The VICToRY Trial

VItamin C in Thermal injuRY: The VICToRY Trial

A phase III multi-center randomized trial

Synopsis:

Background: Worldwide, burn injuries represent a significant public health problem and are ranked the seventh most common cause of unintentional injury. In certain disease states, such as those associated with severe burns and other critical illnesses, the relationship between nutrient deficiencies, altered immune status, and acquired infection has been recognized for many years. More than in any other injury, the inflammation and catabolism associated with severe burns can exacerbate nutrient deficiencies, thereby predisposing patients to impaired immune function and increased risk of developing infectious complications, organ dysfunction, and death. Consequently, over the last few decades numerous trials have evaluated the impact of different nutrition/nutrient strategies in critically ill patients and in particular, severe burns patients. Recently, there has been renewed interest in the role of high dose intravenous vitamin C supplementation in critically ill patients yet the origins of high dose vitamin C supplementation dates back to research done more than 20 years ago in burn patients. Today, few centers routinely administer high-dose vitamin C to severely burned patients, suggesting that a high level of evidence is warranted.

The purpose of this phase III multicentre randomized trial is to demonstrate efficacy and safety of high-dose intravenous vitamin C administration in 666 severe burn injury patients.

What are the principal research questions to be addressed in this Phase III trial?

Primary research question:

In patients with severe, life-threatening burn injury, what is the effect of high dose (200mg/kg/day x 96 hours) intravenous vitamin C in addition to standard of care (SOC) on 28-days composite outcome of Persistent Organ Dysfunction (POD) and all-cause mortality compared to add-on placebo and SOC?

Secondary Research question:

In patients with severe, life-threatening burn injury, what is the effect of high dose (200mg/kg/day x 96 hours) intravenous vitamin C in addition to SOC on time to discharge alive from hospital, hospital mortality, duration of stay in ICU and hospital, and 6-month mortality, health-related quality of life, and health care resources compared to add-on placebo and SOC?

Overall Hypothesis: The administration of high dose, intravenous vitamin C to burned critically ill patients will be associated with less organ dysfunction, improved survival, and a quicker rate of recovery. We hypothesize that the inexpensive therapeutic strategy tested in this randomized controlled trial will be effective in reducing morbidity and mortality in an otherwise disabling injury worldwide.

Study Design: We propose a multicentre, double-blind, randomized controlled trial of 666 patients with severe burns randomly allocated to receive intravenous vitamin C (200 mg/kg/day for 96 hours) or placebo (333 per group).

Setting: 40 or more burn centres from around the world.

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Study population: We plan to include patients 18 years of age or older with deep 2nd and/or 3rd degree burns, who are assessed as requiring skin grafting, with a minimum burn size ≥ 20%of Total Body Surface Area (TBSA). Patients with smaller burns are less likely to require fluid resuscitation and their risk of morbidity and mortality is lower.

Exclusion criteria

1. >24 hrs from admission to participating hospital to consent.
2. Patients admitted to a burn unit >24 from injury or accident.
3. Patients who are moribund (not expected to survive the next 72 hours).
4. Pregnancy (pregnancy will be ruled out as part of standard of care) or lactating.
5. Enrolment in another industry sponsored ICU intervention study.
6. Receiving high-dose IV vitamin C already (enteral or oral vitamin C is allowed).
7. Known glucose-6-phosphate dehydrogenase (G6PD) deficiency.
8. Recent history of kidney stones (within the last year).
9. Concomitant use of hydroxycobalamin (vitamin B12) for suspected cyanide poisoning.

Study Intervention: Patients will be allocated to 2 groups: **Vitamin C group:** patients will receive intravenous vitamin C at 200mg/kg/day in divided doses, every 6 hrs for 96 hrs. We justify this proposed dosing strategy as the "high dose" has been shown overall to be safe and effective in patients with sepsis whereas prior dosing strategies used in the burns literature (66 mg/kg/hour for 24 hours) have safety issues and are not long enough in duration. **Control group:** patients will receive a similar amount of placebo (either D5W or normal saline) delivered in the same manner as the vitamin C.

Outcomes: The primary outcome for this phase III trial is persistent organ dysfunction (PODS)+death at 28 days, a novel composite endpoint that combines being alive and being free of organ support (inotropes or vasopressors, renal replacement therapy and mechanical ventilation). The most important secondary endpoint of this trial will be "time to discharge alive form hospital".

Sample Size and Duration: 666 patients over the next 48 months.

Significance: This study will be the first large international multi-centre trial examining the effects of high dose intravenous vitamin C in burn patients. It represents a follow-on collaboration of burn units worldwide that came together to evaluate enteral glutamine in more than 1200 patients with severe burns from 54 burns units around the world, the results of which were published in the New England Journal of Medicine.

Interested in participating?
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