## Title

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# VITAMIN A TREAMENT FOR SEVERE SEPSIS IN HUMANS; A PROSPECTIVE RANDOMINZED DOUBLE BLIND PLACEBO-CONTROLED CLINICAL TRIAL

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## Abstract

**Purpose:** To test the benefits of Vitamin A treatment in patients with sepsis on length of time in ICU, days on Ventilator, days on intravenous blood pressure support and 28-day mortality. The trial was prospective, randomized and double-blind. As part of a larger sepsis trial, 64 patients with sepsis were randomized to receive either 100,000 IU of Vitamin A intramuscular or placebo over 7-days. Data analysis was by ANOVA with two tailed test and $p<0.05$ as significant.

**Results:** The mean age was 51±2 (mean± SEM) with 54% female. Groups were well matched with regards to APACHE III score, WBC count, and incidence of bacteremia. In addition, all patients had an ACTH stimulation test using 250 mcg of ACTH IV and serum cortisol was measured at time 0, 30 and 60 minutes. Baseline cortisol of 24.6±1 mg/dl increased to 41±2 mg/dl at 30 minutes and 49±2 at 60 minutes. There was no significant difference between the groups. All cortisol responses were greater than 12.9 mg/dl.

Serum Vitamin A level was below normal in 54% of the patients. After randomization, 100,000 IU of Vitamin A daily was given to 32 patients and blinded placebo was given daily to 32 patients for seven days. This was administered as a 1 cc injection of either medication or placebo and was blinded from all but the research pharmacist. The number of days in the ICU was slightly, but not significantly reduced ($p=0.39$) by approximately 2 days in the Vitamin A treated patients. The average number of days on blood pressure agents and the day on ventilator were similar. The 28-day mortality rates were similar between the two groups (28 vs 34% placebo vs Vitamin A group).

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CONFLICT OF INTEREST STATEMENT:

The authors do not have any conflict with manufacture of Aquasol A, the pharmaceutical company that provided the product or any other aspects of this research paper.

Seven days of high dose intramuscular Vitamin A treatment in patients with sepsis where approximately 50% were vitamin A deficient had no benefit in adults with sepsis.

## INTRODUCTION

Vitamin A deficiency predisposed to Staphylococcus aureus infection in animals, which may be due to a reduction in complement lysis activity (1). The clearance of endotoxin may be improved (33 vs 67 minutes) in animals given Vitamin A treatment (2). Sepsis is known to increase urinary retinol loss as over 5 times the 2011 Dietary Reference Intake (5000 IU per day) (3). A large proportion of septic patients (65–81%) have retinal blood levels below the lower limit of a normal reference level (4,5). Enteral nutrition with high levels of antioxidants including Vitamin A at 11,910 IU per liter reduced ICU stay in patients with sepsis (6). This study was to test if additional vitamin A (100,000 IU per day) had an effect on 28-day mortality, ICU length of stay, days of pressors or days on ventilator.

## METHODS

Prospective, randomized, double blind, placebo controlled clinical trial conduction at Harbor-UCLA Medical Center with Internal Review Board (IRB) approval. Simplified Acute Physiology Score (APACHE III) was obtained on day of entry into the study and at day 14. ACTH (Cortropin) stimulation test (250 mcg) was administered intravenously (IV) at time 0 and samples drawn for cortisol at time 0, 30 and 60 minutes. Lab samples were obtained on entry into the study and prior to the first dose on blinded medication. Retinol samples were light protected and measured by High Performance Liquid Chromatography (HPLC). Other assays were determined by the hospital laboratory.

Entry criteria required that patients meet the criteria for severe sepsis or septic shock. Patients were randomized by the pharmacist based on a random table of numbers. Blood stream infection, days in ICU, days on ventilator and days on presser agents were measured both before entry into study and during the stay in the ICU. Aquasol Vitamin A 100,000 IU (NDC 0186 4239–62) or placebo was administered in covered syringes. All patient who were randomized completed the study.

Statistical analysis was by ANOVA with correction for multiple comparisons. Comorbidities were compared between groups for age, gender, number of Intensive Care Unit (ICU) days before randomization, number of ventilatory days, number of days on pressure agents, temperature, blood pressure, pulse, respiratory rate, White Blood Cell (WBC), creatinine, glucose, albumin, bilirubin total, body weight. Nearly 50% of patients required ventilator support. Mortality data was taken from hospital survival at both 14 days and 28 days of hospital stay. A two tailed p value $<0.05$ was used for determining significance, with correction for multiple comparisons. Data was expressed as mean± SEM.

## RESULTS

The mean age was 51±2 (mean± SEM) with 54% female. Heart rate (102±4 vs 96±4), systolic blood pressure (113±4 vs 117±4) diastolic blood pressure (60±3 vs 62±4), and temperature (37.8±0.3 vs 37.6±0.3) were similar in the placebo treated and Vitamin A

treated patients at baseline. All patients had an ACTH stimulation test using 250 mcg of ACTH IV and serum cortisol was measured at time 0, 30 and 60 minutes. Baseline cortisol of 24.6±1 mg/dl increased to 41±2 mg/dl at 30 minutes and 49±2 at 60 minutes. There was no significant difference between the groups. All but one persons cortisol response were greater than 12.9 mg/dl. The one person with a cortisol response of 12.0 mg/dl was randomized by mistake into the vitamin A treatment arm. Serum Vitamin A level was below normal in 54% of the patients tested (n=35). Unfortunately, samples from 28 patients were not protected from light and could not been measured as retinol (vitamin A) is light sensitive. Vitamin A levels were 30±4 mcg/dl in the placebo treated and 41±8 mcg/dl in the vitamin A treated group (NS). Urine retinol was measured in a subgroup of the randomized patients and averaged. Placebo treated patients lost 3064±924 IU per gram urinary creatinine per day, and vitamin A treated patients lost 2453±1034 IU per gram of urinary creatinine per day, NS). Likewise, urinary cortisol was measured and found to be similar in both groups (140±22 vs 111±16 umol/gm creatinine) respectively.

After randomization, 100,000 IU of Vitamin A was given daily for 7 day to 32 patients and placebo was given to 32 patients. This was administered as a 1 cc intra-muscular injection of either medication or placebo and was blinded from all but the research pharmacist.

Table 1 describes the two groups with regard to baseline APACHE III score, baseline labs, days in ICU, days on pressers, days on ventilator and percent of patients with bacteremia. There was no significant difference between the two groups for any of the measured variables prior to administration of the study medication.

Table 2 lists the outcome measurements. Serum albumin measured as part of the APACHE III score was increased in the vitamin A group as compared to the placebo group at Day 14 (See Table 2). The number of days in the ICU was slightly, but not significantly (p=0.13) reduced by approximately 2 days in the Vitamin A treated patients. The average number of days on blood pressure agents, stay in the ICU and days of ventilator were similar between the Vitamin A and Placebo treated groups. The 14-day APACHE score, 14-day mortality and the 28-day mortality were similar between the two groups (See Table 2). The slightly higher mortality rate in the vitamin A group was due to 3 additional deaths. Seven days of high dose Vitamin A Treatment in patients with sepsis where approximately 50% were vitamin A deficient appeared to have no benefit in adults with sepsis.

## DISCUSSION

Meta-analysis of seven trials suggests that vitamin A supplementation reduces sepsis mortality or oxygen requirements at one month in infants (7). In adults with Adult Respiratory Distress Syndrome (ARDS), the antioxidant formula had no effect on ICU mortality but was associated with a reduction in length of stay in the ICU (15 vs 24 days, Vitamin A vs placebo) (6). However, our prospective randomized double blind data failed to show a significant reduction in ICU stay (6.0 vs 7.9, Vitamin A vs Placebo, p = 0.39). The slightly higher mortality rate seen in the Vitamin A group may explain the borderline reduction in ICU length of stay, as it was not adjusted for slight increase in ICU mortality as 3 additional patients given Vitamin A died by Day 14 vs placebo (p=0.083).

Administration of Vitamin A to patients did not increase urinary vitamin A loss. It was associated with an increase in serum albumin at day 14. However, 14 day mortality and 28-day mortality was not reduced. Nor were there any other major clinical parameters improvement noted in the patient with severe sepsis.

## CONCLUSION

The number of days in the ICU was slightly, but not significantly (p=0.39) reduced in Vitamin A treated patients. The average number of days on pressors, the number of days on the ventilator and the 28-day mortality rate were also not significantly reduced in patients randomized to receive intramuscular Vitamin A therapy. Vitamin A treatment in septic adult patients failed to significantly reduce the number of days in the ICU, number of days on the ventilator, number of days on pressor agents or 28-day mortality. Seven days of high dose Vitamin A treatment appears to have no benefit in adult ICU patients with sepsis.

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Kea Osea was responsible for the data management, analysis and interpretation for the abstract presentation. He also contributed to the writing of draft manuscript. Lavanya Cherukuri and Gail Gewirtz helped with data verification, writing and editing the final manuscript. Dr. Tayek was responsible for the design, funding, IRB approval, implementation, completion, statistical analysis and manuscript completion.

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## APPENDIX 1:: Flow Chart

Flow Chart: 200 hospitalized patients were screened for sepsis and 124 were consented for study

(76 did not meet entry criteria or refused to give consent)

A 250 mcg ACTH stimulation test was performed in 124 patients and 63 were considered to have a normal ACTH cortisol axis (63 patients had a plasma cortisol level above 19.9 ug/dl and the increase was > 12.9 ug/dl after 30 or 60 mins of ACTH administration).

Of the 64 patients enrolled into the study, 32 were randomized to treatment and 32 to placebo.

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**Table 1:**

| **Demographic characteristics (n= 64)** | **Placebo (n= 32)** | **Vitamin A (n=32)** |
|---|---|---|
| Age (Years) | 53 ± 17 | 51 ± 15 |
| Gender (Female %) | 62 | 44 |
| Ethnicity (n) | | |
| White | 5 | 5 |
| Hispanic/Latino | 14 | 17 |
| African-American | 8 | 5 |
| Other | 5 | 5 |
| Systolic Blood Pressure (SBP) | 113 ± 23 | 118 ± 21 |
| Diastolic Blood Pressure (DBP) | 60 ± 14 | 62 ± 12 |
| Heart Rate | 102 ± 19 | 97 ± 21 |
| Respiratory Rate | 23 ± 7 | 19 ± 5 |
| Temperature | 37.8 ± 0.7 | 37.6 ± 0.9 |
| WBC | 19.3 ± 14.7 | 14.5 ± 7.6 |
| Hematocrit (Hct) | 21.8 ± 13.6 | 21.1 ± 13.9 |
| Creatinine | 1.8 ± 1.5 | 1.5 ± 1.7 |
| Serum Glucose | 166 ± 79 | 157 ± 78 |

Data presented as mean ± SD or n (%)

**Table 2:**

Baseline Data on Day 1 of Study

| Groups | APACHE | Cortisol | Albumin | Bacteremia | Days in ICU | Days on Pressors | Days on Ventilator |
|---|---|---|---|---|---|---|---|
| Placebo | 45±4 | 25.7±9.1 | 1.8±0.1 | 22% | 5.8±2.8 | 0.6±0.2 | 3.8±1.9 |
| Vitamin A | 44±5 | 24.3±12.9 | 2.1±0.1 | 22% | 3.9±1.1 | 1.0±0.4 | 3.1±1.0 |

**Table 3:**

Day 14 and 28 data study data (end of study)-Pubmed

| Groups | APACHE III (day 14) | 14-Day Mortality | Day 14 Albumin | Days in ICU | Days on Pressors | Days on Ventilator | 28-Day Mortality |
|---|---|---|---|---|---|---|---|
| Placebo | 41±5 | 22±7% | 2.1±0.1 | 7.9±1.1 | 1.5±0.6 | 4.5±1.0 | 28±8% |
| Vitamin A | 40±6 | 31±8% | 2.7±0.1 * | 6.0±1.0 # | 1.7±0.7 | 6.3±1.5 | 34±9% |

* $p < 0.05$,

# $p = 0.39$