

Trauma and Crush Injury

TRAUMA AND CRUSH INJURIES ARE CURRENTLY LEADING CAUSES OF DEATH.

Trauma and crush injuries occur frequently and from multiple sources. For example, automobile or motorcycle accidents, natural disasters, and acts of criminal violence or terrorism can all yield mild to severe trauma and crush injuries. The breadth of life-threatening conditions from trauma-induced injuries, such as lung and bowel rupture, closed head injury, crush injury and rhabdomyolysis, traumatic fractures, penetrating wound injury, and limb loss, creates a very challenging environment for clinicians to employ effective treatment strategies. Better therapies are needed to reduce the mortality in patients with severe trauma injury, reduce the risk of organ failure, reduce complications (e.g. rhabdomyolysis and infection), and decrease hospital stay length.



CYTOKINE STORM AND RHABDOMYOLYSIS IN TRAUMA CAN CAUSE ORGAN FAILURE AND DEATH

Trauma is a well-known trigger of the immune response, and can result in the massive, uncontrolled production of cytokines, or “cytokine storm.” Cytokines are small proteins that normally help stimulate and regulate the immune system to fight infection or injury. However, in trauma, cytokine storm can be toxic, leading to a massive systemic inflammatory response syndrome (SIRS) and a cascade of events that can kill cells and damage organs, leading to organ failure and often death.

Cytokine storm exacerbates physical trauma in many ways. For example, trauma can cause:

- Hemorrhagic shock due to blood loss while cytokine storm causes capillary leak and intravascular volume loss, and the induction of nitric oxide that can lead to myocardial depression and peripheral vasodilation, all of which exacerbate shock
- Severe limb injuries that often require a tourniquet. Upon reperfusion, the distal ischemic limb pours oxygen radicals, cytokines and other inflammatory mediators back into the body that can cause lung injury and organ damage
- Pulmonary contusions, hemorrhage and edema. Cytokine storm can worsen the injury by causing capillary leakage and an influx of inflammatory fluid and immune cells into the alveoli, resulting in acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)
- Intestinal perforation leading to infection and sepsis. Elevated cytokines break down the mucosal lining of the intestines, leading to translocation of endotoxin and bacteria into the body, fueling ongoing septicemia despite surgical “cure”
- A higher risk of infection due to “dirty” contaminated wounds. Pro-inflammatory cytokines cause apoptosis of antigen presenting cells while anti-inflammatory cytokines cause profound unresponsiveness of the immune system to new infectious stimuli (“immune paralysis”), putting patients at high risk of secondary infections and sepsis

Complicating matters is the breakdown of damaged skeletal muscle, or rhabdomyolysis, leading to a massive release into the blood of potassium that can cause fatal cardiac arrhythmias, and myoglobin that can crystallize in the renal tubules, leading to acute tubular necrosis and renal failure. Renal failure and hyperkalemia in trauma are associated with a significant increased risk of death.

CytoSorb® - THE NEXT GENERATION OF “ACTIVE” TREATMENTS FOR TRAUMA AND CRUSH INJURIES

CytoSorb® is the only specifically approved extracorporeal cytokine adsorber in the European Union. In trauma, it is designed to reduce both excessive cytokines and myoglobin in a single device. The heart of the technology is a biocompatible, porous polymer bead, roughly the size of a grain of salt, designed to capture cytokines, inflammatory mediators, and myoglobin in its pores based on size and surface adsorption, while letting larger or smaller substances pass around or through. Treatment is very similar to hemodialysis. As blood is repeatedly pumped out of the body and through the CytoSorb® cartridge using standard hospital dialysis machines or small portable hemoperfusion pumps, cytokines and myoglobin are captured by the beads and removed from blood. The “purified” blood is then recirculated back into the patient. CytoSorb® effectively clears greater than 90% of myoglobin in serum over four hours using an *in vitro* perfusion system that simulates human rhabdomyolysis.¹ CytoSorb® also efficiently clears many different cytokines from whole blood, on the order of 60-90%. CytoSorb® is compatible with regional citrate anti-coagulation (anticoagulation only of the external blood circuit) and does not require systemic anticoagulation, which would otherwise be contraindicated in trauma patients with bleeding injuries.



CytoSorb® ADVANTAGES

- **Broad spectrum device** – Specifically designed to remove a broad range of cytokines, toxins and myoglobin, making this the most logical strategy to treat cytokine storm and rhabdomyolysis in trauma victims
- **Efficient cytokine removal** – Capable of removing a broad range of key cytokines in septic shock patients with multi-organ failure
- **Efficient myoglobin removal** – Capable of removing greater than 90% of myoglobin *in vitro*
- **Excellent safety profile** – Well-tolerated in more than 14,000 human treatments
- **Positive human clinical data** – European Sepsis Trial showed the safe reduction of cytokines and with preliminary data demonstrating encouraging improvements in mortality and organ dysfunction in high risk patients
- **Easy to use** – Minimal learning curve, uncomplicated set up, and high ease of use
- **Works with existing hospital dialysis equipment or portable, small hemoperfusion pumps** – No new equipment needed
- **No extra fluids or dialysate needed** – Makes treatment logistically simple
- **Compatible with both heparin and regional citrate anti-coagulation** – Systemic anticoagulation is not needed if contraindicated
- **ISO 10993 Biocompatible** – Biocompatible, hemocompatible, no genotoxicity/cytotoxicity, no acute sensitivity or complement activation
- **Massive capacity** – A single cartridge has more than seven football fields of surface area to bind cytokines
- **Long Shelf Life** – No biologic components such as antibodies or cells means excellent storage and logistics – three years at room temp
- **High Quality Manufacturing** – CytoSorbents manufactures CytoSorb® at its ISO 13485:2012 manufacturing facility in New Jersey

SEVERAL DIFFERENT APPROACHES IN TRAUMA.

CytoSorb® can be used in several different ways in trauma. The bi-modal aspect of trauma mortality is well-known. If patients survive the original traumatic insult, they are at risk of developing a maladaptive SIRS response that can lead to organ failure and death in late trauma. However, given that the inflammatory response is helpful and adaptive, we recommend intervening with CytoSorb® only when there is evidence of organ injury or dysfunction. In this context, CytoSorb® may have benefit in reducing the dangerous post-traumatic inflammatory response and preventing worsened organ injury. Another way that CytoSorb® can be used is to treat rhabdomyolysis. It is designed as an adjunctive therapy to be used with supplemental hydration, urine alkalinization, and gentle diuresis to prevent renal failure. Unlike standard dialysis and CRRT, which are not very effective in reducing myoglobin from blood, CytoSorb® has been used successfully in many cases to help treat rhabdomyolysis, including a recent published case report, and a number of other cases reports that have been presented at meetings or submitted for publication.²

US ARMY PHASE I & II SBIR GRANTS. CytoSorbents was awarded ~\$1.65M in Phase I, II, and Phase II enhancement SBIR contracts managed by the U.S. Army Medical Research and Materiel Command to further develop its technologies for trauma, hyperkalemia, and burn injury in porcine models under Contract No W81XWH-12-C-0038.

30-PATIENT HUMAN PILOT STUDY FUNDED BY THE U.S. AIR FORCE. The U.S. Air Force is funding a 30-patient randomized controlled pilot study using CytoSorb® to treat trauma patients with rhabdomyolysis with CRRT versus CRRT alone.

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SUMMARY. CytoSorb® is capable of removing both cytokines and myoglobin in trauma patients, a useful combination in treating both trauma and rhabdomyolysis, with the goal of preventing or treating organ failure, a leading cause of death in late trauma. CytoSorb®, the company's flagship product, is now approved in the European Union as a broad, extracorporeal cytokine filter, designed to help fight "cytokine storm" in critical-illnesses such as sepsis, trauma and burn injury, that can cause severe inflammation, organ failure, and often death in our wounded warriors. CytoSorb® has the potential to revolutionize critical care medicine. Case series and case reports can be found at the CytoSorb® website: www.cytosorb.com.

CytoSorb® is approved in the European Union but is not yet FDA-approved.

SELECT REFERENCES

- ¹ Kuntsevich, VI, et al "In-vitro myoglobin clearance by a novel sorbent system". *Artif Cells, Blood Subst, and Biotech*; 37:45-47.
- ² Wiegele M and Krenn CG "Cytosorb™ in a Patient with *Legionella* Pneumonia-Associated Rhabdomyolysis." *ASAIO J* 2015 May-Jun; 61(3):e14-16.

CytoSorbents™

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