(Jurnal Plastik Rekonstruksi, 2020; Vol 7, No 2, 65-76)

BURNS

REVIEW ARTICLE

VITAMIN C AS PREVENTION IN BURN SEPSIS: REVIEW OF LITERATURES

Lucretya Yeniwati Tanuwijaya[1], Yohanes Dona Christi Utama[2], & Ahmad Fawzy Mas'ud[3]

1. General practitioner of St.Elisabeth Hospital, Semarang, Central Java, Indonesia; Intern participant in Plastic Reconstructive and Aesthetic Department, Prof. Dr. Margono Soekardjo Hospital, Purwokerto, Central Java, Indonesia
2. General practitioner of St.Elisabeth Hospital, Semarang, Central Java, Indonesia
3. Department of Plastic, Reconstructive and Aesthetic Surgery of Prof. Dr. Margono Soekardjo Hospital, Purwokerto, Central Java, Indonesia

ABSTRACT

Background: Burns is a severe public health problem. Its poor treatment can lead to the worst complication called sepsis. Since sepsis decreases the immune system, the critical therapy management of burn sepsis ensures adequate end-organ perfusion. According to the Surviving Sepsis Campaign Bundle, immediate identification and management in the initial hours generate a better outcome. The inflammation of burn injury is known to increase ROS production, which causes cellular damage, sepsis, and MODS. This condition initiates the importance of ROS scavenger.
Methods: This literature reviewed from relevant works of literature which searched from major journal databases of WHO, Pubmed, Elsevier, JAMA, Springer, NEJM, which published from 2013 until 2018
Results: Vitamin C is a cheap but effective antioxidant, which acts as a ROS scavenger and reduces the fluid requirement in burn resuscitation for the prevention of burn sepsis
Conclusion: Vitamin C could be recommended as adjuvant therapy in the prevention of burn sepsis

***Keywords**: Sepsis, Burn, ROS scavenger, Vitamin C*

Latar Belakang: Luka bakar merupakan masalah kesehatan yang penting. Penanganan luka bakar yang kurang memadai akan memberikan komplikasi yang buruk yaitu sepsis. Sepsis menurunkan sistem imun sehingga manajemen penting penanganannya yaitu memastikan perfusi organ yang adekuat. Berdasarkan *Surviving Sepsis Campaign Bundle*, penegakan dan penatalaksanaan sepsis pada jam-jam pertama akan memberikan hasil yang lebih baik. Inflamasi yang terjadi pada luka bakar akan meningkatkan produksi ROS yang menyebabkan kerusakan jaringan, sepsis, dan MODS, sehingga *ROS scavenger* memiliki peran yang penting.
Metodologi: Artikel ini mengulas literatur dari WHO, Pubmed, Elsevier, JAMA, Springer, NEJM yang berhubungan dari tahun 2013 hingga tahun 2018.
Hasil: Vitamin C merupakan anti oksidan yang murah namun efektif, yang berperan sebagai ROS scavenger dan menurunkan kebutuhan cairan pada resusitasi luka bakar, yang berperan sebagai pencegahan sepsis pada luka bakar.
Kesimpulan: Vitamin C dapat direkomendasikan sebagai terapi adjuvant dalam mencegah sepsis pada luka bakar.

***Kata Kunci:** sepsis, luka bakar, ROS scavenger, vitamin C*

Conflicts of Interest Statement:
The author(s) listed in this manuscript declare the absence of any conflict of interest on the subject matter or materials discussed.

Received: 07-06-2020, Revised: 20-07-2020, Accepted: 29-09-2020

Copyright by Tanuwijaya, Utama, Mas'ud 2020. P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v7i2.285
Published by Lingkar Studi Bedah Plastik Foundation. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. This article can be viewed at www.jprjournal.com

INTRODUCTION

A burn is an injury to the skin or other organic tissue primarily caused by heat or radiation, radioactivity, electricity, friction, or contact with chemicals. Respiratory damage resulting from smoke inhalation is also considered as burns. Globally, burns cause severe morbidity and mortality events. An estimated 265.000 deaths occur each year from flame alone. This number does not include those from scalds, electrical burns, and other burns due to global data unavailability.[1]

Of those who died of thermal injury, 55% died within 72 hours, 36% died of burn shock defined as acute functional hypoperfusion, and 28% died of subsequent multiorgan failure or sepsis. [2] To avoid any burn-related morbidity and mortality, a proper resuscitation by ensuring adequate end-organ perfusion is critical. Proper fluid management in the immediate phase after significant burn injury is the key to optimizing outcomes.[3] According to the loss of barrier in burn cases, the primary cause of death in burn patients who survive initial burn shock resuscitation is from multiple organ dysfunction syndromes (MODS), directly responding to sepsis.[4] Sepsis and severe sepsis can result in critically-ill conditions, leading to death in non-coronary intensive care units in Western countries. As an example, more than 750.000 new cases of sepsis are diagnosed annually in the United States.[5].

MODS, which is generated by sepsis, is the leading cause of death in all patients admitted to an intensive care unit. Unfortunately, there has been only a moderate improvement in survival in patients suffering from sepsis over several decades. Because of these dire statistics, there has been an effort to improve the speed of diagnosis and shorten the time for treating sepsis, particularly in tropical countries, due to a higher risk of infection.[4] In Indonesia, reports from Dr. Soetomo Hospital Surabaya in 2012 recorded that sepsis mortality level caused by bacteria that produced extended-spectrum beta-lactamase (ESBL) was 16.7% with an average incidence of 47.27 cases per year. Of these cases, 27.08% were severe sepsis, 14.58% was a septic shock, and 53.33% was sepsis.[7] To reduce mortality, methods on preventing sepsis's occurrence need to be improved; however, this information is rarely available. [6]

Beyond the certain pathophysiology, the early treatment has been regulated based on Surviving Sepsis Campaign 2016 Recommendations and the updates in 2018.[8] Using the pathophysiology of burn sepsis, we reviewed the studied published between 2013 and 2018, which examined that free radicals have emerged as important mediators in sepsis at the cellular level. [2,3,8,9,21-24] As the circulating level of vitamin C (ascorbic acid) is low in patients with sepsis; ascorbic acid infusion appears promising as an adjunct in minimizing the effects of free radical injury in septic patients. Parenteral ascorbic acid administration raises the vitamin's plasma and tissue concentrations and may decrease morbidity in sepsis.[3,8,20-24]

METHODS

This literature was collected from significant journal databases such as WHO, Pubmed, Elsevier, JAMA, Springer, NEJM. We included original articles published between 2013 and August 2018. We only included freely accessible journals, using "burn sepsis and vitamin C" as keywords.

RESULTS

Matsuda et al. have shown that for extensive full skin thickness bums, a continuous intravenous (IV) infusion of 340 mg/kg/24 h of vitamin C beginning 0.5 h post bum reduces the resuscitation fluid volume requirements by 75%. The same authors also found that a 75% reduction in the resuscitation fluid volume requirements of deep dermal bums) is achieved with half the dose of vitamin C compared with that used in full skin thickness bums. These findings implied that the number of free radicals generated in deep dermal bums was less than that in full skin thickness burns. [20] A megadose (i.e., .500 mg/day) of the vitamin could be recommended in preventing endothelial dysfunction if oral supplement instead of IV infusion is preferred. [21]

Horton et al. suggested that major trauma produces abundant free radicals and impairs endogenous free radical scavenging mechanisms. Free radicals may directly impair of the functions of the cell membrane or intracellular organelle or may initiate an inflammatory signaling cascade, resulting in the production of numerous mediators of cell injury

Copyright by Tanuwijaya, Utama, & Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

Antioxidants, which either inhibit the free radical formation or to scavenge the burst of free radicals, or to interrupt some aspect of the resulting inflammatory cascade can reduce tissue injury and improve organ functions. [22]

Berger et al. and Kuhn and Bekhit found that vitamin C deficiency is commonly found in critically-ill patients. Short-term high pharmacological doses (up to 16 g ascorbic acid per day in sepsis and 110 g/day in burns) during the acute phase of overwhelming oxidative stress appear well tolerated. More importantly, it is beneficial to promote recovery. High doses of vitamin C are needed to restore deficiency, whereas short-term super-high doses can improve clinical outcomes. [23]

In their studies, Rizzo et al. found that vitamin C can potentially act as a powerful adjunct in burn resuscitation. However, a scarcity of studies demonstrating therapeutic efficacy on clinical outcomes, combined with an incompletely understood side-effect profile, often limits its implementation. [3]

Finally, after almost one century of *in-vitro* experiments and animal models, numerous plausible data are available for determining the protective effects of vitamin C against oxidative-stress-mediated cell damage and organ dysfunction in sepsis and septic shock, respectively.[8,24] However, Kuhn and Bekhit also suggested that vitamin C deficiency can be restored efficiently only with parenteral high-dose administration. [24]

DISCUSSION

Skin is the first barrier to infection that is lost when patients experience burn. As long as the wound remains open, it will continuously be exposed to inflammatory mediators. Such exposure to pathogens may persist for months in patients with extensive burns. Even months after the wound is closed, all burns >15–20% total body surface area (TBSA) will have a persistent "SIRS" **(Figure 1)**. Because of this hypermetabolic response, tachycardia, tachypnoea, leucocytosis likely remains in these patients as indicated by constant higher-than-normal body temperature (38°C). This symptom can be used to diagnose sepsis in the general population.[4]

It is commonly accepted that all patients with burns >20% TBSA have SIRS **(Figure 2)**. The definition for sepsis in burns is as follows: Sepsis: The presence of three or more of the following criteria: (1) Temperature >38 °C or <36.5 °C, (2) Progressive tachycardia >110 beats per minute, (3) Progressive tachypnoea >25 breaths per minute or minute ventilation >12 L/min, (4) Thrombocytopenia <100,000/mcl (does not apply until three days after burning), (5) Hyperglycaemia in the absence of pre-existing diabetes mellitus. (Untreated plasma glucose >200 mg/dl or intravenous insulin >7 units/hr IV, significant resistance to insulin [>25% increase in insulin requirements over 24 h]) (6) Inability to continue enteral feedings >24 h (Abdominal distension, enteral feeding intolerance [two times feeding rate, uncontrollable diarrhea [>2500 ml/day). infection is identified defined as (1) Culture positive infection or (2) Pathologic tissue source identified or (3) Clinical response to antimicrobials[4]

While hypovolemic shock from the initial injury can be immediately treated, sepsis rarely occurs within the first week after the injury. As long as the wound remains open, the burn patient is always at risk for developing sepsis. Therefore, sepsis may appear from weeks to even months after the injury. Under an immunosuppressed condition in which burn patients are experiencing, their body is frequently colonized or infected with multiple organisms. Also, burn patients usually require long-term invasive intubation), increasing the risks of infections, including those caused by viruses or fungi. Severely burned patients thus require constant monitoring, even for most subtle changes, which indicate poor perfusions (e.g., dropping platelet counts, increased fluid requirements, increased respiratory support, confusion, changes in the wound, and high fevers). [4] Poor perfusions ultimately degenerate organ function, which is a crucial indicator of sepsis. When multiple organs fail, a patient is said to have MODS. [26,27]

Copyright by Tanuwijaya, Utama, & Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

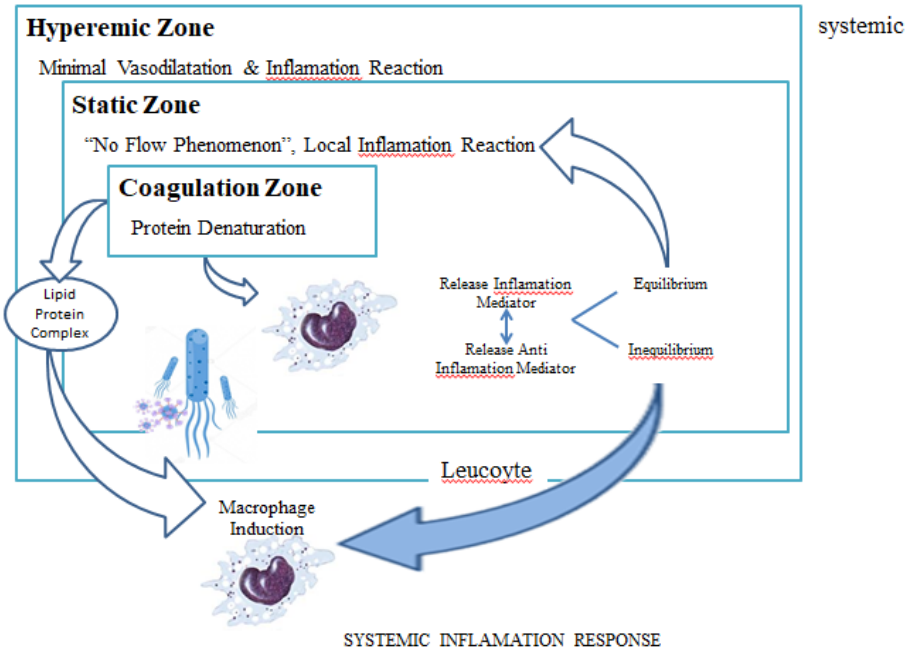

Figure 1. Systemic Inflammation Response. *Modified from (Moenadjat, 2003)* [25]

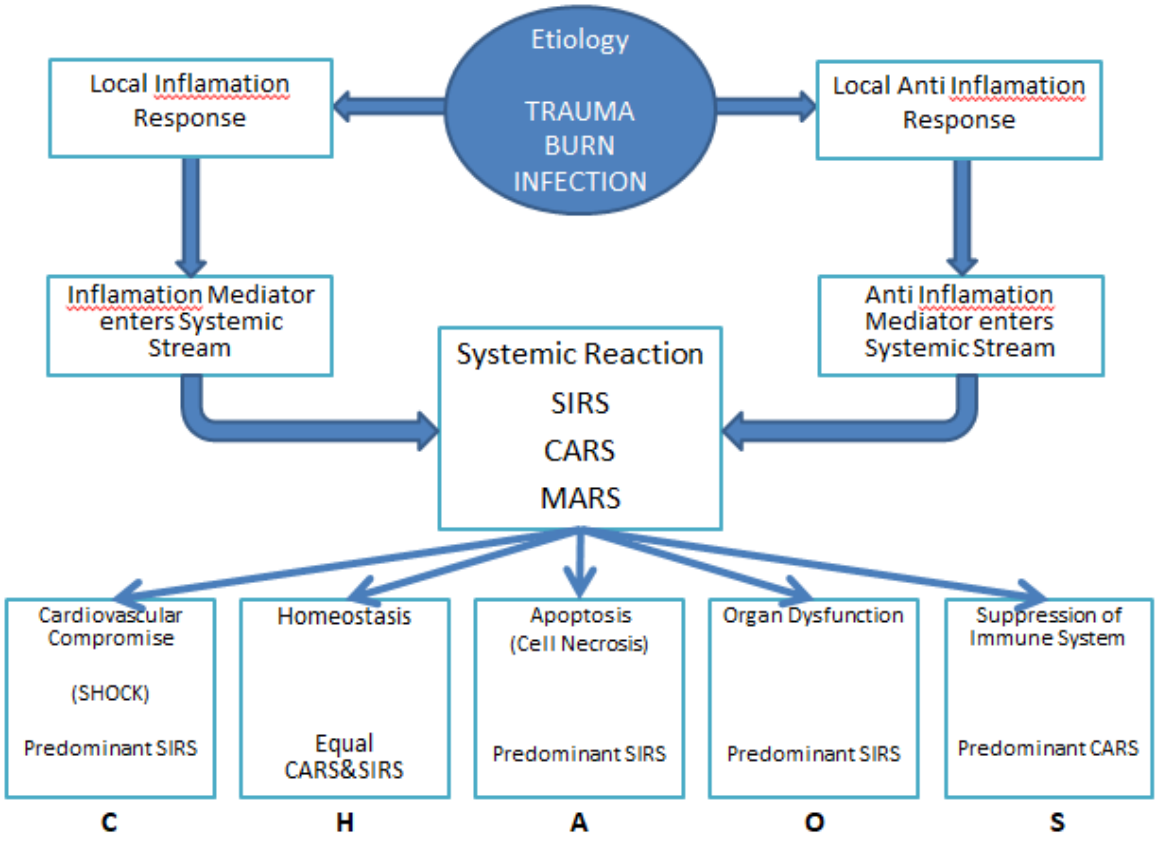

Figure 2. SIRS Cascade. *Modified from (Moenadjat, 2003)*

Copyright by Tanuwijaya, Utama, & Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

Therapy Management of Burn Sepsis

While early diagnosis of burn sepsis is critical to reducing mortality, there is no common signs or symptoms that can be used. Sepsis can appear multiple times in a patient problems, there is a great need to develop early signs and symptoms of sepsis and septic shock in burn patients as any delay in treatment will increase mortality.[4]

Baxter-Parkland developed the following formula to calculate the fluid volume for burn patients experiencing moderate and severe burn injury: 4 mL × patient's body weight × TBSA = Volume to be given in the first 24 hours. *50% of this volume is infused in the first 8 hours, starting from the time of injury, and the other 50% is infused during the last 16 hours of the first day.* [20,28]

According to the update by Surviving Sepsis Campaign Bundle, the initial hours after development of sepsis is critical in improving outcomes **(Table 1 and 2)**. The guidelines state that patients require early identification, urgent assessment, appropriate immediate management and treatments, which may include but not limited to initial fluid resuscitation while pursuing source control, obtaining other laboratory results, and attaining more precise can, however, damage host tissues such as the lung.

Antioxidant Therapy

Although the production of reactive oxygen species (ROS) has been known to exacerbate burn injuries at the cellular level, enzyme activities often create a complex barrier for preventing ROS production. Therapies that block xanthine oxidase's action, for example, can only improve survival in preclinical burn models when inhibitors are administered before burn injury. Therefore, removing ROS from circulation with a scavenger is considered a better strategy for preventing or minimizing increases in capillary permeability following burn injury. Adjunct therapies that scavenge ROS during burn resuscitation can minimize capillary leak, which, in turn, reduces the resuscitative requirements of extensive burns and minimizes edema. Because excess ROS is damaging to lipids, proteins, and nucleic acids, multiple endogenous systems exist to reduce ROS levels. However, these endogenous systems (e.g., superoxide dismutase, catalase, peroxiredoxin, and thioredoxin enzymes) are often compromised by excessive ROS levels produced following a burn injury. Superoxide dismutase, for example, is part of an antioxidant system shown to decrease lipid peroxidation, a process that propagates chain reaction production of ROS.

As the endogenous system is depressed, antioxidants as exogenous ROS scavengers are needed to reduce ROS levels in burn patients. Examples of antioxidants include vitamins (such as C and E), minerals (such as selenium), and glutathione. They are effective ROS scavengers that act as reducing agents and become oxidized to neutralize ROS. Several antioxidant therapies have been evaluated for their efficacy at reducing the capillary permeability after burn injury. Early administration of the histamine-blocker cimetidine reduced resuscitation requirements in thermally injured animals, and the further study suggested antioxidant, ROS-scavenging activity may be responsible for the beneficial effects of cimetidine. [3]

with a massive burn. Consequently, the patient is never free from risk until the burn is discharged. Unfortunately, many of the massively burned patients have died with healed wounds. Because of these unique measurements of hemodynamic status. [29] As a rule of thumb, patients need a detailed initial assessment, followed by an ongoing re-evaluation of their response to treatment. As early recognition and treatment of sepsis result in better outcome[4], the elements of the 2018 bundle, intended to be initiated within the first hour, are listed in Table 2. [29]

Immune Function

During sepsis, there are several ways for polymorphonuclear neutrophils to fight pathogens: (i) by phagocytosis, (ii) by exposure to ROS in phagolysosomes, (iii) by degranulation with release of antibacterial peptides and proteases, and (iv) by the production of cytokines and other inflammatory mediators. A novel death pathway for pathogen killing includes the formation of neutrophil extracellular traps (NETs). NETs collect proteases and antimicrobial proteins in the neighborhood of trapped pathogens. Excessive NET formation in sepsis

Copyright by Tanuwijaya, Utama, & Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score [30]

System	Score				
	0	1	2	3	4
Respiration					
PaO_2/FiO_2 mmHg(kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelet ($x10^3$ µLas)	≥150	<150	<100	<50	<20
Liver					
Bilirubin mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamin <5 or dobutamine (any dose)	Dopamin 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamin>15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System					
Glasgow Coma Scale score	15	13-14	10-12	6-9	<6
Renal					
Creatinine mg/dL(µmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (>440)
Urine output mL/d				<500	<200

Abbreviations: FIO_2, the fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen. Catecholamine doses are given as µg/kg/min for at least 1 hour.
Glasgow Coma Scale scores range from 3–15; a higher score indicates better neurological function.

Table 2. Bundle elements with the strength of recommendation and underpinning quality of evidence. [29]

Bundle Element	Grade of recommendation and level of evidence
Measure lactate level Re-measure if initial lactate is >2mmol/L	Weak recommendation. Low quality of evidence
Obtain blood cultures before administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L	Strong recommendation, low quality of evidence
Apply vasopressor if the patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mmHg	Strong recommendation, moderate quality of evidence

Copyright by Tanuwijaya, Utama, & Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

Vitamin C

Ascorbic acid, or vitamin C, is a naturally occurring, highly-water-soluble essential nutrient that acts as an effective antioxidant and ROS scavenger.[3,8,24] Vitamin C also protects circulating cells (erythrocytes and leukocytes) from ROS damage. The antioxidant effects of vitamin C have been studied as an adjunct in treating sepsis and ischemia/reperfusion injuries. A study by Rizzo et al. showed that vitamin C improves tissue oxygenation and mitigates subsequent organ dysfunction.[3] While the water-soluble property of vitamin C allows it to be removed by the kidney without the risk of toxic accumulation, and it also means that vitamin C cannot directly scavenge ROS within the cell membrane. Vitamin C instead removes ROS that present in the extracellular space.

Vitamin C can boost the immune response via several pathways. First, vitamin C improves chemotaxis, stimulates interferon production, enhances motility, neutrophil phagocytic capacity and oxidative killing, and supports lymphocyte proliferation. In contrast, vitamin C deficiency is associated with impaired cell-mediated immunity. For example, T cytotoxic responses, natural killer activity, and bacterial clearance are suppressed. In dilute fecal samples, vitamin C has been reported to inhibit bacteria replication and lower bacterial counts in blood during bacterial peritonitis in mice. The formation of hydrogen peroxide (H_2O_2) is thought to cause the bacteriostatic effects. Second, a recent study shows NET formation's attenuation in the serum of septic vitamin-C-sufficient mice and vitamin-C-deficient mice treated with the vitamin. In comparison with controls, several studies showed that supplementation of high-dose vitamin C in septic animals diminishes organ damage and improves survival, whereas, in other studies, mortality was higher in vitamin-C-deficient animals. [21,23,24]

Burn injuries trigger the increase of capillary permeability. Immediately after a burn, mast cells release histamine that increases xanthine oxidase activity, which is one of many pathways that contribute to the increased production of ROS observed after burn injury.[3, 23] ROS can cause damage to lipids, proteins, and DNA[24] and has been shown to contribute to the increased capillary leakage associated with burn injury.[3] Critically ill patients suffer from multiple organ failure (MOF) because of sepsis or ischemia/reperfusion. Part of the injury is mediated by reactive oxygen species (ROS).[24]Antioxidants as adjuvant therapy in critically ill patients have been described for many decades, mainly as immune nutrition to restore severe illness deficits.[32]

Vitamin C plasma concentrations depend on absorption and distribution volume, glomerular filtration, tubular reabsorption and urinary excretion, and intracellular uptake and consumption. Critically ill patients have low vitamin C plasma concentrations[8,21], possibly because of insufficient intake, chronic or acute 'consumption' in the setting of increased oxidative stress or increased loss.[21] Yet low plasma concentrations are associated with inflammation, severe organ failure, and even mortality. [8,21] Several studies report the development of severe vitamin C deficiency with scurvy-like symptoms during the systemic inflammatory response syndrome with capillary Leakage associated with interleukin-2 immunotherapy, whereas other vitamins were not deficient.[22] Because ROS acts as an oxidant and vitamin C acts as an antioxidant [3,8,21,24,32]; vitamin C appears to be useful in minimizing the effects of free radical injury in septic patients by scavenging ROS.[3,8] Intravenous ascorbic acid injection offers protection to several microvascular functions such as capillary blood flow, microvascular permeability, and arteriolar responsiveness to vasoconstrictors and vasodilators. In septic models, intravenous injection of vitamin C reverses the maldistribution of capillary blood flow. [8]

Vitamin C Mechanism of Action in Burn Injury

Apart from ROS scavenging, regeneration of vitamin E, and attenuation of lipid peroxidation, vitamin C decreases fluid requirements and wound edema in burn patients. Because a reduced volume of isotonic fluid is required for burn patients treated with vitamin C, the dilutional hypoproteinaemia causing decreased oncotic pressure and subsequent fluid shift into non-burned tissue is minimized, evidenced in preclinical studies by reduced water content in unburned skin. A reduced incidence of intraabdominal hypertension is associated with lower resuscitation volumes, which, in turn, prevent abdominal compartment syndrome.[3] By inhibiting collagen denaturation and enhancing hyaluronic acid removal, wound edema is further

Copyright by Tanuwijaya, Utama, & Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 │ DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

decreased by vitamin C infusion. Besides, vitamin C offers protection to burned tissue capillary endothelium by scavenging ROS from the extracellular space, compromised by thermal injury **(Figure 3 and 4).**

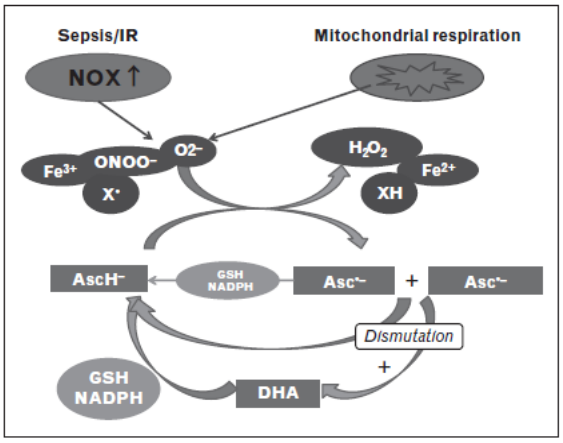

Figure 3. Oxidative metabolism of vitamin C. Sepsis and ischemia/reperfusion (IR) generate reactive oxygen species (ROS) by the activation of NADPH oxidase (NOX) and mitochondrial respiration. Ascorbate ($AscH^-$) scavenges free radicals from peroxynitrite, superoxide, or other damaging ROS or oxidized antioxidants (X^+), thereby generating the ascorbyl radical (Asc^-), which is far less damaging than X^-. The dismutation of two Asc^- molecules produces one molecule of ascorbate and one molecule of dehydroascorbate (DHA). DHA is rapidly reduced by glutathione or by NOX-dependent reductases.[24]

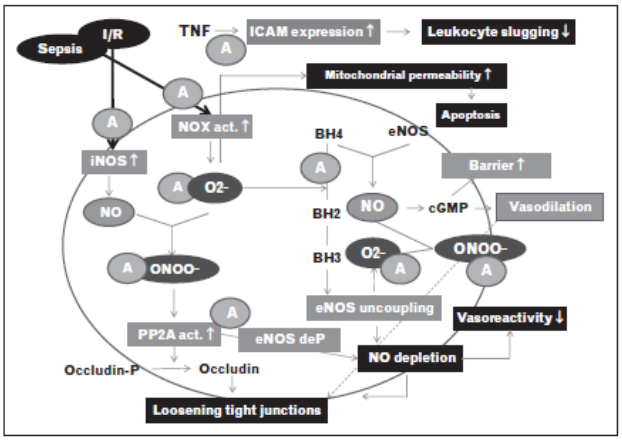

Figure 4. Antioxidant properties of vitamin C. Ascorbate (A) inhibits the formation of superoxide (O2) and peroxynitrite (OONO_) by inhibiting the activation of NADPH oxidase (NOX), which produces superoxide (O_2_) and inhibiting inducible nitric oxide (iNOS) mRNA expression, preventing the abundant production of nitric oxide (NO) which generates OONO_ in the presence of O_2. Ascorbate protects pathological vasoconstriction and loss of endothelial barrier by inhibiting tetrahydrobiopterin (BH4) oxidation, the cofactor of endothelial nitric oxide synthetase (eNOS), thereby preventing eNO depletion and eNOS uncoupling, which generates O_2. Vitamin C protects against vascular leakage by inhibiting protein phosphatase 2A (PP2A) activation, which dephosphorylates occluding. Phosphorylated occluding is crucial for the maintenance of tight junctions. Ascorbate protects against mitochondrial permeability transition, which initiates apoptotic pathways. Ascorbate inhibits tumor necrosis factor (TNF)-induced intracellular adhesion molecule (ICAM) expression, which increases stickiness and slugging of leukocytes in the microcirculation.[24]

Copyright by Tanuwijaya, Utama, & Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

The mechanism by which vitamin C Might Prevent Endothelial Dysfunction

There are several mechanisms by which vitamin C may prevent endothelial dysfunction due to oxidized LDL.

1. Vitamin C can decrease LDL oxidation by directly acting as a ROS scavenger. By forming the first-line defense against free radicals andperoxides generated during cellular metabolism in the plasma, vitamin C is a potent antioxidant.
2. *In vitro* study: suggested that vitamin C can recycle a-tocopherol in LDL, preventing LDL oxidation. Vitamin C is considered the best co-antioxidant for a-tocopherol. The α-tocopherol radical can assume a pro-oxidant role and continue or even enhance the chain reaction of lipid peroxidation in LDL. Such direct effects of vitamin C on LDL oxidation most likely occurs in the subintimal space, where LDL is oxidized. Although vitamin C is present in atherosclerotic lesions, its concentrations in the subintimal space are unknown.
3. Vitamin C can decrease endothelial cell damage by suppressing oxidized LDL. In cultured cells, oxidized LDL is directly toxic to endothelial cells, causing intracellular glutathione (GSH) depletion and cell lysis. In rabbit aortas, oxidized LDL diminishes endothelial-dependent vascular relaxation. Studies showed that vitamin C within cells could protect them against the damage caused by oxidized LDL. For example, the treatment of cultured vascular smooth muscle cells with physiologic concentrations of vitamin C protects them against the toxic effects of oxidized LDL. In endothelial cells, a similar extent of protection requires a combination of vitamin C with other antioxidants.
4. The presence of vitamin C in the intracellular space can decrease endothelial cells' ability to modify LDL. Endothelial cells in culture are known to oxidatively modified LDL by metal ion-dependent mechanisms. Martin and Frei found that loading cultured human aortic endothelial cells with vitamin C decreases their capacity to oxidize LDL; a more significant vitamin C concentration in the intracellular space is associated with more excellent protection. Significantly, these authors also showed that the capability of vitamin C in the intracellular space to decrease extracellular LDL modification is not due to the leak of the vitamin out of the cells.[34]

Preclinical Burn Studies of Vitamin C

The benefit of treating ocular alkali burns in a rabbit model and attenuating burn wound tissue necrosis when administered in the intraperitoneal space is among the early evidence showing the use of vitamin C in a burn injury. Preclinical studies have since evaluated vitamin C's utility as an adjunct to burn resuscitation to decrease total intravenous fluid requirement after a large burn. In a guinea pig model, the administration of high-dose vitamin C (14.2 mg/kg/h) to large burn (70% total body surface area [TBSA] burn) effectively reduced the total fluid requirement. It also does not compromise the hemodynamic parameters of the animals. When vitamin C was administered within 6 hours of burn injury, and for at least 6 hours, the cardiac output increased directly to a hematocrit decrease.[4] Following vitamin C administration, burn wound edema significantly decreases, likely due to decreased interstitial fluid hydrostatic pressure, lymph flow, and loss of protein from the interstitial space. When these findings were reproduced in a large animal burn model (i.e., sheep with 40% TBSA burn), 15 mg/kg/h of vitamin C is needed to result in a 30% less fluid at 6 hours and a 50% less fluid at 48 hours while maintaining adequate hemodynamic. Furthermore, animals demonstrated decreased plasma thiobarbituric acid reactive substances, an index of reduced lipid peroxidation. Although most of the preclinical studies of vitamin C in burn models have been from one group, they provide the framework for clinical investigations.[3]

Vitamin C Side Effects

Despite the readily excreted property of vitamin C by the kidney, the challenge of applying a high dose of vitamin C in burn patients is a possible osmotic diuresis and a worsening acute kidney injury that is also observed as side effects in burn patients. Possibly because intravenous administration of high-dose vitamin C is so well-tolerated, studies examining the potential toxicity profile or side effects from high-dose vitamin C therapy are limited. The intravenous formulation of vitamin C is

Copyright by Tanuwijaya, Utama, & Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 │ DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

hyperosmolar unless specific effort is made to create an isotonic, diluted solution. Osmotic diuresis necessitates extra precautions to ensure that acute kidney injury or hypovolemia does not occur due to resuscitated burn patients. Consequently, it is critical to monitor hematocrit levels and clinical signs of hypovolemia. Oxalate nephropathy has also been observed in the post-mortem examinations of a small number of burned patients treated with high-dose (66 mg/kg/h) vitamin C as rescue therapy during difficult resuscitations. It is also observed from a build-up of water-insoluble calcium oxalate when vitamin C has been used as an alternative therapy for cancer and amyloidosis because absorbed vitamin C is metabolized to threose oxalic acid. Hyperoxaluria from high-dose vitamin C can worsen existing kidney injury or delay kidney recovery. Future studies should focus on renal toxicity, especially in patients with pre-existing kidney injury. Another concern with vitamin C administration is the false elevation of point-of-care (POC) glucose measurements reported. In vitro studies showed that vitamin C interferes electrochemical assays used to test POC glucose measurements. Therefore, standard laboratory measurements are necessary to determine accurate glucose levels for up to 24 hours after discontinuing vitamin C infusion.3.

Vitamin C Dose

While the recommended adult daily intake of vitamin has been known, the optimal dosing of vitamin C for burn resuscitation has not yet been determined. Preclinical studies in guinea pig examined different doses of vitamin C (7 to 28.3 mg/kg/h) and found that 14.2 mg/kg/h is adequate to aid resuscitation. We found that a 66 mg/kg/h dose of vitamin C was used during the two existing human studies, although it remains unclear why such dose was selected for clinical studies, especially concerning preclinical investigations that used substantially lower doses. One possible explanation is that larger mammals may need larger vitamin C doses due to the more complex nature of ROS generating systems. Further investigation is thus required because there may be a dose-dependent increase in the incidence of renal toxicity, especially in the presence of existing kidney injury, although 66 mg/kg/h of vitamin C has been well-tolerated existing human studies. Over a 24-hour resuscitation period, 66 mg/kg/h of vitamin C for a 70-kg patient could lead to a total dose of 110 g of vitamin C, potentially increasing the risk for adverse effects. 3

CONCLUSION

An antioxidant is a potential adjuvant therapy in preventing sepsis for burn patients who survive the initial resuscitation. Compared with other antioxidants, vitamin C is less expensive and has shown promising results. However, during systemic inflammatory response syndrome (SIRS), a decreasing level of vitamin C is observed, whereas other vitamins have not. Vitamin C has some functions for preventing sepsis, such as minimizing the effects of free radical injury in a septic patient by scavenging ROS at the cellular level. Overall, vitamin C offers several microvascular functions, including capillary blood flow, microvascular permeability, arteriolar responsiveness to vasoconstrictor and vasodilators. In burn patients, vitamin C has a role in reducing the need for fluid resuscitation in the acute phase of burn injury. Despite all the potentials, the application of high dose vitamin C for burn patients still need further research to discover the appropriate dosage and side effects, especially for pregnant women, elderly patients, or patients with other prior medical histories such as renal disease, or patients who consume other medicine.

Correspondence regarding this article should be addressed to:
Lucretya Yeniwati Tanuwijaya. ; Intern participant in Plastic Reconstructive and Aesthetic Department, Prof. Dr. Margono Soekardjo Hospital, Purwokerto, Central Java, 50164, Indonesia.
E-Mail: lucretya.tan@gmail.com

REFERENCES

1. WHO. Burns. 2018. Retrieve from: http://www.who.int/violence_injury_prevention /other_injury/burns/en/
2. Swanson JW, Otto AM, Gibran NS, Klein MB, Kramer CB, Heimbach DM, Pham TN. Trajectories to death in patients with burn injury. Journal of Trauma and Acute Care Surgery. 2013; 74(1), 282-8.
3. Rizzo JA, Rowan MP, Driscoll IR, Chung KK, Friedman BC. Vitamin C in Burn

Copyright by Tanuwijaya, Utama, Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 | DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

Resuscitation. Critical Care Clinics, 2016; 32(4),539–46.
4. Greenhalgh DG. Sepsis in the burn patient: a different problem than sepsis in the general population. Burns & Trauma, 2017; 5(1).
5. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 2013; 41:1167–74.
6. D'Acremont V, Kilowoko M, Kyungu E, Philipina S, Sangu W, Kahama-Maro J, Lengeler C, Cherpillod P, Kaiser L, Genton B. Beyond malaria— causes of fever in outpatient Tanzanian children. N Engl J Med, 2014; 370: 809–17.
7. Bramantono, Purwati, Hamidah. The Prevalence of Extended Spectrum Beta-Lactamase (ESBL) in Third Generation Cephalosporin Usage Among Sepsis Patient in The Department of Internal Medicine RSUD Dr. Soetomo Surabaya. Folia Medica Indonesiana. 2013; 49(4): 244-51.
8. Bekhit M. Ascorbic Acid (Vitamin C) in Sepsis. Surgicalcriticalcare.net. Surgical Critical Care Evidence-Based Medicine Guidelines Committee 2018.
9. Chen L, Meng K, Su W, Fu Y. The Effect of Continuous Sedation Therapy on Immunomodulation, Plasma Levels of Antioxidants, and Indicators of Tissue Repair in Post-Burn Sepsis Patients. Cell Biochemistry and Biophysics,2015; 73(2), 473–8.
10. You B, Zhang YL, Luo GX, Dang YM, Jiang B, Huang GT, Liu XZ, Yang ZC, Chen Y, Chen J, Yuan ZQ, Yin SP, Peng YZ. Early application of continuous high-volume haemofiltration can reduce sepsis and improve the prognosis of patients with severe burns. Critical Care, 2018;22(1).
11. 11. Neeraj, Pramod J, Singh S, Singh J. Role of Free Radicals and Antioxidants in Human Health and Disease. International Journal of Current Research and Review, 2013; 5(19); 14-22.
12. Chen MC, Chen MH, Wen BS, Lee MH, Ma H. The impact of inhalation injury in patients with small and moderate burns. Burns, 2014; 40(8), 1481–86.
13. Culnan DM, Capek KD, Sheridan RL. Etiology and Prevention of Multisystem Organ Failure. Total Burn Care, 2018; 307–17.e5.
14. Gupta P, Chhibber S, Harjai K. Efficacy of purified lactonase and ciprofloxacin in preventing systemic spread of Pseudomonas aeruginosa in murine burn wound model. Burns, 2015; 41(1), 153–62.
15. Chai J, Sheng Z. Postburn Multiple Organ Dysfunction. Chinese Burn Surgery, 2014; 353–66.
16. Ellison DL. Burns.Critical Care Nursing Clinics of North America,2013;25(2),273-85.
17. Emekli-Alturfan E, zdemir G,Saglam E, Özdamar EN , ¬¬ehirli z, ener G. Angiotensin-converting enzyme inhibitor captopril ameliorates renal damage in a rat model of thermal injury. Asian Biomedicine, 2013, 7(3); 381-389.
18. Hill A, Wendt S, Benstoem C, Neubauer C, Meybohm P, Langlois P, Adhikari NKJ, Heyland DK, Stoppe C. Vitamin C to Improve Organ Dysfunction in Cardiac Surgery Patients—Review and Pragmatic Approach. Nutrients, 2018; 10(8), 974.
19. Sivayoganathan T. Metformin Attenuates Hepatic Mitochondrial Dysfunction and Oxidative Stress in a Model of Burn Injury. Institute of Medical Science University of Toronto, 2018. Available at: https://tspace.library.utoronto.ca/handle/1807/91701
20. Matsuda T, Tanaka H, Shimazaki S, Matsuda H, Abcarian H, Reyes H, Hanumadass M. High-dose vitamin C therapy for extensive deep dermal burns. Burns, 1992; 18(2), 127-131.
21. May JM. How does Ascorbic Acid Prevent Endothelial Dysfunction? Free Radical Biology & Medicine, 2000; 28(9): 1421–1429.
22. Horton JW. Free Radicals and lipid peroxidation mediated injury in burn trauma: the role of antioxidant therapy. Toxicology, 2003; 189: 75-88.
23. Friedl HP, Till GO, Trentz O, Ward PA. Roles of histamine, complement and xanthine oxidase in thermal injury of skin. Am J Pathol, 1989;135(1):203–17.
24. Berger MM, Straaten HMO. Vitamin C Supplementation in the critically ill patient. Curr Opin Clin Nutr Metab Care, 2015;18(2):193–201.

Copyright by Tanuwijaya, Utama, Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 │ DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0

25. Moenadjat Y. Luka Bakar Pengetahuan Klinik Praktis: Second Edition: FKUI; 2003. p.11-14.
26. Schaefer TJ, Szymanski KD. Burn Evaluation and Management. StatPearls 2017.
27. Murray KA. Burn Basics: How to Assess and Treat. The Canadian Journal of CME 2007; 62-64.
28. Alharbi Z, Piatkowski A, Dembinski R, Reckort S, Grieb G, Kauczok J, Pallua N.Treatment of burns in the first 24 hours: simple and practical guide by answering 10 questions in a step-by-step form. World Journal of Emergency Surgery, 2012; 7(13): 1-10.
29. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 Update. Springer: Intensive Care Med 2018; 44:925–928.
30. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, Poll TVD, Vincent J-L, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016; 315(8): 801–810.
31. Friedl HP, Till GO, Trentz O, Ward PA. Roles of histamine, complement and xanthine oxidase in thermal injury of skin. Am J Pathol, 1989;135(1):203–17.
32. Kuhn S-O, Meissner K, Mayes LM, Bartels K. Vitamin C in Sepsis. Current Opinion in Anaesthesiology, 2017;30(00): 1-6
33. National Center for Biotechnology Information. Ascorbic Acid. PubChem. 2018. Retrieve from: https://pubchem.ncbi.nlm.nih.gov/compound/ascorbic_acid
34. Sorice A, Guerriero E, Capone F, Colonna G, Castello G, Costantini S. Ascorbic acid: its role in immune system and chronic inflammation diseases. Mini Rev Med Chem, 2014 ;14(5):444-52.

Copyright by Tanuwijaya, Utama, Mas'ud (2020).
P-ISSN 2089-6492; E-ISSN 2089-9734 │ DOI: 10.14228/jprjournal.v7i2.285
This work is licensed under a Creative Commons License Attribution-Noncommercial No Derivative 4.0