Vitamin C – breathing new life into septic acute lung injury therapy?

Professor Alpha (Berry) Fowler III, from the VCU Johnson Center for Critical Care and Pulmonary Research, is focused on investigating the molecular basis of sepsis-induced lung injury. Through collaborative efforts, Professor Fowler has discovered that vitamin C could be a novel therapeutic option for mitigating the effects of acute lung injury, saving many lives.

Following infection, the immune system normally releases potent chemicals that attack invading pathogens. However, this natural defence system can sometimes go into overdrive, causing widespread inflammation and multi-system organ dysfunction, in a condition called sepsis. Sepsis is not a rare disease. Estimates are that over 51 million people develop sepsis globally every year. The consequences of sepsis can be fatal. Mortality rates in patients who develop septic shock are as high as 30–50%, with symptoms that often include critically low blood pressure, abnormal heart rate, breathing difficulties and a loss of consciousness.

SEPSIS-INDUCED LUNG INJURY

Bacterial infections of lung, urinary tract, abdomen and other body cavities promote growth of germs in the blood and are common causes of severe sepsis that can result in lethal Acute lung injury (ALI). This condition has a high incidence rate – over 200,000 people per year suffer from sepsis-induced ALI in the United States alone. Typically, severe septic shock is treated by administering large volumes of intravenous fluid, broad spectrum antibiotics, and catecholamine vasopressors – drugs that cause blood vessel constriction, increasing blood pressure. However, vasopressors can lead to detrimental side effects that include cardiac arrest, skin necrosis and low sodium levels. Furthermore, there are no direct therapeutic options available to specifically treat ALI.

To address this urgent issue, Professor Alpha Fowler, in collaboration with scientists from Virginia Commonwealth University School of Medicine, has spent over a decade investigating a potential therapy to treat sepsis-induced ALI. Amazingly, Professor Fowler and his team's ground-breaking research has indicated that ascorbic acid (vitamin C) has the potential to be an effective therapeutic agent.

HOW THE MOLECULAR BASIS OF SEPSIS CAUSES ALI

Sepsis is induced when a key protein, called Nuclear Factor kappa B (NFκB), a transcription factor that drives the expression of genes encoding pro-inflammatory cytokines is activated. Cytokines are essential components of the immune response that help the body to attack bacteria. Cytokines become

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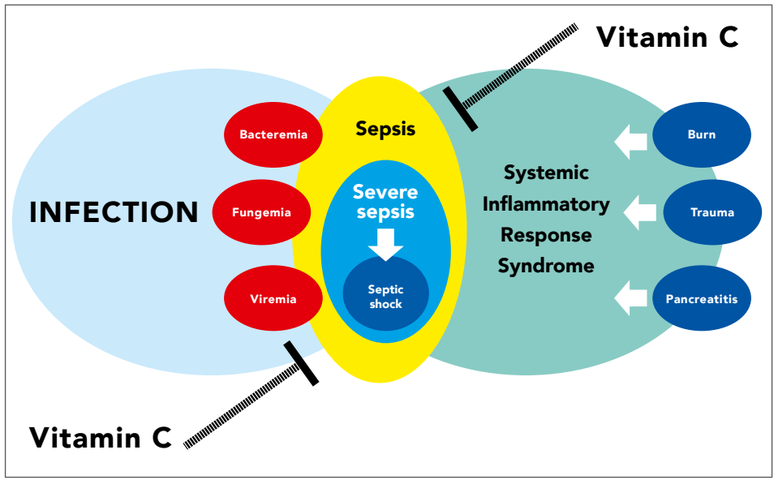

activated by small molecules produced by bacteria called lipopolysaccharides (LPS). LPS essentially acts as a flag to the body's immune cells that produce cytokines, indicating that a dangerous pathogen is present. However, over-expression of cytokines can be detrimental, leading to injury of the body's blood vessels causing coagulation, or blood clotting. This situation is incredibly damaging as the lung's tiny microvessels become blocked, disrupting blood flow and resulting in inflammation and organ failure.

Furthermore, the presence of LPS also triggers the formation of neutrophil extracellular traps (NET) by polymorphonuclear neutrophils (PMN). Essentially, NETs are extruded DNA from PMN which entangle and kill bacteria. High concentrations of powerful antimicrobial enzymes such as neutrophil elastase and myeloperoxidase are released into the NETs which then destroy the pathogen's physical integrity. NETosis is a dramatic and violent event and can severely damage delicate lung capillaries, enhancing vascular damage.

Damaged lung capillaries adversely impact important structures of the lung called alveoli – the sites of gas exchange. For the lungs to function normally, the surface of these tiny sac-like structures must be kept dry. This is achieved by ion pumps and channels, located on the surface of the alveoli, which actively drive water movement from the inner alveolar space into the blood. However, sepsis-damaged capillaries leak water back into the alveolar space, giving sepsis-injured lungs a loss of the lung's barrier function. The abnormal 'barrier function' makes the lungs 'leaky'. Because of this, the lungs are no longer able to separate blood from air and oxygen cannot be transferred into the blood.

ASCORBIC ACID EASES SEPSIS-INDUCED ALI

Studies in humans have shown that sepsis significantly reduces plasma ascorbic acid concentrations. Interestingly, low ascorbic acid levels are associated with an increase in organ failure and a decrease in survival in septic patients. This relationship inspired Professor Fowler and his colleagues to further explore the role of ascorbic acid. The promising results from this confirmed that ascorbic acid could actually mitigate the adverse effects caused by sepsis.

In one study, the team artificially induced ALI in mice, following injections with high levels of LPS. Control mice (which were given no ascorbic acid) had a mortality rate of 100% after 28 hours. However, those treated with 200 mg/kg of ascorbic acid had a 60% survival rate. This is because ascorbic acid moderates increased coagulation by indirectly inhibiting NfκB activation and reducing levels of Tissue Factor, (the protein that leads to coagulation in sepsis). Essentially, capillaries are 'unplugged', re-establishing normal blood flow.

Professor Fowler and his colleague Professor Ramesh Natarajan hypothesise that endoplasmic reticulum stress, autophagy (an intracellular degradation system), histone citrullination (which controls gene expression) and NFkB activation could all play key roles in the molecular pathways that stimulate NETosis. Therefore, modulation of these pathways could be the reason the team saw attenuated NETosis in subjects treated with ascorbic acid.

Furthermore, ascorbic acid increases the synthesis and activity of ion pumps and channels located on the alveolar surface, restoring normal water movement.

ASCORBIC ACID AS A HUMAN TREATMENT

The team from Virginia Commonwealth University have also used ascorbic acid as an interventional drug to treat sepsis-induced lung injury, conducting trials on humans suffering from acute respiratory failure. Twenty-four patients with severe sepsis were given intravenous infusions of ascorbic acid every six hours for four days. Overall, not only did the results show that ascorbic acid had no adverse safety issues, it also significantly reduced proinflammatory biomarkers, supporting Professor Fowler's earlier work.

However, further research is needed before ascorbic acid can be approved as a legitimate treatment for sepsis-induced lung injury. Therefore, Professor Fowler is currently conducting a larger-scale Phase II proof of concept trial, in collaboration with four medical centres (Virginia Commonwealth University, The Cleveland Clinic, The Medical College of Wisconsin and The University of Kentucky).

The aim of this trial is to determine whether intravenous ascorbic acid will decrease multiple organ failure of sepsis and reduce inflammation and coagulation, indicated by reduced levels of pro-inflammatory biomarkers associated with this condition.

Professor Fowler's innovative research has provided much evidence to show that ascorbic acid can be an effective drug to mitigate the effects of sepsis-induced lung injury, saving tens of thousands of lives.

The promising results from Dr Fowler's study confirmed that ascorbic acid could actually mitigate the adverse effects caused by sepsis

Q&A

Sepsis is caused by the immune system sometimes going into overdrive. What causes this drastic response?
Conditions that predispose to sepsis are chronic intravenous lines, systemic inflammatory diseases, treatment for solid tumours and leukaemia with chemotherapy. The extent to which a patient's immune system goes into overdrive is totally unpredictable. Largely, it has to do with a patient's basic genetic make up. Some individuals will have a "much brisker immune response" to infection than others. Very importantly, there are certain predisposing conditions that predispose to severe sepsis. Patients who have systemic inflammatory diseases such as rheumatological diseases (Systemic Lupus, certain forms of arthritis), patients who are being treated for solid tumours like lung cancer, bowel cancer, genitourinary cancers, and leukaemia patients being treated with chemotherapy. Unfortunately, there is no test in clinical medicine today which lets doctors know which patient will go into "sepsis overdrive".

What initially inspired you to research the anti-sepsis effects of vitamin C?
I have been a critical care physician for 40 years. During this time, I've lost many patients to sepsis. I was determined to find a treatment that saves lives.

What are the benefits of using vitamin C to treat sepsis-induced lung injury, compared to other drugs that are currently used?
Vitamin C is non-toxic, safe to use in the critically ill, and can be used alongside other treatments such as antibiotics, intravenous fluids, and vasopressor agents. Vitamin C if proven effective does not measurably add to the cost of critical care.

Can vitamin C be used to treat other organs affected by sepsis?
Yes. We showed in our early phase I safety study that other organ function (e.g., kidney function, liver function) improved in patients receiving the high dosage vitamin C.

What further research needs to be conducted before vitamin C is approved to treat sepsis induced lung injury?
If the current phase II trial proves to be effective, I feel that it will become the standard of care in intensive care units across the world and that no other trials will be needed.

The Vitamin C Research Team at the VCU Johnson Center for Critical Care and Pulmonary Research. From left: Ramesh Natarajan, Stella Hamman, Bernard Fisher, Aamer Syed, Christine DeWilde, Anna Priday and Alpha (Berry) Fowler. Credit: The Virginian Pilot

Detail

RESEARCH OBJECTIVES

Professor Fowler's research focuses on the molecular basis of lung injury and the role of ascorbic acid, (vitamin C), in reducing the effects of septic acute lung injury and organ failure.

FUNDING

- National Heart, Lung and Blood Institute (NHLBI)
- National Institutes of Health (NIH)

COLLABORATORS

- Ramesh Natarajan, PhD, VCU School of Medicine
- Bernard Fisher, BS, MS, VCU School of Medicine
- Christine DeWilde, RN, MSN, VCU School of Medicine
- Anna Priday, BS, VCU School of Medicine
- Aamer Syed, MD, VCU School of Medicine
- Stella Hamman, RN, MSN, VCU School of Medicine

BIO

Professor Fowler received his MD from the Medical College of Georgia. Following this, he did his post-graduate medical training at Virginia Commonwealth University School of Medicine. He later received Pulmonary Disease and Critical Care Medicine training at the University of Colorado Health Sciences Center, before returning to Virginia Commonwealth University.

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