VIEWPOINT

High-Dose Intravenous Ascorbic Acid: Ready for Prime Time in Traumatic Brain Injury?

Stefan W. Leichtle^{1*} , Anand K. Sarma², Micheal Strein³, Vishal Yajnik⁴, Dennis Rivet⁵, Adam Sima⁶ and Gretchen M. Brophy^{3,5}

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Abstract

Traumatic brain injury (TBI) is one of the leading public health problems in the USA and worldwide. It is the number one cause of death and disability in children and adults between ages 1–44. Despite efforts to prevent TBIs, the incidence continues to rise. Secondary brain injury occurs in the first hours and days after the initial impact and is the most effective target for intervention. Inflammatory processes and oxidative stress play an important role in the pathomechanism of TBI and are exacerbated by impaired endogenous defense mechanisms, including depletion of antioxidants. As a reducing agent, free radical scavenger, and co-factor in numerous biosynthetic reactions, ascorbic acid (AA, vitamin C) is an essential nutrient that rapidly becomes depleted in states of critical illness. The administration of high-dose intravenous (IV) AA has demonstrated benefits in numerous preclinical models in the areas of trauma, critical care, wound healing, and hematology. A safe and inexpensive treatment, high-dose IV AA administration gained recent attention in studies demonstrating an associated mortality reduction in septic shock patients. High-quality data on the effects of high-dose IV AA on TBI are lacking. Historic data in a small number of patients demonstrate acute and profound AA deficiency in patients with central nervous system pathology, particularly TBI, and a strong correlation between low AA concentrations and poor outcomes. While replenishing deficient AA stores in TBI patients should improve the brain's ability to tolerate oxidative stress, high-dose IV AA may prove an effective strategy to prevent or mitigate secondary brain injury due to its ability to impede lipid peroxidation, scavenge reactive oxygen species, suppress inflammatory mediators, stabilize the endothelium, and reduce brain edema. The existing preclinical data and limited clinical data suggest that high-dose IV AA may be effective in lowering oxidative stress and decreasing cerebral edema. Whether this translates into improved clinical outcomes will depend on identifying the ideal target patient population and possible treatment combinations, factors that need to be evaluated in future clinical studies. With its excellent safety profile and low cost, high-dose IV AA is ready to be evaluated in the early treatment of TBI patients to mitigate secondary brain injury and improve outcomes.

Keywords: Traumatic brain injury, Secondary brain injury, Oxidative stress, Antioxidant, Free radical scavenger, Vitamin C, Ascorbic acid

*Correspondence: stefan.leichtle@vcuhealth.org

¹ Division of Acute Care Surgical Services, Department of Surgery, Virginia Commonwealth University School of Medicine, Richmond, USA
Full list of author information is available at the end of the article

Traumatic Brain Injury

Traumatic brain injury (TBI) is one of the leading public health problems in the USA and worldwide, resulting in 2.8 million Emergency Department (ED) visits and 56,000 deaths per year [1]. Already the leading cause of death and disability in children and adults between ages 1–44, the incidence of TBI continues to rise [1]. In addition to the direct brain injury caused by traumatic impact, secondary brain injury due to local tissue ischemia, edema, metabolic changes, and damage from reactive oxygen species (ROS) results in further neurologic deterioration [2–10]. Current treatment strategies to mitigate secondary brain injury are limited to the optimization of a patient's general clinical condition, including maintenance of adequate cerebral perfusion pressures, management of intracranial hypertension, and prevention of hypotension, hypoxia, and seizures. No proven, effective treatment exists to provide neuroprotection in the acute phase or to promote neuroregeneration in the delayed therapeutic window after TBI [11, 12].

Ascorbic Acid (Vitamin C)

Ascorbic acid (AA, vitamin C) is an essential nutrient that functions as an important reducing agent, free radical scavenger, and co-factor in numerous biosynthetic reactions [13–15]. The recommended dietary allowance for AA for healthy individuals is 75 mg and 90 mg per day for women and men, respectively, though some guidelines recommend higher doses of up to 200 mg per day [16]. AA is readily absorbed from the intestinal tract when consumed orally, and higher doses above 1000 mg per day are excreted renally [17, 18]. While oral administration of AA is adequate to maintain homeostasis, intake of substantially higher doses is required to achieve supra-normal, ROS-scavenging AA concentrations, particularly in states of acute injury and critical illness [18, 19].

While not universally defined, normal AA concentrations range from 21 $\mu\text{mol/L}$ (0.37 mg/dL) to 100 $\mu\text{mol/L}$ (1.76 mg/dL) [17, 20, 21]. In a small cohort of healthy volunteers, mean peak plasma concentrations of AA reached 134.8 ± 20.6 $\mu\text{mol/L}$ after oral administration of 1250 mg AA. In contrast, IV administration of this dose resulted in peak plasma concentrations of 885 ± 201.2 $\mu\text{mol/L}$. Predicted maximum peak plasma concentrations were no more than 220 $\mu\text{mol/L}$ with oral administration of 3000 mg AA every 4 h, but reached 1760 $\mu\text{mol/L}$ for IV administration of this dose [22]. Based on these and other data, any effective AA treatment regimen for critically ill patients must be administered IV rather than orally. In 20 critically ill patients with multiple organ dysfunction, 2000 mg AA per day given IV restored normal AA plasma concentrations, but only a daily dose of 10,000 mg IV AA elevated plasma AA

concentrations to above 1000 $\mu\text{mol/L}$, the optimal concentration for free radical scavenging effects [20, 22–24]. In 24 critically ill patients with sepsis, Fowler et al. demonstrated that IV administration of 200 mg/kg per day (as compared to 50 mg/kg/d) in four bolus doses effectively and consistently elevated steady-state plasma concentrations to above 1000 $\mu\text{mol/L}$ within 24 h of the first dose [23]. Therefore, a treatment regimen of 50 mg/kg IV AA given every 6 h (for a total of 200 mg/kg per day) is most likely to result in consistently supra-normal, ROS-scavenging plasma AA concentrations in critically ill patients. In its oxidized form dehydroascorbic acid (DHA), AA is actively and preferentially transported into the central nervous system (CNS), crossing the blood–brain barrier (BBB) by facilitative transport. This mechanism results in substantially higher AA concentrations in the CNS than in plasma [25, 26]. Therefore, plasma concentrations of AA may not be reflective of CNS concentrations, but their correlation is unclear.

AA administration has few clinically relevant adverse effects. As a highly water-soluble compound, AA is readily excreted through kidneys and urine, limiting the potential for systemic toxicity. Therefore, direct renal toxicity and formation of oxalate stones is the most frequently noted concern with high-dose AA treatment [27]. Healthy individuals did not experience relevant adverse effects or laboratory abnormalities with daily doses of 7500 mg IV for 6 days [28], critically ill patients tolerated daily administration of 4500 mg IV for 28 days [29], and even higher doses were found to be safe in phase-1 cancer and sepsis trials [23, 30–32]. Occasionally reported adverse effects include gastrointestinal discomfort and headache, but overall, high-dose IV AA is regarded to have a good safety profile with a low risk of toxicity over a wide range of doses.

Ascorbic Acid Deficiency in Critical Illness, Trauma, and Burns

Critical illness is marked by depletion of AA stores [33–35]. The administration of antioxidants, including AA, in states of critical illness has re-emerged as a promising area for study due to significant success in small patient cohorts with septic shock [23, 36] and supported by basic science research in trauma, wound healing, and hematology [37–40]. Traumatic injuries, acute infection, and critical illness result in a pro-inflammatory state marked by dysregulation of the immune system, high levels of ROS, and capillary leak due to endothelial damage and increased permeability [41–43]. Antioxidants, most importantly AA, have the potential to influence these pathomechanisms.

In rodent models of bacterial- or endotoxin-induced sepsis, AA administration attenuated the inflammatory

response and decreased microvascular permeability, decreasing their risk for organ dysfunction and mitigating lung damage [44, 45]. Clinically, lung-protective effects of AA were described by Nathens et al. [29] in a cohort of severely injured trauma patients in the ICU setting. IV administration of 1000 mg AA three times per day, enterally supplemented by 1000 IU alpha-tocopherol, resulted in modest but significant reduction of pulmonary complications. Berger and colleagues studied a mix of antioxidant supplements (2700 mg AA per day, and selenium, zinc, and vitamin B1) in a randomized trial involving a heterogeneous surgical population of 200 patients, 30% of which were trauma patients. This antioxidant cocktail reduced C-reactive protein (CRP) concentrations, but had no measurable effect on organ dysfunction [46].

In a porcine model of severe polytrauma and hemorrhage, Reynolds et al. demonstrated that AA supplementation mitigated end-organ damage on histopathologic assessment, severity of lung injury, and decreased levels of the pro-inflammatory markers interleukin (IL)-1 β , IL-8, TNF α , plasminogen activator inhibitor-1, and tissue factor [37]. While similar effects have been corroborated in numerous prior small animal studies, there are no conclusive data from clinical trials in (poly)trauma patients. In animal and clinical studies of severe burn injuries, AA administration decreases capillary leak and significantly reduces resuscitation fluid requirements [47-49]. Doses evaluated ranged from 15 mg/kg/h in animal studies to 66 mg/kg/h in clinical trials. Similar to other fields of study, animal studies far outnumber clinical trials, and results in the clinical setting are less impressive than in animal models.

Ascorbic Acid in TBI

Oxidative stress is an important contributor in the pathogenesis of secondary brain injury [2, 4-10]. Cellular defense mechanisms against this damage are impaired

in acute illness due to the depletion of free radical scavengers such as AA [7, 8, 34, 50, 51]. Figure 1 shows one of the proposed mechanisms of neuroprotection of high-dose IV AA in TBI. In a small cohort of patients with TBI and hemorrhagic stroke, plasma concentrations of AA were found to be low and inversely correlated with injury severity. In this 2001 study, 13 patients with TBI had significantly lower plasma concentrations of AA (29 ± 8 $\mu\text{mol/L}$) than healthy controls (52 ± 8 $\mu\text{mol/L}$), and AA plasma concentrations inversely correlated with hemorrhage size [34]. In a 1984 study of AA concentrations in the cerebrospinal fluid (CSF) of 41 patients with neurologic disorders, five patients with TBI had lower AA concentrations than all other patients, including those with hydrocephalus and seizure disorders. AA concentrations in the CSF of patients with head and cervical trauma were 77 ± 56 $\mu\text{mol/L}$ compared to the reference cohort with an average of 203 ± 49 $\mu\text{mol/L}$ [7].

These few clinical studies on AA deficiency in patients with TBI are in contrast to more robust literature in animal models. In rodent models of ischemic stroke, DHA exhibited neuroprotective effects in both pre-treated animals and those that received DHA after the ischemic insult [52, 53]. In a rodent model of TBI, combined administration of moderate doses of AA and vitamin E resulted in improved cellular defense mechanism and confirmed depletion of important antioxidants after TBI [54]. In a rodent model of spinal cord injury, high-dose AA administration significantly reduced tissue necrosis and improved functional performance in rats [55].

In addition to its potent action as free radical scavenger, AA may stabilize the endothelium and promote integrity of the BBB. Following the mechanical impact of TBI, ischemia, reperfusion, and the imbalance between diminished protective factors such as free radical scavengers and NF-E2 related factor-2 [56, 57] and upregulated damaging factors such as

Fig. 1 Proposed reactive oxygen-scavenging-mechanism of high-dose IV ascorbic acid in TBI. TBI, traumatic brain injury; O_2^- , reactive oxygen species; DNA, deoxyribonucleic acid

metalloproteinase (MMP)-9 lead to disruption of transmembrane tight junction proteins in the basal lamina of the BBB [55, 56, 58–61]. ROS cause cell damage through lipid peroxidation of the fatty acids in cell and mitochondrial membranes [62, 63]. With its potent antioxidant properties, high-dose AA may mitigate this cascade [57, 61].

Unfortunately, clinical data on the therapeutic use of antioxidants to date have been inconclusive or disappointing [64]. Strategies that showed promise in animal models and preclinical testing such as mitochondrial protection, progesterone administration, anticonvulsants, and several antioxidant strategies like resveratrol, flavonoids, and omega-3 polyunsaturated fatty acids have not translated into successful clinical trials [65–68]. Compared to other states of critical illness, there is a paucity of data on the clinical use of AA in TBI. Table 1 provides an overview of studies on AA in patients with critical illness in the last two decades, fewer than 10% of which included patients with severe TBI. In the only randomized controlled trial on AA in TBI, high-dose (10,000 mg days 1 and 4; 4000 mg days 5 through 7) IV AA administration in 23 patients resulted in decreased perilesional edema on CT imaging ($p=0.01$), but no improvement in outcomes [69]. Due to the dosing regimen, it is unlikely that ROS-scavenging plasma levels were reached in this trial.

The most appropriate dose of AA in TBI is not known. However, higher doses have shown benefit in other critically ill patients without causing harm. Therefore, moderate to high doses of IV AA (10,000–20,000 mg per day) may be required to replenish deficient AA stores in patients with TBI experiencing oxidative stress several days after injury. Due to the limited data on prevalence and extent of AA deficiency in TBI, it is unclear if and to what degree this would translate into protection from secondary brain injury and improved clinical outcomes. Contemporary data on AA concentrations in plasma and CSF of patients with varying degrees of TBI may allow for the identification of a high-risk patient population that would benefit most from AA repletion and is currently being studied by our research group. Based on animal data [70, 71], the aging brain may be particularly susceptible to oxidative damage due to an inability to take up and mobilize AA. Clinically, lower CNS/plasma AA ratio in older adults compared to younger patients with TBI may indicate a high-risk patient group for further study.

Administration of high-dose IV AA (≥ 200 mg/kg per day) would harness the anti-inflammatory, ROS-scavenging, and cell membrane-stabilizing properties of AA. These mechanisms of action may be most beneficial in patients with significant cerebral edema and elevated intracranial pressure when administered within hours

Table 1 Pertinent clinical trials of IV ascorbic acid in the last two decades

References	Design	Type of injury	Patients	Ascorbic acid dosing ^a	Results
Marik et al. 2017 [36]	Retrospective before-after	Severe sepsis/septic shock	94 adults	6 g $\times$ 4 days ^b	Mortality reduction
Fowler et al. 2014 [23]	Randomized double-blind placebo-controlled	Severe sepsis (mostly respiratory)	24 adults	50 mg/kg/day or 200 mg/kg/day $\times$ 4 days	Reduced SOFA scores and inflammatory markers
Razmkon et al. 2011 [69]	Randomized double-blind placebo-controlled	TBI with GCS ≤ 8	100 adults (four groups, 23 patients received high-dose AA)	10 g in day 1, 10 g on day 4, 4 g daily for three more days ^b	High-dose AA decreased perilesional edema on head CT
Barbosa et al. 2009 [49]	Randomized double-blind placebo-controlled	Burns with TBSA 10–50%, at least partial thickness	32 children	Up to 2.7 g daily ^b (1.5 $\times$ upper daily intake based on age) for 5 days	Decreased lipid peroxidation and faster wound healing
Berger 2008 [18]	Randomized double-blind placebo-controlled	Complex cardiac surgery, major trauma, or SAH	200 adults (21 with SAH)	2.7 g for two days, 1.6 g for three days ^b	Decreased inflammatory response (CRP)
Nathens et al. 2002 [29]	Randomized prospective trial	Trauma patients, excluding isolated TBI and patients with GCS ≤ 6	595 patients	1 g TID for up to 28 days or length of ICU stay ^b	Decreased risk for MSOF, shorter ICU stay
Tanaka et al. 2000 [47]	Randomized prospective trial	Burns with TBSA $\geq 20\%$	37 adults	66 mg/kg/hr as continuous infusion for 24 h	Decreased IVF requirements and improved respiratory function

CRP C-reactive protein, CT computed tomography, GCS Glasgow Coma Scale, IVF intravenous fluid, MSOF multi-system organ failure, SAH subarachnoid hemorrhage, SOFA sequential organ failure assessment, TBI traumatic brain injury, TBSA total body surface area

^a Only AA dosing shown

^b AA was part of a treatment regimen including other medications

of TBI. Many animal studies that examined the administration of antioxidant cocktails and vitamins, including AA, did not employ such high doses. However, these higher doses are required in critically ill patients to reliably achieve protective antioxidant concentrations and beneficial clinical outcomes, as recently demonstrated in patients with septic shock [23, 36].

Prehospital administration of IV AA to patients with (suspected) TBI could be even more effective in mitigating damage to the blood–brain barrier and mitochondria of the brain parenchyma, which starts to occur within minutes of the traumatic event [62, 63]. However, prehospital administration of AA would add substantial complexity to a clinical trial; challenges would include the correct identification of TBI as the cause for altered mental status in (poly-)trauma patients, the possible lack of knowledge of comorbidities that could increase the risk profile of high-dose AA administration, and the logistical challenge of storing solutions of high-dose AA on ambulances. For the latter, promising data exist on the stability of solutions containing low- to moderate AA doses [72]. If results of a solid clinical (in-hospital) trial indicate therapeutic efficacy of AA in TBI, studies on the prehospital administration of AA for TBI in select patient populations should certainly be considered.

Limitations and Challenges

Primary TBI and ROS-mediated damage to brain parenchyma and the BBB occur at the time of injury and shortly thereafter [62, 63], making administration of neuroprotective agents challenging. Even in mature trauma systems, the first dose of AA may realistically not occur until hours after injury rather than minutes after the initial traumatic event as in preclinical models. Therefore, the effect of high-dose AA will likely be of particular benefit in those with areas of substantial ischemic penumbra, cerebral edema, and elevated intracranial pressure. Additional benefit would be expected from the general effect of high-dose AA on the state of TBI-related critical illness.

In rodent models of TBI, the oxidized form of AA, DHA, is more effective in crossing the BBB [52] and concentration-dependent downregulation of AA transporters across the BBB might impede the accumulation of supra-normal, ROS-scavenging concentrations of AA in the CNS [73]. DHA is not currently FDA-approved and is only used in experimental models. However, the AA plasma concentrations that can be achieved with high-dose IV administration will provide a steep plasma concentration gradient [74] ensuring uptake into the CNS. Lastly, both continuous and intermittent administration regimens of AA may need to be examined. In Fowler et al.'s phase I study on high-dose IV AA in patients with

sepsis, doses of 200 mg/kg per day, given in four doses every 6 h, rapidly led to plasma AA concentrations of $\geq 1000 \mu\text{mol/L}$ [23]. In de Grooth et al.'s study comparing low- vs. high-dose and intermittent vs. continuous administration of IV AA in septic patients, bolus dosing provided rapid plasma peak concentrations and continuous dosing was effective in achieving high steady-state concentrations [20]. For TBI patients in an ICU environment, both regimens of administration would be feasible.

Conclusion

Inflammatory processes, ROS, and endothelial dysfunction are well-established contributors to secondary brain injury. The promising results achieved with antioxidants and free radical scavengers in animal studies are in stark contrast to disappointing clinical results. Based on its mechanisms of action, animal data, and clinical results in critical illness, high-dose AA has exceptional potential to be an effective treatment strategy in the acute phase of TBI. It may be able to mitigate secondary brain injury due to its antioxidant, anti-inflammatory, and cell membrane-stabilizing properties, while the low adverse effect and cost profile of AA make it well suited for clinical studies in patients with TBI. A key challenge will be to identify the ideal TBI patient population that is most likely to benefit from this treatment strategy. Based on the existing data from related fields, patients with moderate to severe TBI, significant brain edema with elevated intracranial pressure, and the older adult population may represent ideal patient groups for high-dose IV AA in the acute setting. Clinical trials in such high-risk populations, rather than a more heterogeneous patient group with TBI, may be the key to translating the promising animal data into actual improved patient outcomes. In summary, the existing ample animal and limited clinical data suggest that for the right patient population and at the appropriate dose, high-dose IV AA can benefit patients with TBI.

Author details

¹ Division of Acute Care Surgical Services, Department of Surgery, Virginia Commonwealth University School of Medicine, Richmond, USA. ² Department of Neurology, Wake Forest School of Medicine, Winston-Salem, USA. ³ Department of Pharmacotherapy and Outcomes Sciences, Virginia Commonwealth University School of Pharmacy, Richmond, USA. ⁴ Division of Critical Care, Department of Anesthesiology, Virginia Commonwealth University School of Medicine, Richmond, USA. ⁵ Department of Neurosurgery, Virginia Commonwealth University School of Medicine, Richmond, USA. ⁶ Department of Biostatistics, Virginia Commonwealth University, Richmond, USA.

Author Contributions

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Conflict of interest

The authors declare that they have no conflict of interest.

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