
Systemic Therapies

A second potential therapeutic option for the parenchymal damage caused by inhalation injury is systemic administration of intravenous agents. The unique nature of the effects of the burn and smoke on lung physiology and immunology create new opportunities for systemic treatments targeting specific aspects of the response to injury. In addition, systemic therapies could be either isolated or combined with inhalation therapies to achieve optimal clinical response. The two articles in this section of the compendium address different, yet promising, systemic therapies: antithrombin and vitamin C. (J Burn Care Res 2009;30:184-189)

Vitamin C and Smoke Inhalation Injury

Steven E. Wolf, MD

Smoke inhalation injury is induced by airway exposure to noxious chemicals from incomplete combustion of organic compounds; these induce a chemical injury to the airway epithelium. Because of the noxious nature of smoke, most patients will take shorter breaths and take great lengths to escape the smoke. Thus, because prolonged closed space exposure with normal tidal volumes are required to smoke distally to the alveoli, injury is confined mostly to the upper airways. Therefore, in general practice, the term inhalation injury is a chemical burn to the upper airways. This incites an inflammatory response which is highlighted by recruitment of neutrophils with increased activity, degranulation, and release of proteases and toxic oxygen free radicals. In fact, the increase in neutrophil activity with smoke inhalation injury is associated with decreases in anti-oxidant activity,¹ and inhibition of neutrophils with pre-injury nitrogen mustard dramatically decreased the extent of injury in a pre-clinical smoke inhalation injury model.²

Because at least part of the injury is due to inflamma-

tion and oxidative damage, a potential treatment would be administration of an anti-oxidant to prevent further injury. One such agent is vitamin C, which was shown to decrease oxidative damage in a number of in vitro and pre-clinical models outside the lungs through decreasing low-density lipoprotein oxidation, scavenging intracellular superoxide, and increasing nitric oxide activity by releasing nitric oxide from tissue S-nitrosothiols, and direct reduction of nitrite to nitric oxide, and enhancing nitric oxide synthase activity.³ However, no investigators to date have investigated the effects of vitamin C on smoke inhalation injury specifically. We do have data on two relevant studies, one a clinical trial in burned subjects where high-dose vitamin C was given during acute resuscitation from burn; most subjects also had inhalation injuries. A second pre-clinical study gave high dose vitamin C during resuscitation in burned sheep for comparison.

Experimental Studies

In 2000, Tanaka et al from Kyorin University in Tokyo, Japan reported a clinical trial in severely burned subjects randomized to receive high dose vitamin C or not during acute resuscitation from injury.⁴ This study was based on the finding that antioxidant therapy with high-dose ascorbic acid reduced lipid peroxidation,⁵ burn and non-burned tissue edema,⁶ and resuscitation fluid volume requirement in burned animals.⁷ They randomized 37 subjects with greater than 30% TBSA burns to receive placebo or 66 mg/kg/hr of vitamin C intravenously for 24 hours. They

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Table 1. Outcomes in severely burned patients with vitamin C

	No Vitamin C (n = 18)	Vitamin C (n = 19)	P
LOS	49 ± 44	40 ± 28	.46
Vent days	21 ± 16	12 ± 9	.03
Pneumonia	6	7	.86
Operations	2.4 ± 1.4	2.3 ± 1.3	.82
Fasciotomies	8	4	.45
Deaths	7	9	.97

Most (73%) also had inhalation injury. Adapted with permission from Tanaka H, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration. *Arch Surg* 2000; 135:326–31. Copyright © 2000 American Medical Association. All rights reserved.

measured resuscitation volumes, weight, vital signs, and ventilatory parameters. Resuscitation was started with lactated Ringers' solution as recommended by the Parkland formula, then adjusted to maintain urine output between 0.5 and 1.0 ml/kg/hr with a normal blood pressure.

Demographics of the subjects showed no differences between groups, including those with a diagnosis of inhalation injury (12 of 18 in the control group, and 15 of 19 in the vitamin C group). No differences were found in heart rate, blood pressure, base deficit, or central venous pressure between groups; however, the 24 hour resuscitation volume in the vitamin C group decreased by 40% compared with control (5.5 ± 3.3 ml/kg/% TBSA burned in controls and 3.0 ± 1.7 ml/kg/% TBSA burned with vitamin C). Urine outputs were similar between groups. This was also reflected in weight gained after resuscitation, which was $17.8 \pm 6.9\%$ in controls, and $9.2 \pm 8.2\%$ in the vitamin C group. These data were the main endpoints of the study, and showed that vitamin C given in high doses (approximately 4.5 gms of vitamin C infused over a 24 hour period in a 70 kg man) significantly reduced resuscitation volumes. End mortality was not different between groups.

It must be noted that 73% of the subjects in this study were diagnosed with inhalation injury by bronchoscopy at admission, with equal distribution between groups. When lung outcomes were considered specifically, no differences were seen between groups in the amount of positive end-expiratory pressure or fraction of inspired O_2 (F_iO_2) used in the first 4 days after injury, but significant differences ($P < .05$) were seen in the ratio of partial pressure of arterial O_2 (P_aO_2)/ F_iO_2 beginning at 18 hours after injury until at least 96 hours after injury. In addition, the number of ventilator days in the control group was 21 ± 16 in the controls, and 12 ± 9 in the vitamin C group, intimating im-

proved lung function. No differences were seen between groups in the number diagnosed with pneumonia (Table 1). These outcomes indicate improved oxygenation and perhaps decreased lung damage in the vitamin C group that may be related in part to specific effects on lung inflammation induced by inhalation injury, or may be a reflection of the whole-body response to systemic vitamin C to reduce generalized effects of the burn. A different study design incorporating subjects with inhalation injury alone would be required to test this notion.

A second related study from Dubick et al from the US Army Institute of Surgical Research in San Antonio, TX, showed similar findings in a large animal model of severe burn alone.⁸ Chronically instrumented sheep underwent a 40% TBSA full-thickness burn, and were assigned to receive either placebo or high-dose vitamin C given as 10 gms (250 mg/kg) in the first 500 ml of resuscitation volume followed by a 15 mg/kg infusion for the 48 hours of the study. Resuscitation was adjusted to maintain urine output between 1 and 2 ml/kg/hr. None of the animals underwent smoke inhalation injury. Similar to the clinical trial results, these investigators showed a 40% decrease in cumulative net fluid given to maintain equivalent urine output. No significant differences were seen among tissue antioxidant status or tissue antioxidant enzyme activity in the lungs among these animals. It is enticing to conclude that the reduction in resuscitation volume required after severe burn appears to be generalized and not related to lung damage because of the approximately 40% reduction in resuscitation volumes with (human data) and without inhalation injury (animal data); however, these are two vastly different models. Therefore, the thought that high dose vitamin C infusion has direct effects to decrease specific lung damage after smoke inhalation injury cannot be excluded.

In an extensive search of the literature, only one other study was found that addresses inhalation injury and vitamin C therapy. It was in the Chinese literature available only in abstract form where Jiang examined the effects of an antioxidant cocktail including vitamin C on smoke inhalation injury induced in 42 dogs.⁹ These animals were randomized and treated with intravenous shenmai zhusheye, ketoprofen, anisodamine, sodium aesculin, hydrocortisone succinate, vitamin C and E, penicillin, and amikacin. The results showed reductions in extravascular lung water volume, pulmonary vascular resistance, carboxemia, hypoxia, and acidosis with treatment. Mortality related to the model was also significantly reduced from 47.6% in the control group to 19.1% in the treatment group. Unfortunately, none of the details of this study are available outside the Mandarin language,

but the results can be used to suggest that antioxidant therapy including vitamin C might be beneficial in smoke inhalation injury.

CONCLUSIONS

The studies mentioned above are compelling to justify the notion that vitamin C given in high doses after inhalation injury might improve outcomes. From the Tanaka et al study, it appears to improve oxygenation and decrease ventilator days in those with both burn and inhalation injury, although the effect might be due to amelioration of the burn and not inhalation injury per se if animal data from burn alone are examined in the same light. However, other pre-clinical studies on inhalation injury alone indicate that indeed oxidant damage does occur in the lungs after smoke inhalation injury,¹ and the effects might be abrogated by the use of anti-oxidants.^{4,9} It must be emphasized that no direct data exist to confirm the idea that vitamin C has effects on the lung to improve outcomes from smoke inhalation in particular; all of the data are eccentric at this point, and a new trial with specific endpoints is required.

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Use of Antithrombin III in Inhalation Injury

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Antithrombin (AT), a serine protease inhibitor produced in liver, is one of the major physiologic anticoagulants. It has marked antiinflammatory properties, most notably by complexing with thrombin, thereby removing it from circulation. The anticoagulant potential of heparin is AT dependent. Antithrombin III (AT III) inhibits thrombin by forming thrombin-AT III complex, a process that requires heparin. AT III inhibits all known coagulation pathways, including thrombin, factors Xa, XIa, XIIa, and IXa as well as

inhibiting fibrin formation. Without heparin, AT binds to endothelial surfaces and functions as an anticoagulant on its own.

AT III also has two antiinflammatory mechanisms of action. First, it promotes prostacyclin release from endothelial cells, thereby reducing the expression of adhesion molecules on endothelial cells, inhibiting proinflammatory cytokine production and platelet aggregation. AT III also inhibits the inflammatory signal transduction in endothelial cells. Thus, AT directly alters inflammatory processes and attenuates lung inflammation and edema after inhalation and/or cutaneous thermal injury.

Commercially available AT comes in two forms: plasma-derived and recombinant. One plasma-derived AT product is Thrombate®, produced by Bayer. Recombinant AT (rhAT) is made on a large scale in the milk of transgenic goats and is available as ATryn® from GTC Biotherapeutics. The two forms

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of AT differ only in their affinity for heparin, which is higher in the recombinant form.¹

Most of the research investigating intravenous AT involves congenital AT III deficiency, the major cause of thrombophilia, leading to acute deep venous thromboses that are not amenable to heparin therapy.² The majority of clinical trials are in patients with sepsis and disseminated intravascular coagulation, with improved xenograft transplant survival theorized to be due to the prevention of systemic coagulopathy.³ Thermal injury represents acquired AT deficiency, due to a combination of factors including increased consumption during disseminated intravascular coagulation, systemic inflammatory response syndrome/sepsis, blood loss during surgery and/or multiple lab draws, and reduced synthesis due to liver dysfunction. This acquired AT deficiency is a frequent event on post burn day 1 to 5 in patients with significant thermal injury and is an independent predictor of length of stay and mortality.⁴⁻⁶

In the largest clinical trial for acquired AT III deficiency (known as the KyberSept trial), Warren et al. performed a randomized controlled trial using high-dose AT III in severe sepsis.⁷ There were 2314 patients with severe sepsis. Patients treated with AT had a lower incidence of new onset pulmonary dysfunction but there were excess bleeding events in patients receiving heparin prophylaxis. Patients not getting heparin had an improved 90 day survival. In this study, the AT dose was not weight adjusted and burn patients were not included.

Murakami et al studied rhAT and pulmonary inflammation after smoke inhalation and pneumonia in sheep.⁸ In this prospective, randomized study, sheep received inhalation injury, inhalation injury with rhAT, or inhalation injury with rhAT plus pseudomonas. Sheep who received rhAT at 100 μ /kg for 24 hours had decreased airway obstruction by casts. They maintained their blood pressure and urinary outputs but the pulmonary shunt fraction was not helped.

In a randomized, double-blind, placebo-controlled human study, Leitner et al studied 30 healthy male volunteers.⁹ Half of the patients were given infusions of rhAT to increase AT levels to 200 and 500% of normal, followed by infusions of endotoxin. AT dose dependently decreased tissue factor-triggered coagulation as well as IL-6 release in those subjects receiving AT.

Kowal-Vern et al have performed several small studies involving AT deficiency in burn patients.¹⁰⁻¹³ In one study where patients chose whether to receive AT(H), nine patients with burns $\geq 20\%$ TBSA $\pm$ inhalation injury who elected to receive AT(H) had improved pulmonary function compared to nine pa-

tients who received standard therapy alone. In another study of two pediatric patients with burns of 56 and 83% TBSA who received AT(H) every 8 hours to maintain AT plasma levels at 200%, burn wound excision was virtually bloodless. There were no untoward effects from the AT(H). Most recently Kowal-Vern et al investigated AT levels in burn patients who developed intraabdominal hypertension or abdominal compartment syndrome. Although nonsurvivors had decreased plasma levels of AT, there was no difference in the amount of AT levels in peritoneal fluid between survivors and nonsurvivors.

In the only large study investigating AT deficiency and its relationship to severe burns, Niedermayr et al investigated 201 consecutive patients with severe burns.¹⁴ By post burn day 2, 41% had deficient AT levels and overall, 54% developed AT deficiency $\leq 70\%$ normal. Patients received substitution AT therapy by continuous infusion to maintain physiological activity of 70 to 120%. TBSA and inhalation injury showed a significant correlation with the severity of AT deficiency. Age and full thickness burn size did not relate to AT deficiency but AT deficiency was an independent predictor of length of stay and mortality. Unfortunately, Niedermayr et al did not provide us with significant details of the study such as burn size, time frame over which the study was conducted, number of operative interventions, or length of stay.

CONCLUSIONS

AT deficiency after burn injury has been associated with poor outcomes after burn injury in humans and burn/inhalation injury in an animal model. Repletion of AT thus has the potential to improve survival and decrease the inflammatory response after inhalation injury.

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Proposed Multicenter Studies

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The use of systemic antiinflammatory agents in the treatment of inhalation injury differ based on the results of previous studies. Although anti-thrombin III (AT) had both animal and clinical investigation in inhalation injury and burns, the evaluation of vitamin C's potential role in treating inhalation injury is less clear. Below are two proposal recommendations from each of the authors.

Proposal 1: Evaluation of Vitamin C Use in an Ovine Model of Inhalation Injury

Rationale. We know that part of the pathophysiology of smoke inhalation injury is inflammatory in nature with probable oxidative damage as a major component. However, we do not know enough about the potential effects of treatment with antioxidants, and in particular vitamin C. Vitamin C holds excellent prospects as a candidate antioxidant following smoke inhalation for two reasons, first, it is presumed to be quite safe with a very low risk profile, and second, it is already used in high doses in many burn centers during resuscitation from severe burn based on the studies of Tanaka. However, at this point we simply do not have enough preclinical

justification for a trial of vitamin C treatment for smoke inhalation injury.

Specific Aim. To determine the efficacy of vitamin C treatment in smoke inhalation injury alone and in combination with severe burn in a sheep model.

Hypothesis. Vitamin C therapy will be associated with decreased resuscitation volumes, decreased extravascular lung water, and improved ventilatory and lung inflammatory parameters.

Methods. Vitamin C will be administered to sheep with combined burn/smoke inhalation injury during the resuscitative phase. The initial animal study will determine the optimal dose of vitamin C for use in a sheep model of burn/inhalation injury. Subsequent animal studies will compare outcomes of sheep treated with vitamin C vs sham and control groups.

Comments

Data from these studies might be used to design a clinical trial in patients to determine the utility of vitamin C in the abrogation of lung injury in victims of smoke inhalation with and without severe burn. Such a study would ideally be multi-center with stratification for severity of injury with endpoints of mortality, resuscitation volume, morbidity events such as abdominal compartment syndrome, fasciotomies, renal failure, and colloid use. Specific lung parameters should be an index of oxygenation, anatomic airway changes, ventilator-free days, and perhaps a 'lung status' composite endpoint devised by the investigators.

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Proposal 2: Randomized Trial of AT Use in Inhalation Injury

AT is a natural anticoagulant which neutralizes activated serine proteases and inhibits the inflammatory process as it complexes with thrombin and removes it from circulation. The microthrombi inhibition may assist healing and/or maintain more vascularized subcutaneous tissues. Severe thermal injury leads to a loss of interstitial body fluids, inflammation, and coagulation + fibrinolysis leading to DIC. AT loss equates to a thrombin excess with the attendant inflammation and microvascular edema. The next logical step is conducting a prospective, randomized, double-blinded, adequately powered study investigating the effect of AT on defined end-points and patient outcomes.

Specific Aim. The specific aim of the proposal is to determine if AT improves lung function and decreases mortality after inhalation injury.

Hypothesis. Patients receiving AT will have a statistical decrease in P/F ratios, ventilator days, pneumonias, organ failure, and mortality compared with patients not receiving AT.

Methods. This prospective, randomized, double-blinded study will involve 200 patients (100 patients in each arm) and 15 to 20 burn centers. Study inclusion criteria include: $\geq 20\%$ TBSA burn and/or inhalation injury, ages 2 to 80 years, plasma AT levels $\leq 70\%$ normal, admission to the burn center within 24 hours of injury, and study enrollment within 36 hours of injury. Study exclusion criteria would be pregnancy, coagulation disorders, and any comorbidities affecting interpretations of AT levels such as cancer/chemotherapy, transplant, stroke, CHF,

HIV, Hepatitis B & C, or congenital heart disease. Patients at each participating burn center will be randomized to either receive AT or a placebo, and only the dispensing pharmacist will have knowledge of what the patient is receiving. Those patients in the AT group will receive AT IV every 8 hours to maintain AT plasma levels @ 200% of normal. The initial units required will be calculated according to the formula: units required = ([desired-baseline AT level] $\times$ admit weight in kg)/1.4. The next nine doses will be calculated at 2/3 loading dose. The lyophilized AT (H) concentrate is reconstituted in 250 ml NS that is infused over 1 hour. Patients in both groups will have blood collected every 8 hours on study days 1 to 4.

Study Endpoints. Study endpoints will evaluate resource-based outcomes: length of stay, costs/charges, and intensive care unit procedures required. Companies who produce AT are the logical source to provide funding for this study, which is anticipated to require 18 months for completion. The estimated study cost is \$2.5 million.

Comments

This proposed study illustrates several common challenges for inhalation injury researchers. First, multiple centers will be needed for any definitive clinical outcome study in inhalation injury. Second, the costs associated with such studies are extremely high, making meticulous study design and conduct paramount. Third, the extent of cutaneous burn injury may well impact study outcomes and needs to be included in the stratification scheme and data analysis. Finally, this study will need to be prioritized with other inhalation and burn trials.