therapy between pre-clinical and clinical studies. The neutral effect observed in human studies may be explained by a marked difference in dosing regimens, whereby the median dose in animal studies has been 10-fold greater than in human trials. Human studies using pre-clinical doses of parenteral vitamin C appear desirable.

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