Sepsis Tedavisinde Hidrokortizon, C vitamini, Tiamin

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YEDİTEPE ÜNİVERSİTESİ HASTANESİ

TÜRK İÇ HASTALIKLARI UZMANLIK DERNEĞİ 1995

TDCY

ESICM EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

KEPAN KLİNİK ENTERAL PARENTERAL NÜTRİSYON DERNEĞİ


Marik Cocktail:
Vitamin C 1.5g IV q6h
Hydrocortisone 50 mg IV q6h
Thiamine 200mg IV q12h
Infused, not stirred.

- Tartışma
- Bu

CHEST

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

PODCAST

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP

BACKGROUND: The global burden of sepsis is estimated as 15 to 19 million cases annually, with a mortality rate approaching 60% in low-income countries.

METHODS: In this retrospective before-after clinical study, we compared the outcome and clinical course of consecutive septic patients treated with intravenous vitamin C, hydrocortisone, and thiamine during a 7-month period (treatment group) with a control group treated in our ICU during the preceding 7 months. The primary outcome was hospital survival. A propensity score was generated to adjust the primary outcome.

RESULTS: There were 47 patients in both treatment and control groups, with no significant differences in baseline characteristics between the two groups. The hospital mortality was 8.5% (4 of 47) in the treatment group compared with 40.4% (19 of 47) in the control group ($P < .001$). The propensity adjusted odds of mortality in the patients treated with the vitamin C protocol was 0.13 (95% CI, 0.04-0.48; $P = .002$). The Sepsis-Related Organ Failure Assessment score decreased in all patients in the treatment group, with none developing progressive organ failure. All patients in the treatment group were weaned off vasopressors, a mean of 18.3 ± 9.8 h after starting treatment with the vitamin C protocol. The mean duration of vasopressor use was 54.9 ± 28.4 h in the control group ($P < .001$).

CONCLUSIONS: Our results suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine, are effective in preventing progressive organ dysfunction, including acute kidney injury, and in reducing the mortality of patients with severe sepsis and septic shock. Additional studies are required to confirm these preliminary findings.

CHEST 2017; 151(6):1229-1238

Sepsis / septik şok hastaları

Sıvı replasmanı, antibiyotik, vazopressör, inotrop, DMAH, Nutrisyon,RRT,

47 hasta , tedavi grubu

- Ocak 2016 –Temmuz 2016
- Prokalsitonin > 2ng/ml
- Hidrokortizon 50 mg x 4 , 7 gün
- C vitamini 1,5 gr x4 4 gün
- Thiamin 200 mg x2 4 gün

- Standart tedaviler

47 hasta kontrol grubu

- Haziran 2015- Aralık 2015
- Prokalsitonin < 2 ng / ml

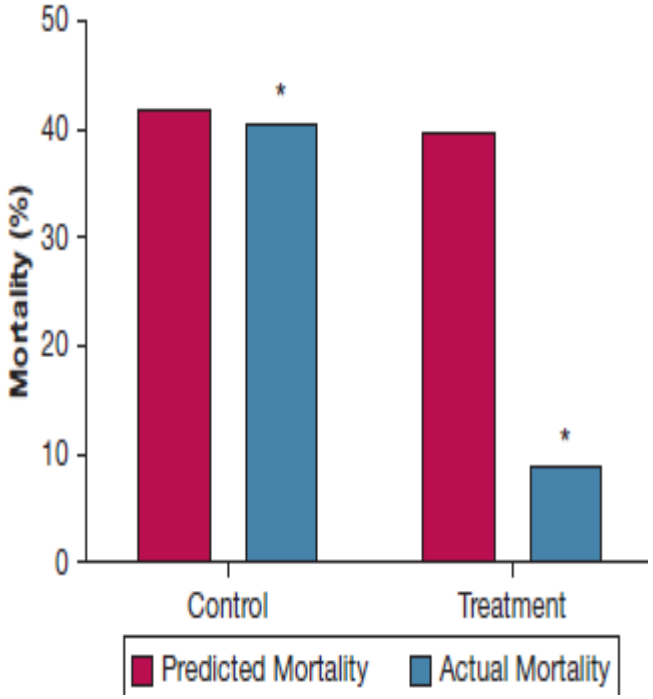
- Standart Tedaviler

Baseline Characteristics of Treated and Control Patients

Variable	Treated (n = 47)	Control (n = 47)
Age, mean ± SD, y	58.3 ± 14.1	62.2 ± 14.3
Sex, male, No. (%)	27 (57)	23 (49)
Comorbidities, No. (%)		
None	2 (4)	1 (2)
Diabetes	16 (34)	20 (42)
Hypertension	20 (43)	25 (53)
Heart failure	15 (32)	16 (34)
Malignancy	5 (11)	7 (15)
COPD	8 (17)	7 (15)
Cirrhosis	6 (13)	3 (6)
CVA	8 (17)	5 (11)
CRF	7 (15)	8 (17)
Morbid obesity	6 (13)	8 (17)
Immunocompromised[a]	6 (13)	4 (9)
Drug addiction	5 (11)	5 (11)
Primary diagnosis, No. (%)		
Pneumonia	18 (38)	19 (40)
Urosepsis	11 (23)	10 (21)
Primary bacteremia	7 (15)	7 (15)
GI/biliary	6 (13)	6 (13)
Other	5 (11)	5 (11)
Mechanical ventilation, No. (%)	22 (47)	26 (55)
Vasopressors, No. (%)	22 (46)	22 (46)
Acute kidney injury, No. (%)	31 (66)	30 (64)
Positive blood cultures, No. (%)	13 (28)	13 (28)
WBC,[b] mean ± SD, × 10^9	20.6 ± 13.5	17.1 ± 13.4
Lactate, mean ± SD, mM	2.7 ± 1.5	3.1 ± 2.8
Creatinine,[c] mean ± SD, mg/dL	1.9 ± 1.4	1.9 ± 1.1
Procalcitonin, median and IQR, ng/ml	25.8 (5.8-93.4)	15.2 (5.9-39.0)
Day 1 SOFA, mean ± SD	8.3 ± 2.8	8.7 ± 3.7
APACHE II, mean ± SD	22.1 ± 6.3	22.6 ± 5.7
APACHE IV, mean ± SD	79.5 ± 16.4	82.0 ± 27.4
Predicted mortality, mean ± SD	39.7 ± 16.7	41.6 ± 24.2

There were no significant differences in baseline characteristics between groups. APACHE = Acute Physiology and Chronic Health Evaluation; CRF = chronic respiratory failure; CVA = cerebrovascular accident; IQR = interquartile range; SOFA = Sepsis-Related Organ Failure Assessment.
[a]HIV infection, neutropenia, post-transplantation, and so on.
[b]Excluding neutropenic patients.
[c]Excluding patients with chronic renal failure.

Bazal karekteristikler bakımından fark yok



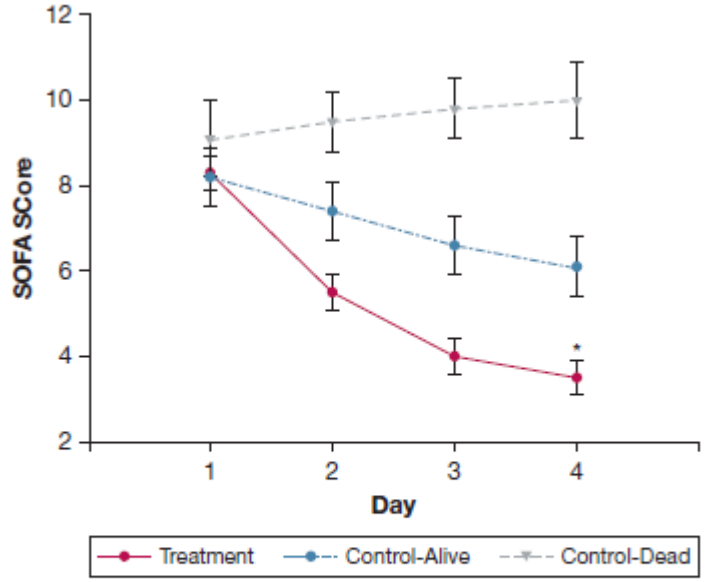


Figure 3 – *Time course of the SOFA score over the 4-day treatment period in the treatment group and in the control group survivors and nonsurvivors. *P < .001 for comparison of treatment group vs control group (see text). SOFA = Sepsis-Related Organ Failure Assessment.*

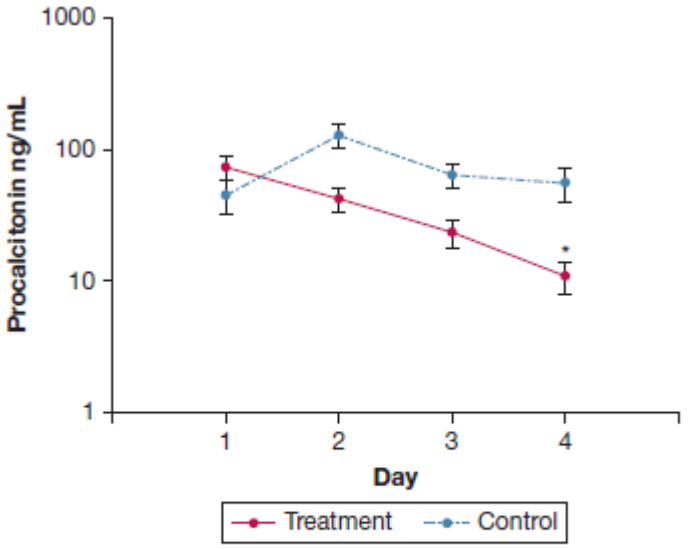


Figure 4 – *Time course of the PCT score over the 4-day treatment period in the treatment group and in the control group plotted on a semilog scale. *P < .001 for comparison of treatment group vs control group (see text). PCT = procalcitonin.*

Outcome and Treatment Variables

Variable	Treated (n = 47)	Control (n = 47)
Hospital mortality, No. (%)	4 (8.5)	19 (40.4)[a]
ICU LOS, median and IQR, d	4 (3-5)	4 (4-10)
Duration of vasopressors, mean ± SD, h	18.3 ± 9.8	54.9 ± 28.4 [a]
RRT for AKI, No. (%)	3 of 31 (10%)	11 of 30 (33%)[b]
ΔSOFA, 72 h	4.8 ± 2.4	0.9 ± 2.7[a]
Procalcitonin clearance, median % and IQR, 72 h	86.4 (80.1-90.8)	33.9 (−62.4 to 64.3)[a]

Bu çalışmaya yapılan itirazlar

confirm the findings of our study. Because of the lack of clinical equipoise and the ethics of withholding a potentially lifesaving intervention, we were unable to initiate a randomized controlled trial in our center. Furthermore, while our observational study suggests that

- **Randomize kontrollü çalışma değildir**
- **Bu kombine tedaviye ilişkin ClinicalTrials.gov yoktur.**
- **C vit ile ilgili 1 çalışma vardır, thiamin ile ilg sonuç bildirilmemiştir.**
- **Baseline karekteristikleri farklıdır**
- **Uygun antibiyotiğin kullanılma zamanı bilinmiyor**
- **Kontrol grubunda 28 hastaya hidrokortizon verilmiştir.**
- **C vitamini güvenliği ve etkinliği için yeterli çalışma yoktur.**
- **Tek merkez, örneklem küçük, mevsimsel farklılık var.**
- **Hastane mortalitesi iyi tanımlanmamıştır, mortalite oranı taburculuk kriterlerinden etkilenmiş olabilir**

- Son yıllarda yoğun bakım araştırmalarına bakıldığında 15 yeni (tedavi / girişim) uygulamanın 8' inde zaman içinde mortalite artışı bildirilmiş ve vazgeçilmiştir.


Feature Articles

Mortality in Multicenter Critical Care Trials: An Analysis of Interventions With a Significant Effect*

Giovanni Landoni, MD[1]; Marco Comis, MD[2]; Massimiliano Conte, MD[3]; Gabriella Finco, MD[4]; Marta Mucchetti, MD[1]; Gianluca Paternoster, MD, PhD[5]; Antonio Pisano, MD[6]; Laura Ruggeri, MD[1]; Gabriele Alvaro, MD[7]; Manuela Angelone, MD[6]; Pier C. Bellomo, MD[1]; Speranza Bocchino, MD[1]; Giovanni Borghi, MD[1]; Tiziana Bove, MD[1]; Giuseppe Buscaglia, MD[8]; Luca Cabrini, MD[1]; Lino Callegher, MD[9]; Fabio Caramelli, MD[10]; Sergio Colombo, MD[1]; Laura Corno, MD[1]; Paolo Del Sarto, MD[11]; Paolo Feltracco, MD[12]; Alessandra Forti, MD[13]; Marco Ganzaroli, MD[2]; Massimiliano Greco, MD[1]; Fabio Guarracino, MD[14]; Rosalba Lembo, MSc[1]; Rosetta Lobreglio, MD[15]; Roberta Meroni, MD[1]; Fabrizio Monaco, MD[1]; Mario Musu, MD[16]; Giovanni Pala, MD[17]; Laura Pasin, MD[1]; Marina Pieri, MD[1]; Stefania Pisarra, MD[18]; Giuseppe Ponticelli, MD[6]; Agostino Roasio, MD[19]; Francesco Santini, MD[20]; Simona Silvetti, MD[1]; Andrea Székely, MD[21]; Massimo Zanobori, MD[1]; Maria Chiara Zucchetti, MD[22]; Alberto Zangrillo, MD[1]; Rinaldo Bellomo, MD[23]

*See also p. 1767.

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[18]Cardiac and Vascular Department, Casa di Cura Villa Verde, Taranto, Italy.
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ACELE ETMEYELİM

PulmCrit- Metabolic sepsis resuscitation: the evidence behind Vitamin C

March 27, 2017 by Josh Farkas — 109 Comments

MİTOKONDRİ ÇALIŞMIYORSA ÇABALAR BOŞA GİDEBİLİR

MAKRO RESUSSİTASYON KADAR METABOLİK RESUSSİTASYON ÖNEMLİDİR

Sepsis resuscitation generally focuses on hemodynamics. Rivers of ink have been spilled writing about oxygen delivery and fluid responsiveness. This is clearly important, but it's possible that our focus on easily [illegible] can deliver all the oxygen we want to the tissues, but if the mitochondria are failing it won't work.

Very brief overview of the scientific rationale

Vitamins become depleted during sepsis

Sepsis causes increased consumption of thiamine and Vitamin C:

- Vitamin C levels invariably fall during sepsis, sometimes dropping below the level of detection. Vitamin C deficiency correlates with multiorgan failure and death (Wilson 2009).
- Thiamine deficiency is common in sepsis, occurring in perhaps one-third of patients. This is associated with increased mortality (Manganese 2011).

Sepsiste thiamin ve c vitamininde ciddi eksiklik olur Mortalite artışı ile ilişkilidir.

İnflamatuar mediatörler C Vitamininin endotel içine alınmasını azaltmaktadır1

Neden C vitamini ?

Total vitamin C, ascorbic acid, and dehydroascorbic acid concentrations in plasma of critically ill patients[1–3]

Christopher J Schorah, Christopher Downing, Antonia Piripitsi, Louise Gallivan, Adel H Al-Hazaa, Marion J Sanderson, and Andrew Bodenham

Effect of patient variables on plasma total vitamin C and ascorbic acid concentrations in the intensive care unit (ICU) patients[1]

Variable	Total vitamin C	Ascorbic acid
	μmol/L	
Age		
<30 y (*n* = 9)	19.8 (13.9)	18.7 (13.1)
>75 y (*n* = 8)	13.7 (13.5)	8.3 (8.6)
Blood transfusion[2]		
None (*n* = 10)	12.1 (10.8)	9.9 (8.4)
Present (*n* = 7)	15.2 (10.8)	12.2 (9.3)
TPN		
None (*n* = 57)	14.5 (10.8)	12.4 (8.9)
Present (*n* = 5)	16.9 (10.3)	14.4 (9.3)
Days in ICU[3]		
≤2 d (*n* = 13)	20.6 (21.8)	17.8 (15.0)
≥8 d (*n* = 15)	12.2 (10.0)[4]	9.7 (8.7)[4]
Days after surgery[5]		
2 d (*n* = 8)	14.9 (11.2)	10.1 (9.3)
14 d (*n* = 8)	14.3 (10.9)	11.2 (9.5)

[1] $\tilde{x}$; median in parentheses.
[2] Postoperative patients only.

Concentration of plasma vitamin C metabolites in patients in the intensive care unit (ICU) compared with other patient groups[1]

Study group	Age	Total vitamin C	Ascorbic acid	Dehydroascorbic acid
	y	*μmol/L*	*μmol/L*	*μmol/L*
ICU (*n* = 37M, 25F)	60	11.0 (8–22)[2]	9.0 (5–15)[2]	1.4 (−0.8 to 2.9)
Healthy (*n* = 17M, 17F)	29	61.8 (55–72)	61.4 (56–68)	2.3 (−2.9 to 5.8)
Gastritis (*n* = 21M)	49	47.4 (28–57)	45.7 (29–57)	2.3 (0.6–2.9)
Diabetes (*n* = 15M, 9F)	66	44.9 (27–60)	41.5 (22–57)	2.8 (0.0–6.3)

[1] Median; interquartile range in parentheses.
[2] Significantly different from concentrations in all other groups, $P < 0.001$ (Wilcoxon's rank test).

1 Schorah, C. *Total vitamin C, ascorbic acid, and dehydroascorbic acid concentrations in plasma of critically ill patients. The American Journal of Clinical Nutrition, 63(5), 760–763.*

Vitamin C Eksikliği

- Normal plazma vitamin C : 23 to 100 µmol/L.
- Hipovitaminoz C <23 µmol/L
- Eksiklik <11 µmol/L

- Carr, A.C.; Rosengrave, P.C.; Bayer, S.; Chambers, S.; Mehrtens, J.; Shaw, G.M. Hypovitaminosis c and vitamin c deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit. Care 2017, 21, 300.

c vitamini ne yapıyor ?

Biofactors. 2009 ; 35(1): 5–13. doi:10.1002/biof.7.

Mechanism of action of vitamin C in sepsis: Ascorbate modulates redox signaling in endothelium

John X. Wilson*
Department of Exercise and Nutrition Sciences, University at Buffalo, Buffalo, NY, USA

Abstract

Circulating levels of vitamin C (ascorbate) are low in patients with sepsis. Parenteral administration of ascorbate raises plasma and tissue concentrations of the vitamin and may decrease morbidity. In animal models of sepsis, intravenous ascorbate injection increases survival and protects several microvascular functions, namely, capillary blood flow, microvascular permeability barrier, and arteriolar responsiveness to vasoconstrictors and vasodilators. The effects of parenteral ascorbate on microvascular function are both rapid and persistent. Ascorbate quickly accumulates in microvascular endothelial cells, scavenges reactive oxygen species, and acts through tetrahydrobiopterin to stimulate nitric oxide production by endothelial nitric oxide synthase. A major reason for the long duration of the improvement in microvascular function is that cells retain high levels of ascorbate, which alter redox-sensitive signaling pathways to diminish septic induction of NADPH oxidase and inducible nitric oxide synthase. These observations are consistent with the hypothesis that microvascular function in sepsis may be improved by parenteral administration of ascorbate as an adjuvant therapy.

IV askorbik asit mikrovaskuler fonksiyonları korur
Etki hızlı ve uzun sürelidir
Kapiller kan akımını düzeltir
Mikrovasküler permeabilite bariyerini iyileştirir
Vazokonstruktör ve vasodilatörlere arteryel yanıtı iyileştirir
Reaktif oksijen radikalleri temizler

Yüksek Doz C vitamininin Güvenle Kullanılabilirliği

- genel cerrahi (5)
- travmatik hasar (6)
- sepsis (4,8)
- pankreatit (9)
- yanık (10)
- ARDS (12)

hastalarında güvenle kullanılmış, yan etki bildirilmemiştir.

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Neden Kombinasyon ?

- Hidrokortizon ve C vitamini inflamatuar kaskadın birçok yerinde sinerjistik davranmaktadır. Hidrokortizon C vitamini transporterin, sitokine bağlı downregülasyonunu iyileştirir böylece C vitamininin hücre içi uptake i artar bu da glukokortikoid reseptör duyarlılığını iyileştirir

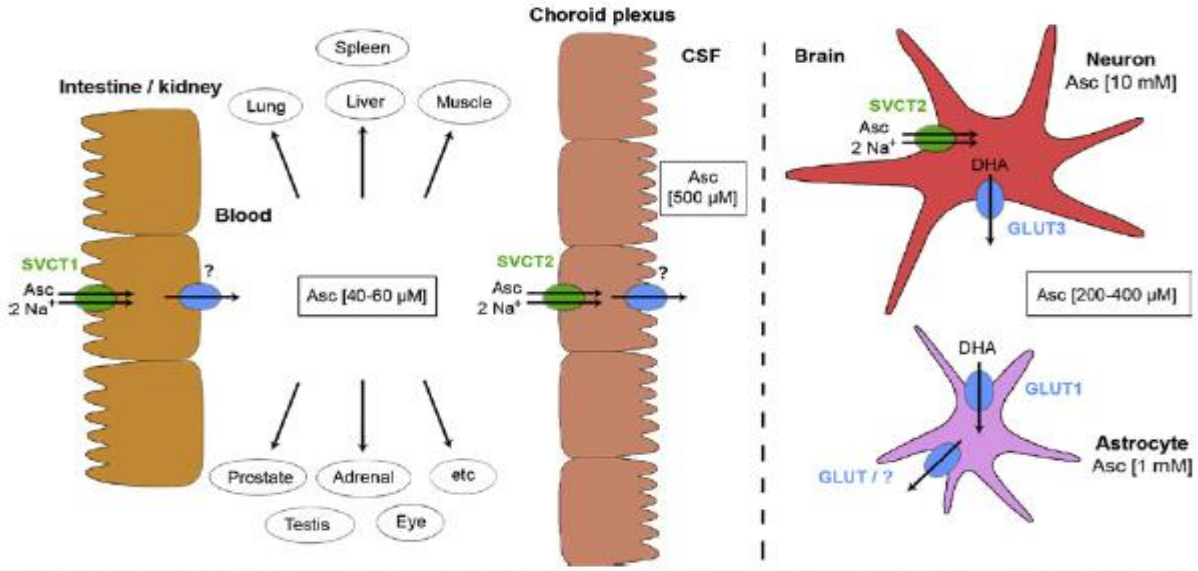
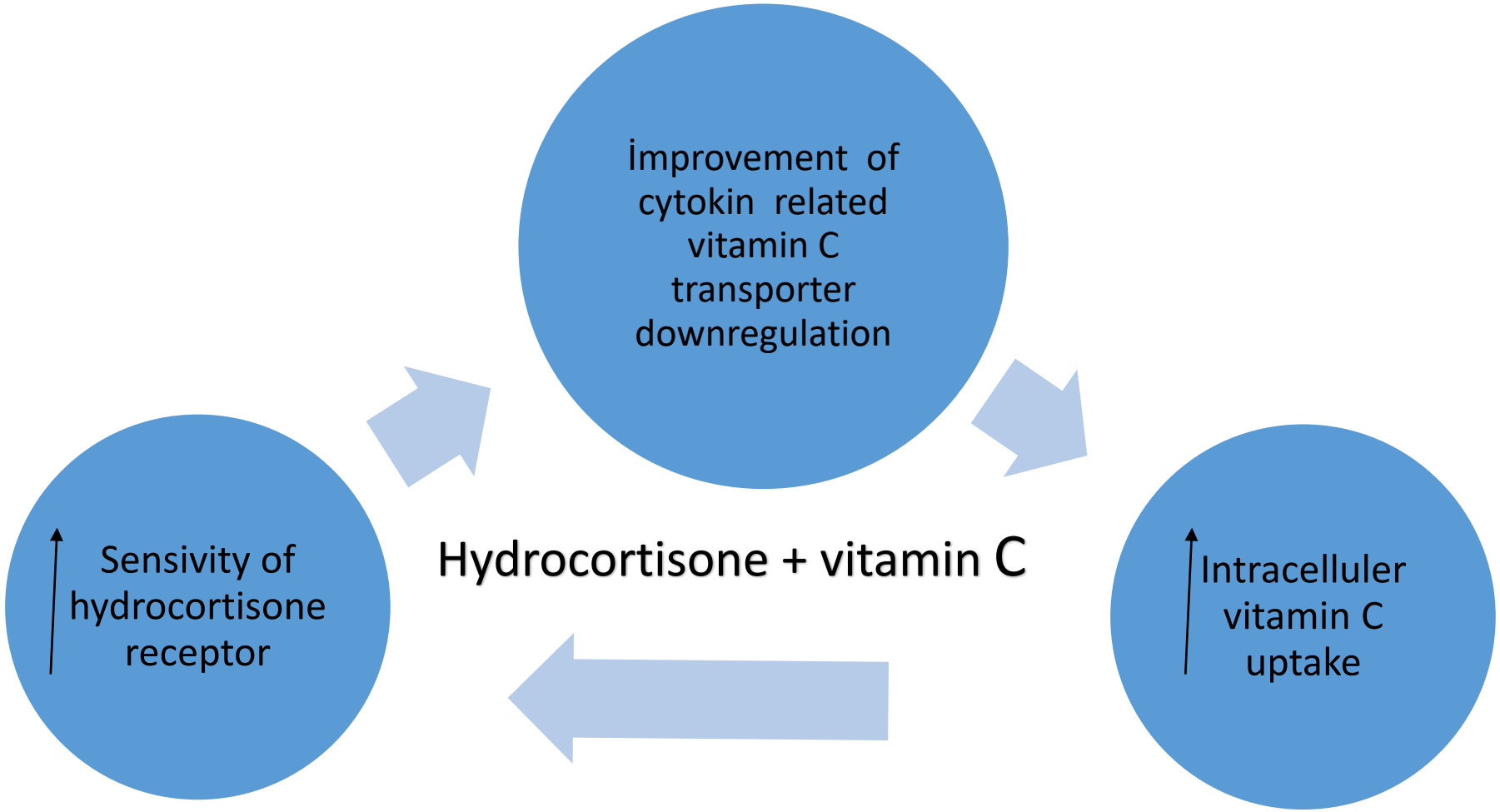


Figure 3 Whole body representation of the physiological roles of the SVCT1 and SVCT2 transporters. Expression and function of SVCT1 and SVCT2 is shown in different tissues and cell types of the human body. Transport pathways of vitamin C to brain and between specific cells of the brain are presented. See the color plate.


İmprovement of cytokin related vitamin C transporter downregulation
Sensivity of hydrocortisone receptor
Hydrocortisone + vitamin C
Intracelluler vitamin C uptake

[Original Research **Critical Care**]

CHEST

CrossMark

Hydrocortisone and Ascorbic Acid Synergistically Prevent and Repair Lipopolysaccharide-Induced Pulmonary Endothelial Barrier Dysfunction

Nektarios Barabutis, PhD; Vikramjit Khangoora, MD; Paul E. Marik, MD; and John D. Catravas, PhD

BACKGROUND: Sepsis refers to the dysregulated host immune response elicited by microbial infections resulting in life-threatening organ dysfunction. Sepsis represents a medical challenge, since it is associated with a rate of death as high as 60%. Septic shock is strongly associated with vascular dysfunction and elevated pulmonary capillary permeability. We recently reported that the combination of hydrocortisone (HC), ascorbic acid (vitC), and thiamine dramatically improves outcomes and reduces mortality in patients with sepsis. In the present study, we provide experimental evidence in support of the hypothesis that the combination of HC and vitC enhances endothelial barrier function.

METHODS: Human lung microvascular endothelial cells were exposed to lipopolysaccharide (LPS) in the absence or presence of HC and vitC.

RESULTS: LPS alone induced profound hyperpermeability, as reflected in decreased values of transendothelial electrical resistance. vitC alone did not exhibit barrier enhancement properties nor did it affect the LPS-induced hyperpermeability. Similarly, HC alone exhibited only a minor barrier-enhancing and protective effect. Conversely, the combination of HC and vitC, either as before or after treatment, dramatically reversed the LPS-induced barrier dysfunction. The barrier-protective effects of HC and vitC were associated with reversal of LPS-induced p53 and phosphorylated cofilin downregulation and LPS-induced RhoA activation and myosin light chain phosphorylation.

CONCLUSIONS: These data provide a novel mechanism of endothelial barrier protection and suggest one possible pathway that may contribute to the therapeutic effects of HC and vitC in patients with sepsis.

CHEST 2017; 152(5):954-962

KEY WORDS: barrier function; endothelial permeability; endothelium

Aynı Ekip

& Mikrovasküler endotel hücreleri , LPS ile karşılaştırdılar

& Transendotelial elektriksel rezistans azalmasını permeabilite artışı ile ilişkilendirdiler

& HC, C vit , HC+Cvit

Sadece C vit

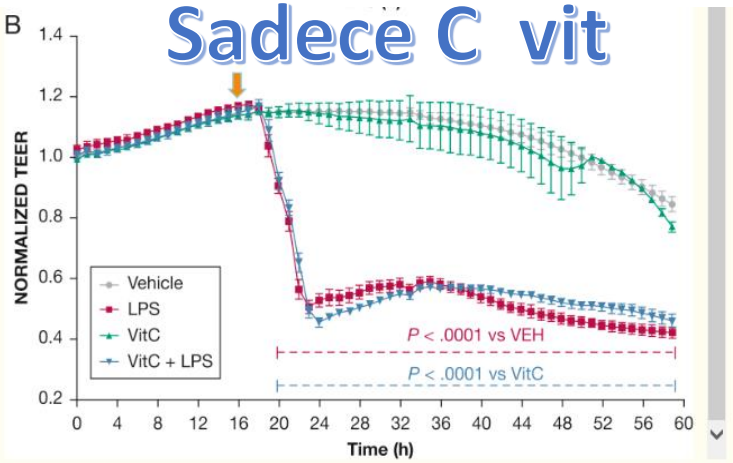


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Figure 1

Effect of vitC on endothelial barrier function. Vehicle (phosphate-buffered saline [PBS]) or vitC (250, 500, 1,000 μM) was added to the media of confluent HLMVEC monolayers at 0 hours. A, vitC did not cause a biologically significantly change in the TEER of the endothelial monolayers. B, Cells were pretreated for 16 hours with either vehicle (PBS) or vitC (1,000 μM) and were consequently exposed to LPS (0.5 endotoxin units/mL [arrow]). A gradual increase in endothelial permeability (reduced TEER) was observed in the LPS-treated cells of both groups (n = 3 per group; means ± SEM). HLMVEC = human lung microvascular endothelial cell; LPS = lipopolysaccharide; TEER = transendothelial resistance; VEH = vehicle; vitC = ascorbic acid.

Sadece HC

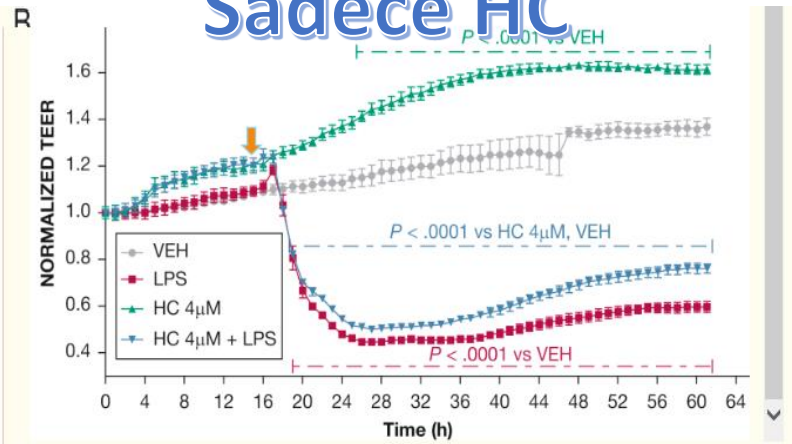

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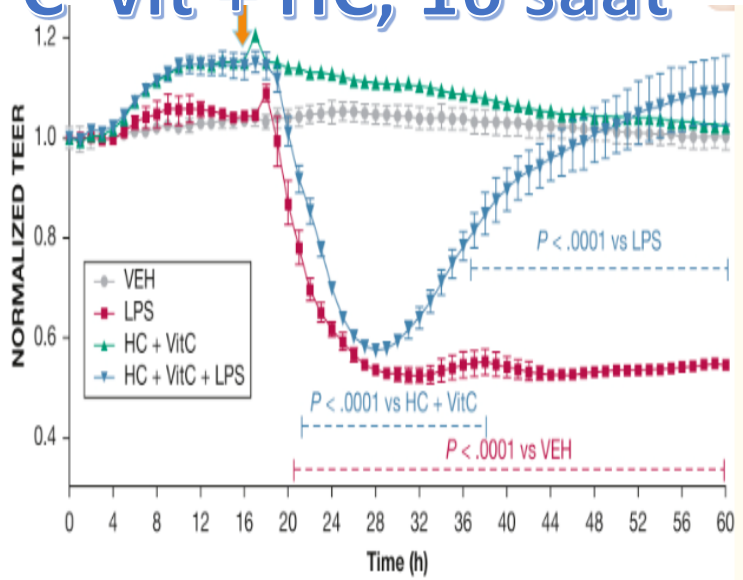
Figure 2

Effect of HC on endothelial barrier function. A, Vehicle (phosphate-buffered saline [PBS]) or HC (4 μM, 6 μM) was added to the media of confluent HLMVEC monolayers at 0 hours. HC in both concentrations caused a dose-dependent induction of TEER (n = 3 per group; means ± SEM). B, Cells were pretreated for 16 hours with either vehicle (PBS) or HC (4 μM) and were exposed to LPS (0.5 endotoxin units/mL). A gradual increase in endothelial permeability (reduced TEER) was observed in both groups of the LPS-treated cells (n = 4 per group; means ± SEM). HC = hydrocortisone. See Figure 1 legend for expansion of other abbreviations.

C vit + HC, 16 saat



C vit + HC hemen

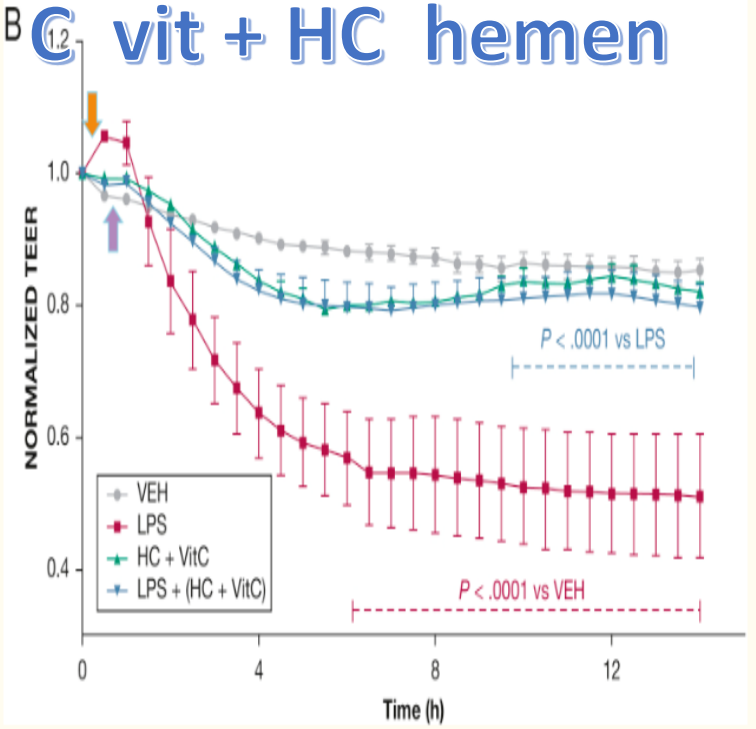


Figure 3

The effect of the combination of HC and vitC on LPS-induced hyperpermeability. HLMVECs were seeded on gold electrodes and allowed to reach confluence (time = 0). A, Cells were pretreated for 16 hours with either vehicle or a combination of vitC (1,000 μM) and HC (6 μM) and then exposed to LPS (0.5 endotoxin units/mL [arrow]). A gradual increase in endothelial permeability (reduced TEER) was observed in all groups receiving LPS. However, HLMVECs pretreated with vitC and HC experienced a complete restoration of barrier function 24 hours after LPS treatment. B, Confluent HLMVECs received LPS (0.5 endotoxin units/mL down arrow]) and 15 min later were treated with vehicle or a combination of vitC (1,000 μM) and HC (6,μM) (up arrow). HC + vitC completely prevented the LPS-induced decrease in TEER (n = 3 per group; means ± SEM). See Figure 1 and 2 legends for expansion of abbreviations.

Klinik olarak da sepsiste hidrokortizon ve C vitamini tek tek uygulandığında sonlanmalarda olumlu etki çok az olmuştur.

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure
The CITRIS-ALI Randomized Clinical Trial

JAMA. 2019;322(13):1261-1270. doi:10.1001/jama.2019.11825

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Plasebo ile C vitamini infüzyonu arasında organ yetmezliği skoru , inflamasyon ve vasküler hasar göstergeleri bakımından fark yoktur.

INTERVENTIONS Patients were randomly assigned to receive intravenous infusion of vitamin C (50 mg/kg in dextrose 5% in water, n = 84) or placebo (dextrose 5% in water only, n = 83) every 6 [illegible]

MAIN OUTCOMES AND MEASURES The primary outcomes were change in organ failure as assessed by a modified Sequential Organ Failure Assessment score (range, 0-20, with higher scores indicating more dysfunction) from baseline to 96 hours, and plasma biomarkers of inflammation ([illegible] vascular injury ([illegible] levels) measured at [illegible]

RESULTS Among 167 randomized patients (mean [SD] age, 54.8 years [16.7]; 90 men [54%]), 103 (62%) completed the study to day 60. There were no significant differences between the vitamin C and placebo groups in the primary endpoint of change in the modified Sequential Organ [illegible] from baseline to 96 hours (5.8 points in the vitamin C group [3 points] and from 10.3 to 6.8 in the placebo group [3.5 points]; difference, −0.10; 95% CI, −1.23 to 1.03; P = .86) or in C-reactive protein levels (54.1 vs 46.1 µg/mL; difference, 7.94 µg/mL; 95% CI, −8.2 to 24.11; P = .33) and thrombomodulin levels (14.5 vs 13.8 ng/mL; difference, 0.69 ng/mL; 95% CI, [illegible] .70) at 168 hours.

CONCLUSIONS AND RELEVANCE In this preliminary [illegible] patients with sepsis and ARDS, a 96-hour infusion of vitamin C compared with placebo did not significantly improve organ dysfunction scores or alter markers of inflammation and vascular injury. Further research is needed to evaluate the potential role of vitamin C for other outcomes in sepsis and ARDS.

Visual Abstract
Editorial page 1257
Supplemental content

HYPRESS (hidroko
Shock) çalışmasın
mortalite üzerine

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIEN

Effect of Hydrocortisone on Developn Among Patients With Severe Sepsis

The HYPRESS Randomized Clinical Tria

Didier Keh, MD; Evelyn Trips; Gernot Marx, MD; Stefan P. Wirtz, MD; Emad Abduljawwad, MD
Josef Briegel, MD; Christoph Engel, MD; Herwig Gerlach, MD, PhD, MBA; Anton Goldmann, M
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Table 2. Primary and Secondary End Points[a]

End Point	Placebo (n = 176)	Hydrocortisone (n = 177)	Total (N = 353)	*P* Value
Primary				
Septic shock, No./total No. (%) [95% CI]				
ITT population	39/170 (22.9) [17.2-30.0]	36/170 (21.2) [15.6-28.1]	75/340 (22.1) [17.9-26.9]	.70
PP population	33/156 (21.2) [15.4-28.4]	29/155 (18.7) [13.3-25.7]	62/311 (19.9) [15.8-24.8]	.59
Secondary				
Mortality, No./total No. (%) [95% CI]				
28 d	14/170 (8.2) [5.0-13.4]	15/171 (8.8) [5.4-14.0]	29/341 (8.5) [6.0-12.0]	.86
90 d	28/168 (16.7) [11.8-23.0]	34/171 (19.9) [14.6-26.5]	62/339 (18.3) [14.5-22.8]	.44
180 d	37/167 (22.2) [16.5-29.0]	45/168 (26.8) [20.7-34.0]	82/335 (24.5) [20.2-29.4]	.32
ICU	14/172 (8.1) [4.9-13.2]	13/171 (7.6) [4.5-12.6]	27/343 (7.9) [5.5-11.2]	.85
Hospital	22/172 (12.8) [8.6-18.6]	23/171 (13.5) [9.1-19.4]	45/343 (13.1) [10.0-17.1]	.86
LOS, median (IQR), d				
ICU	9 (6-17)	8 (5-15)	8 (5-16)	.23
Hospital	25 (16-40)	26 (16-46)	26 (16-43)	.36
Mechanical ventilation, No./total No. (%) [95% CI]	103/172 (59.9) [52.4-66.9]	91/171 (53.2) [45.8-60.5]	194/343 (56.6) [51.3-61.7]	.21
MV-free time, median (IQR), d	5 (2-7)	4 (2-7)	4 (2-7)	.34
RRT, No./total No. (%) [95%CI]	21/172 (12.2) [8.1-17.9]	21/171 (12.3) [8.2-18.0]	42/343 (12.2) [9.2-16.1]	.98
RRT-free time, median (IQR), d	7 (4-14)	6 (4-12)	7 (4-13)	.35
SOFA score until day 14, median (IQR)[b]	5.0 (3.5-6.8)	4.7 (3.5-6.5)	4.8 (3.5-6.6)	.69
Delirium, No./total No. (%) [95% CI]	25/102 (24.5) [17.2-33.7]	11/98 (11.2) [6.4-19.0]	36/200 (18.0) [13.3-23.9]	.01

Yüksek Doz C vitaminin İmmünite Üzerine Etkileri

- Kemotaksis ve lenfosit proliferasyonunu arttırır
- Eksikliğinde , natural killer hücrelerin bakteri öldürmesi gecikir, sitotoksik T hücre aktivitesi baskılanır
- Bakteriostatik etkisi de vardır. İnvitro çalışmalarda C vitamini varlığında bakterial replikasyon önemli oranda inhibe olur
- TNF' nin uyardığı hücre içi adhesion molekülleri üretimini inhibe eder, lökosit yapışkanlığı azalır, mikrosirkülasyon iyileşir
- Makrofaj ve T hücre fonksiyonlarını iyileştirir

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Yüksek Doz C vitaminin Mikrosirkülasyon Üzerine

- Zabet' in çalışmasında 6 saat ara ile 25 mg / kg C vitamini verilen da anlamlı azalma

Journal of Research in Pharmacy Practice

Original Article

Effect of high-dose Ascorbic acid on vaso septic shock

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ABSTRACT

Objective: Effects of ascorbic acid on hem evaluated in nonsurgical critically ill patie the effect of high-dose ascorbic acid on va in surgical critically ill patients with septic

Methods: Patients with septic shock who re arterial pressure >65 mmHg were assign ascorbic acid every 6 h or matching placel were considered as the primary outcomes and 28-day mortality has been defined as

Findings: During the study period, 28 patien dose of norepinephrine during the study p $P = 0.004$) and duration of norepinephrine ac $P = 0.007$) were significantly lower in th statistically significant difference was detec of ICU stay. However, 28-day mortality was the placebo group (14.28% vs. 64.28%, re

Conclusion: High-dose ascorbic acid may b therapy in surgical critically ill patients w ascorbic acid and the best time for its administration should be determined in future studies.

Received: January 2016
Accepted: February 2016

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Table 4: Primary and secondary outcomes of the study in ascorbic and placebo groups

Characteristics	Ascorbic acid group (n=14)	Control group (n=14)	P
Mean dose of norepinephrine (mcg/min) during the study period (72 h)	7.44±3.65	13.79±6.48	0.004
Mean dose of norepinephrine (mcg/min) during first 24 h (mcg/min)	6.51±3.53	12.58±5.99	0.003
Total dose of norepinephrine during the first 24 h (mcg)	156.42±84.81	302.14±143.85	0.003
Duration of norepinephrine administration (h)	49.64±25.67	71.57±1.60	0.007
Length of ICU stay (days)	21.45±10.23	20.57±13.04	0.85
28-day mortality	2 (14.28)	9 (64.28)	0.009

Data presented as mean±SD or n (%). SD=Standard deviation, ICU=Intensive Care Unit

Yüksek Doz C vitaminin Mikrosirkülasyon Üzerine

- Fawler' in çalışmasında şiddetli sepsis hastalarında C vitamininin infüzyonunun güvenliği çalışılmıştır. 28 hasta , Bir gruba 50 mg / kg / 24 saat, diğer gruba 200 mg / kg , 48 saat , toplam 96 saat tedavi uygulanmıştır. Yüksek doz C vitamini uygulanan grupta SOFA' da hızlı düşme olmuş kontrol grubunda azalma olmamıştır.

Fowler et al. Journal of Translational Medicine 2014, 12:32
http://www.translational-medicine.com/content/12/1/32

RESEARCH

Phase I safety trial of intrave patients with severe sepsis

Alpha A Fowler III[1*], Aamer A Syed[1], Shelley Knowlson[2], Robin S Christine A Farthing[4], Terri L Larus[4], Erika Martin[5], Donald F Brop Care Unit Nursing[2], Bernard J Fisher[1] and Ramesh Natarajan[1]

Abstract

Background: Parenterally administered ascorbic acid modulates experimental animal models. The objective of this randomized, d determine the safety of intravenously infused ascorbic acid in pa

Methods: Twenty-four patients with severe sepsis in the medical i intravenous infusions every six hours for four days of ascorbic a (200 mg/kg/24 h, n = 8), or *Placebo* (5% dextrose/water, n = 8). and tolerability, assessed as treatment-related adverse event fr for worsened arterial hypotension, tachycardia, hypernatremia, Organ Failure Assessment (SOFA) scores and plasma levels of a thrombomodulin were monitored.

Results: Mean plasma ascorbic acid levels at entry for the entire c Ascorbic acid infusion rapidly and significantly increased plasma observed in ascorbic acid-infused patients. Patients receiving asc scores while placebo patients exhibited no such reduction. Ascorbi biomarkers C-reactive protein and procalcitonin. Unlike placebo patients exhibited no significant rise, suggesting attenuation of

Conclusions: Intravenous ascorbic acid infusion was safe and well tolerated in this study and may positively impact the extent of multiple organ failure and biomarkers of inflammation and endothelial injury.

Trial registration: ClinicalTrials.gov identifier NCT01434121.

Keywords: Ascorbic acid, Biological markers, Clinical trials phase I as topic, Multiple organ failure, Organ dysfunction scores, Sepsis

Ascorbik asit

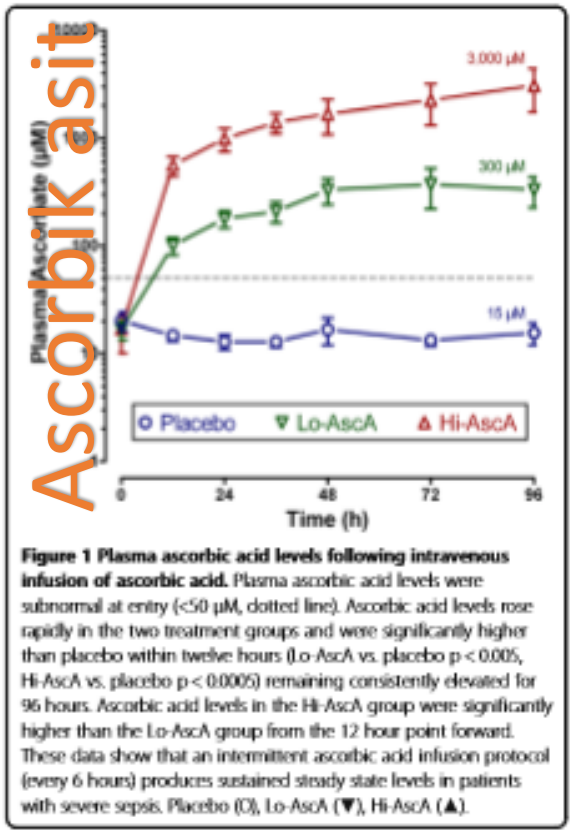


Figure 1 Plasma ascorbic acid levels following intravenous infusion of ascorbic acid. Plasma ascorbic acid levels were subnormal at entry (<50 μM, dotted line). Ascorbic acid levels rose rapidly in the two treatment groups and were significantly higher than placebo within twelve hours (Lo-AscA vs. placebo $p < 0.005$, Hi-AscA vs. placebo $p < 0.0005$) remaining consistently elevated for 96 hours. Ascorbic acid levels in the Hi-AscA group were significantly higher than the Lo-AscA group from the 12 hour point forward. These data show that an intermittent ascorbic acid infusion protocol (every 6 hours) produces sustained steady state levels in patients with severe sepsis. Placebo (○), Lo-AscA (▼), Hi-AscA (▲).

SOFA

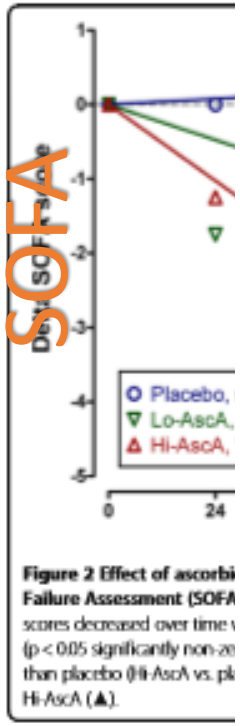


Figure 2 Effect of ascorbi Failure Assessment (SOFA scores decreased over time ($p < 0.05$ significantly non-z than placebo (Hi-AscA vs. pl Hi-AscA (▲).

Prokalsitonin CRP

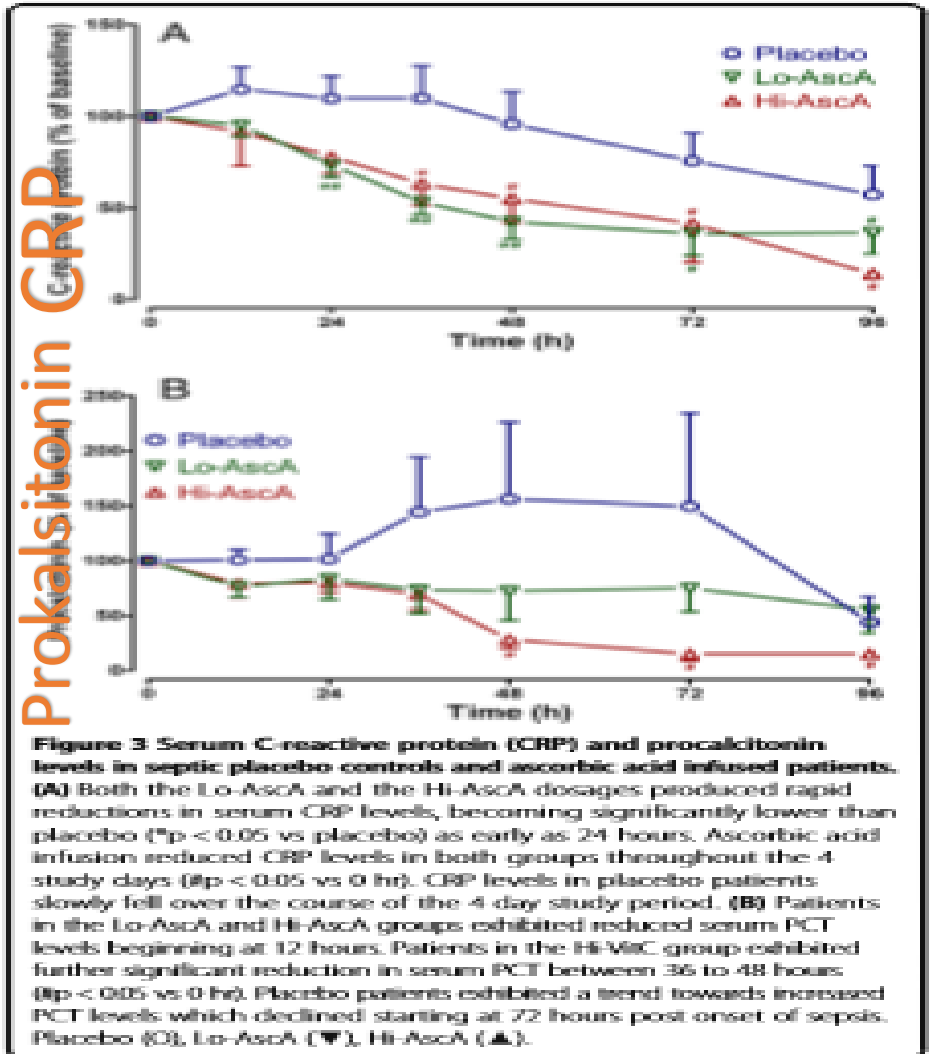


Figure 3 Serum C-reactive protein (CRP) and procalcitonin levels in septic placebo controls and ascorbic acid infused patients. **(A)** Both the Lo-AscA and the Hi-AscA dosages produced rapid reductions in serum CRP levels, becoming significantly lower than placebo (*$p < 0.05$ vs placebo) as early as 24 hours. Ascorbic acid infusion reduced CRP levels in both groups throughout the 4 study days (#$p < 0.05$ vs 0 hr). CRP levels in placebo patients slowly fell over the course of the 4 day study period. **(B)** Patients in the Lo-AscA and Hi-AscA groups exhibited reduced serum PCT levels beginning at 12 hours. Patients in the Hi-VitC group exhibited further significant reduction in serum PCT between 36 to 48 hours (#$p < 0.05$ vs 0 hr). Placebo patients exhibited a trend towards increased PCT levels which declined starting at 72 hours post onset of sepsis. Placebo (○), Lo-AscA (▼), Hi-AscA (▲).

Yüksek Doz C vitaminin Hormonal / Adrenerjik Etkileri

- Stres durumlarında adrenal glanddan salgılandığı, nütrient olmaktan çok stress hormonu olarak çalıştığı bildirilmiştir
- Norepinefrin ve vazopressinin endojen sentezini arttırarak vasomotor yanıtı arttırır
- Vazopressin sentezinde kofaktördür
- Sepsiste vazopressin erken fazda fazla artar ancak hipotansiyon ve şok ilerledikçe vazopressin ve vitamin C deplase olur
- Kritik hastada katekolamin sentezi azalmıştır. Bunda adrenal askorbik asit deplesyonu sorumlu tutulmuştur.

Furthermore, SVCT-mediated ascorbic acid uptake plays a crucial role in catecholamine biosynthesis and adrenal steroidogenesis (Patak, Willenberg, & Bornstein, 2004; Wu et al., 2008),

C vitamini verilmesiyle vazopressör ilişkili sonlanmalar

Table 1 Summary of studies of ascorbate administration with vasopressor-related endpoints

Study type	Study group	Intervention	Findings	Reference
Pre-clinical	24 rats (8/group)	Centrally administered ascorbate (0, 200, 600 nmol)	↑ vasopressin release	[62]
			↑ antidiuresis	
			↑ natriuresis	
Case report	Hospital patient	Intravenous ascorbate (1,500 mg/day)	↑ arterial pressure	[35]
			↓ heart rate	
			Normalised central venous pressure	
			↓ need for catecholamines	
			Improved multiple organ dysfunction	
Case report	Hospital patient	Oral ascorbate (500 mg/day)	Resolution of orthostatic hypotension	[36]
Clinical (retrospective)	33 severely burned patients (16–17/group)	Intravenous ascorbate (0, 66 mg/kg/h)	↓ fluid requirement	[39]
			↓ number of patients requiring vasopressors	
Clinical (randomised, prospective)	37 severely burned patients (17–18/group)	Intravenous ascorbate (0, 66 mg/kg/h)	↓ resuscitation fluid volume	[38]
			↑ diuresis	
			↓ length of mechanical ventilation	
Clinical (phase I randomised controlled trial)	24 severe sepsis patients (8/group)	Intravenous ascorbate (0, 50, 200 mg/kg/24 h)	↓ systemic organ failure	[12]
			↑ systolic blood pressure[a]	
			↑ mean arterial pressure[a]	

[a]Previously unpublished data (R. Natarajan and A. Fowler)
↑ increase, ↓ decrease

Vazopressin salınımı artar

Arterial basınç artar

Sıvı ihtiyacı azalır

Katekolamin ihtiyacı azalır

Ortalama arter basıncı artar

Diürez artar

Sistemik organ yetmezliği azalır

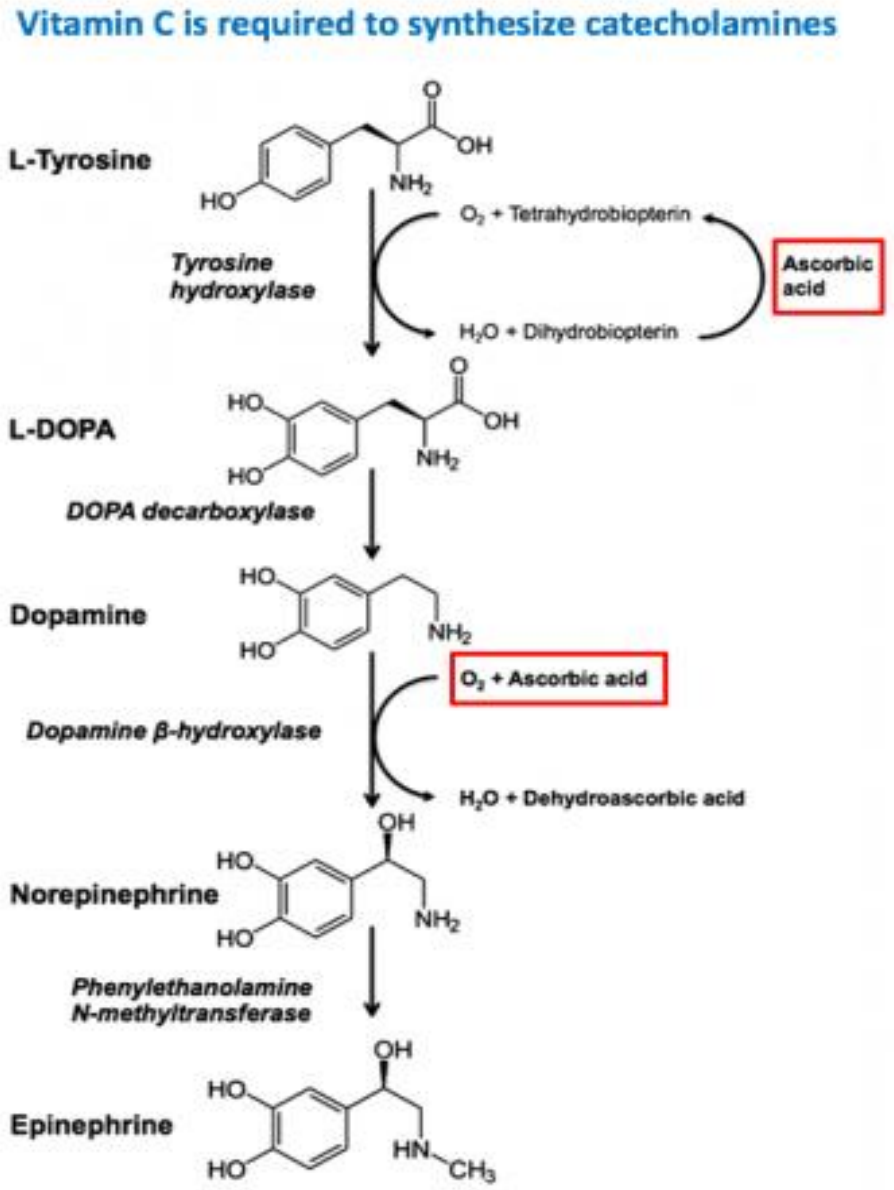
Mekanik ventilasyon süresi azalır

Katekolamin sentezinde 2 basamakta c vitaminine ihtiyaç vardır.

Bunlardan birisi L DOPA sentezinde hız belirleyici kofaktördür ki Ldopa da dopaminin prekürsörüdür.

İkincisi de dopamin beta hidroksilaz enziminde kofaktördür. Dopaminden norepinefrin yapımını katalizlemektedir.

Böylece vasopressör yanıt, alfa, beta adrenerjik reseptör aktivitesi artar, vasküler tonus ve kardiyak autput artar.



nutrients

MDPI

Article

Estimating Vitamin C Status in Critically Ill Patients with a Novel Point-of-Care Oxidation-Reduction Potential Measurement

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Received: 26 March 2019; Accepted: 2 May 2019; Published: 8 May 2019

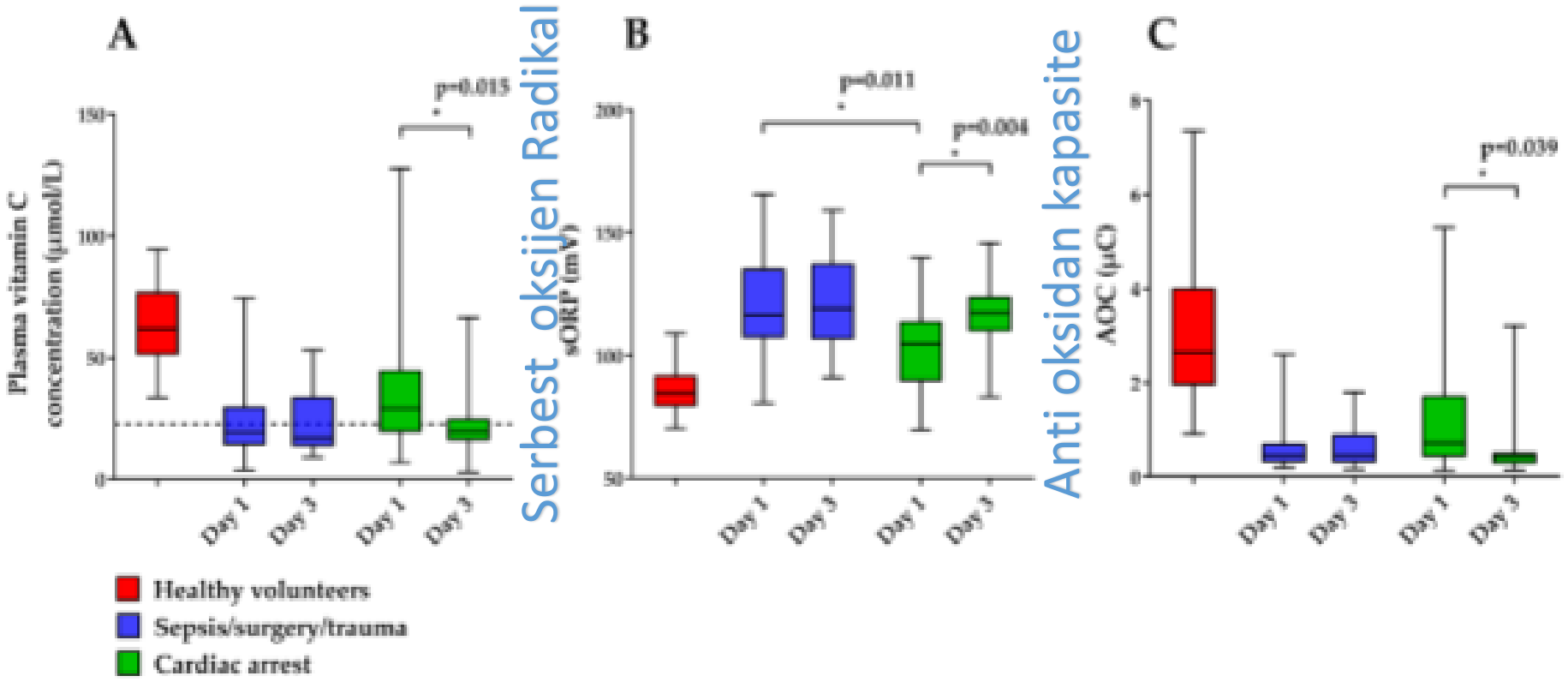

Figure 3. Boxplots of plasma vitamin C concentrations (**A**), static oxidation reduction potential (sORP) (**B**) and antioxidant capacity (AOC) (**C**) in the vitamin C status study at day 1 and 3. The dashed line (**A**) represents the lower limit of normal plasma vitamin C concentrations (23 µmol/L). sORP and AOC were measured in non-acidified samples.

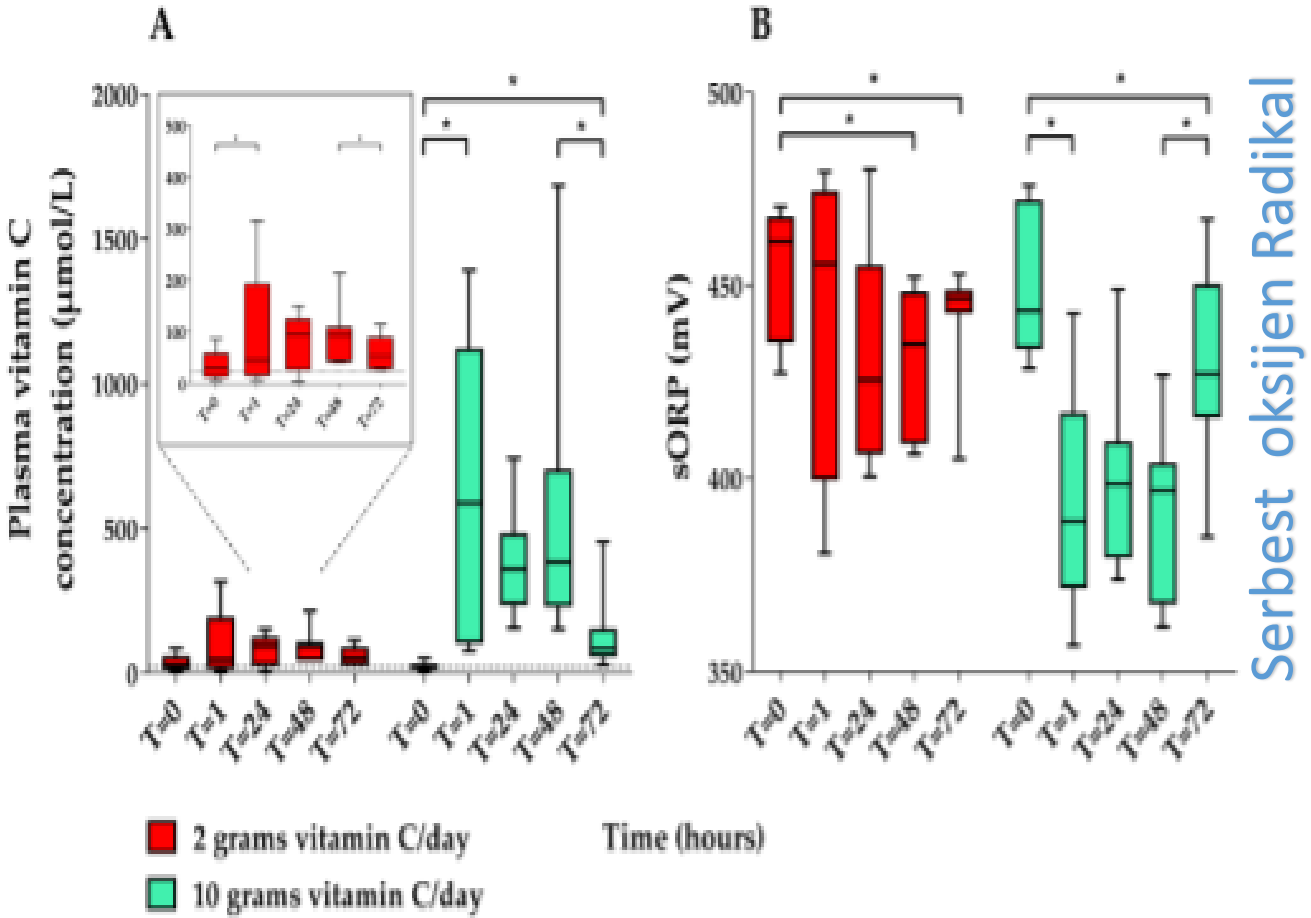

Figure 4. Boxplots of plasma vitamin C concentrations (**A**) and static oxidation reduction potential (sORP) (**B**) in the pharmacokinetic study at five different time points (hours). The dashed line (**A**) represents the lower limit of normal plasma vitamin C concentrations (23 µmol/L). Asterisks represent significant differences at $p < 0.05$. Vitamin C concentrations at T24 and T48 are trough concentrations. T72 represents a wash-out phase sample. sORP was measured in acidified samples.

Neden Tiamin Kullanıldı ?

- Yüksek doz C vitamini verilmesi ile oxalata metabolik konversiyon oranı artar
- Tiamin eksikliğinde oksalata dönüşüm artmaktadır Tiamin renal oxalat kristalizasyonu riskini azaltmak için kullanılmaktadır.
-
- Donino ‘nun pilot çalışmasında thiamin defisiti olan septik grupta suplement alanlarda laktat seviyesi ilk 24 saatte kontrol grubuna göre anlamlı olarak düşmüştür. Mortalite thiamin alan grupta %13 almayan grupta % 46 bulunmuştur .
- Ayrıca Thiamin verilen grupta renal replasman uygulanan hasta %3 , kontrol grubunda % 21 bulunmuştur .

Clinical studies of IV thiamine in sepsis

Donning MW 2016: Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: A pilot study

This was a RCT investigating the effect of thiamine (200 mg IV q12hr) in 88 patients with septic shock. Thiamine had no effect on lactate levels or mortality within the entire population (figure below, left). This may be explained by the fact that only 35% of the patients had thiamine deficiency. Within this pre-specified subgroup, thiamine administration did reduce lactate levels and mortality (figure below, right).

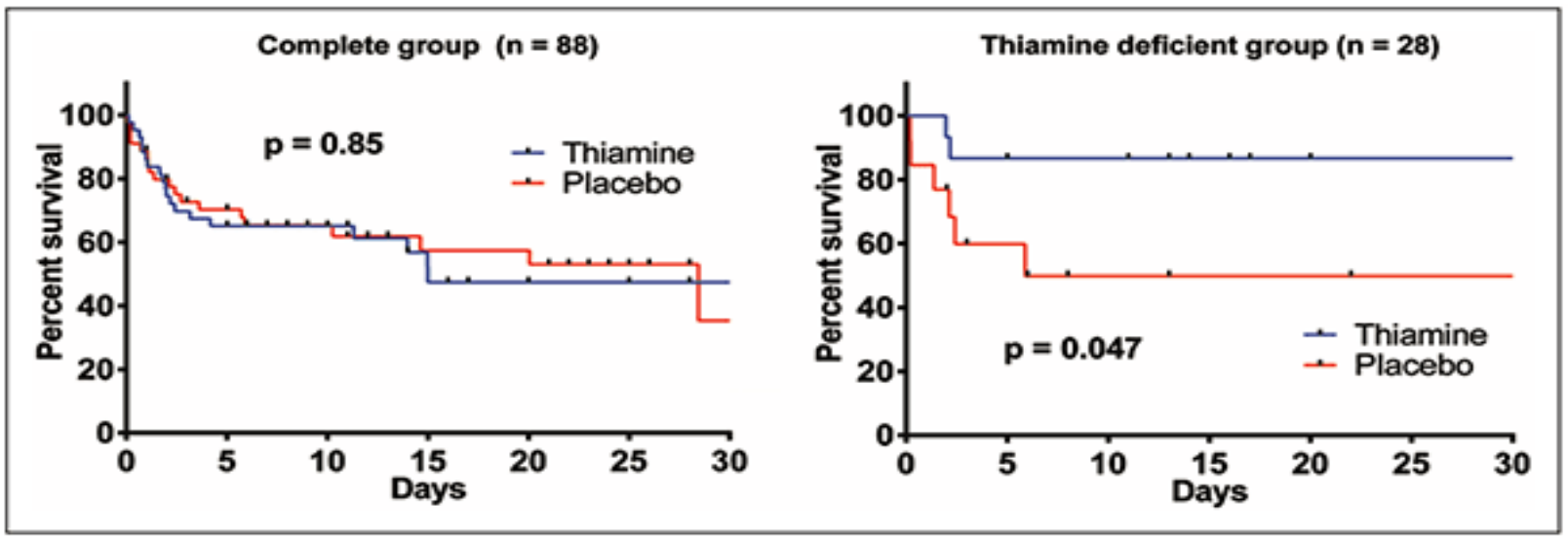

Figure 3. Kaplan Meier survival curves. Survival curves for the thiamine and placebo groups in the full study group (left) and the thiamine deficient group (right). Patients were censored at hospital discharge. The graph is truncated at 30 days for illustrative purposes. Vertical lines represents censored patients and the p-value is from the log-rank test.

J Crit Care. 2018 Feb;43:230-234. doi: 10.1016/j.jcrc.2017.09.031. Epub 2017 Sep 18.

Vitamin C: The next step in sepsis management?

Teng J[1], Pourmand A[2], Mazer-Amirshahi M[3].

Author information

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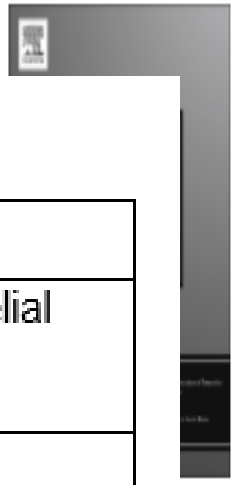

Table 2: Summary of key roles of vitamin C in sepsis

Key role	Mechanism
Antioxidant	Scavenges ROS and RNS, prevents endothelial damage maintaining microvascular integrity
Synthesis of Catecholamines	Acts as cofactor in synthesis of epinephrine, dopamine, and vasopressin allowing for maintenance of vascular tone and cardiac output
Immune Function	Supports lymphocytic proliferation, assists in neutrophilic killing of bacteria, improves chemotaxis

ROS=reactive oxygen species, RNS=reactive nitrogen species

https://doi.org/10.1186/s13054-019-2538-y

LETTER Open Access

Vitamin C administration in the critically ill: a summary of recent meta-analyses

Anitra C. Carr

This comment refers to the article available at https://doi.org/10.1186/s13054-018-2191-x.

Since 2018, there has been a dramatic upsurge in publications relating to the use of vitamin C in critically ill patients, particularly those suffering from sepsis [1]. This has primarily been in response to the well-publicized before-and-after study of Marik et al. [2], which indicated that intravenous administration of 6 g/day vitamin C (in combination with thiamine and hydrocortisone) could improve the outcomes of patients with sepsis, including decreasing mortality. Over the past year, seven meta-analyses assessing the effects of vitamin C administration in critically ill patients have been published, with four appearing in the past 4 months alone (see Table 1 summary).

The most recently published and largest meta-analysis included 44 randomized controlled trials (16 intensive care and 28 cardiac surgery) [9]. Although meta-analyses that include a larger number of studies have increased power, they run the risk of comparing disparate studies. This is particularly the case with vitamin C studies whereby the dose (milligrams vs grams), rout of administration (oral vs intravenous), duration (hours vs days), and disease (e.g., sepsis vs cardiac surgery) can have a large impact on outcomes [10, 11]. Therefore, appropriate subgroup analyses should be carried out, although this is currently challenging due to the low number of comparable studies.

All but one of the current meta-analyses have focused on mortality as a primary outcome, despite many of the included trials having relatively low numbers of patients. In most cases, no effect of intervention was observed on mortality, except in specific subgroup analyses (e.g., sepsis and higher dose intravenous vitamin C). However, there have been few of these studies published to date, and even fewer of high methodological quality [6]. Other commonly assessed outcomes included ICU and hospital length of stay, duration of vasopressor support and mechanical ventilation, and acute kidney injury. Some of the meta-analyses showed decreases in several of these secondary outcomes, while others showed no effect, depending on the selection criteria used for study inclusion (Table 1).

There are currently over a dozen randomized controlled trials registered on clinicaltrials.gov that are assessing the effects of vitamin C administration in critically ill patients, particularly those with sepsis. One would hope that in the short term, no more meta-analyses appear every time another small study is published, but instead wait until some of the larger trials (such as VICTAS and LOVIT) have been completed. Otherwise, there may end up with more meta-analyses than published trials.

Kanıt değeri yüksek olmayan az sayıda çalışmada yüksek doz C vitamininin sepsiste mortaliteyi azalttığı gösterilmiştir.

Yoğun bakım süresi , ventilatör süresi , renal replasman oranı, vasopressör ihtiyacı gibi parametrelerde bazı yayınlar iyileşme bildirirken bazı yayınlar faydalı etki bildirmemiştir.

Bu konuda randomize kontrollü çalışmaya ihtiyaç vardır.

Intensive Care Med. 2020 Aug 11 : 1–11.
doi: 10.1007/s00134-020-06191-3 [Epub ahead of print]
PMCID: PMC74
PMID: 327

Combination therapy of vitamin C and thiamine for septic shock: a mul
centre, double-blinded randomized, controlled study

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Tae Gun Shin,[✉#1] Won Young Kim,[✉#2] and Korean Shock Society (KoSS)

Conclusion

In this study, vitamin C and thiamine administration in the early phase of septic shock did not improve organ function compared with placebo, despite improvements in vitamin C and thiamine levels.

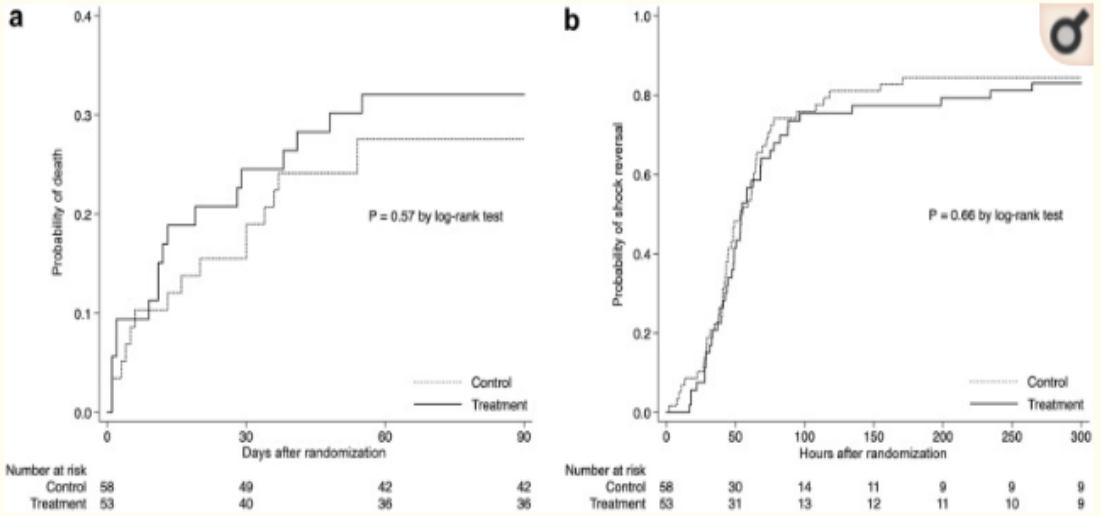

Fig. 3

Kaplan–Meier analysis for mortality and shock reversal

Mortalite ve şokun iyileşme oranları ayn

...the ... and p... reversal ... [11 ... ively, p = 0.16], or vasopressor dose (at 24 h, 48 h, 72 h and maximal dose for 72 h). No other secondary outcomes showed significant differences between the treatment and placebo groups, including ventilator-free days [11 ... = 0.6 ... [3 ... 8.8 ... vs. ...), p = 0.65) or reduction of procalcitonin [49.2% (− 31.9 to 74.7) vs. 40.3% (− 3.4 to 82.8), p = 0.27].

50 mg / kg c vit 12 saat ara ile 3 gün
200 mg Thiamin 12 saat ara ile 3 gün
Gruplar 55 kişi

JAMA. 2020 Feb 4; 323(5): 423–431.
Published online 2020 Jan 17. doi: 10.1001/jama.2019.22176
PMCID: PMC7029761
PMID: 31950979

Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock

The VITAMINS Randomized Clinical Trial

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Glenn M. Eastwood, PhD,[1,7] Craig J. French, MB, B

Fark Yok

Primary and Secondary Outcomes

Outcomes	Intervention (n = 107)	Control (n = 104)	Difference (95% CI)	*P* Value
Primary Outcome				
Time alive and free of vasopressors, median (IQR), h	122.1 (76.3 to 145.4)	124.6 (82.1 to 147.0)	–0.6 (–8.3 to 7.2)[a]	.83
Secondary Outcomes				
28-d Mortality, No. (%)	24 (22.6) [n = 106]	21 (20.4) [n = 103]	2.3 (–8.9 to 13.4)	.69
90-d Mortality, No. (%)	30 (28.6) [n = 105]	25 (24.5) [n = 102]	4.1 (–8.0 to 16.1)	.51
ICU mortality, No. (%)	21 (19.6)	19 (18.3)	1.4 (–9.2 to 11.9)	.80
Hospital mortality, No. (%)	25 (23.4)	21 (20.4) [n = 103]	3.0 (–8.2 to 14.1)	.60
28-d Cumulative vasopressor-free days, median (IQR)	25.6 (17.8 to 26.8) [n = 106]	25.8 (19.6 to 26.8) [n = 103]	–0.2 (–1.7 to 1.2)	.66
28-d Cumulative mechanical ventilation-free days, median (IQR)	25.3 (5.2 to 28.0) [n = 106]	24.8 (9.5 to 28.0) [n = 103]	0.4 (–2.6 to 3.4)	.73
28-d Renal replacement therapy–free days, median (IQR)	28.0 (23.5 to 28.0) [n = 105]	28.0 (21.0 to 28.0) [n = 103]	0.0 (–0.6 to 0.6)	.71
Change in SOFA score at day 3, median (IQR)[b]	–2 (–4 to 0) [n = 82]	–1 (–3 to 0) [n = 75]	–1.0 (–1.9 to –0.1)	.02
28-d ICU-free days, median (IQR)	21.9 (0 to 25.8) [n = 106]	22.1 (3.9 to 25.8) [n = 103]	–0.2 (–4.1 to 3.7)	.66
Hospital length of stay, median (IQR), d	12.3 (6.2 to 26.0)	12.3 (6.2 to 26.1) [n = 103]	0.0 (–4.9 to 4.9)	.75
Prespecified Exploratory Outcome				
Acute kidney injury, No. (%)				
Stage 1	18 (16.8)	14 (13.5)	3.4 (–6.3 to 13.0)	
Stage 2	18 (16.8)	22 (21.2)	–4.3 (–14.9 to 6.2)	.80
Stage 3	39 (36.4)	39 (37.5)	–1.1 (–14.1 to 12.0)	

Med Drug Discov. 2020 Mar; 5: 100028.
Published online 2020 Mar 26. doi: 10.1016/j.medidd.2020.100028
PMCID: PMC7167497
PMID: 32328576

Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?

Richard Z. Cheng

1 High-dose intravenous VC has also been successfully used in the treatment of 50 moderate to severe COVID-19 patients in China. The doses used varied between 10 g and 20 g per day, given over a period of 8–10 h. Additional VC bolus may be required among patients in critical conditions. The oxygenation index was improving in real time and all the patients eventually cured and were discharged [18]. In fact, high-

Open access Protocol

BMJ Open

Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial

Fang Liu, Yuan Zhu, Jing Zhang, Yiming Li, Zhiyong Peng

To cite: Liu F, Zhu Y, Zhang J, *et al*. Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. *BMJ Open* 2020;**10**:e039519. doi:10.1136/bmjopen-2020-039519

► Prepublication history for this paper is available online. To view these files, please visit

ABSTRACT

Introduction The rapid worldwide spread of COVID-19 has caused a global health crisis. To date, symptomatic supportive care has been the most common treatment. It has been reported that the mechanism of COVID-19 is related to cytokine storms and subsequent immunogenic damage, especially damage to the endothelium and alveolar membrane. Vitamin C (VC), also known as L-ascorbic acid, has been shown to have antimicrobial and immunomodulatory properties. A high dose of intravenous VC (HIVC) was proven to block several key components

Strengths and limitations of this study

- ► This is one of the first prospective randomised controlled trials applying high dose of intravenous vitamin C (HIVC) to treat COVID-19.
- ► 'High-dose' vitamin C therapy lacks a universal definition. A previous meta-analysis considered high doses as equal to or greater than 10 g/day. In this trial, we will administer 24 g vitamin C per day for 7 days intravenously.

Gruplarda 150 hasta , ICU, Solunum yetmezliği indeksi < 300 , ARDS Covıd 19 +,

24 Gram C vitamini , 7 gün

Sonlanmalar
28 Günde ventilatörden bağımsız gün

Sekonder Sonlanma
Mortalite
Delta SOFA
Biyomarker değişimi
ICU günü

We predict that HIVC could suppress cytokine storms caused by COVID-19, help improve pulmonary function and reduce the risk of ARDS of COVID-19.

Lancet Diabetes Endocrinol. 2020 Jul; 8(7): 570.
Published online 2020 May 20. doi: 10.1016/S2213-8587(20)30183-2

PMCID: PMC7239633
PMID: 32445630

Vitamin-D and COVID-19: do deficient risk a poorer outcome?

Fiona Mitchell

Randomize kontrollü çalışma yok ancak , kullanılması gerektiği konusunda öneriler daha ön planda

Pandemi döneminde daha uzun süre evde kalınması öneriliyor.

Özellikle siyah ırkta covid sıklığı daha fazla

İmmmun sistem fonksiyonlarını iyileştirdiğine ilişkin kanıtlar var

Catelisidin ve defensin üzerinden anti viral etki

Proinflamatuar sitokinlerde azalma , anti inflamatuar sitokinlerde azalma

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2017;356:i6583
http://dx.doi.org/10.1136/bmj.i6583

Accepted: 01 December 2016

ABSTRACT

OBJECTIVES

To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, and to identify factors modifying this effect.

DESIGN

Systematic review and meta-analysis of individual participant data (IPD) from randomised controlled trials.

DATA SOURCES

Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and the International Standard Randomised Controlled Trials Number registry from inception to December 2015.

ELIGIBILITY CRITERIA FOR STUDY SELECTION

Randomised, double blind, placebo controlled trials of supplementation with vitamin D_3 or vitamin D_2 of any duration were eligible for inclusion if they had been approved by a research ethics committee and if data on incidence of acute respiratory tract infection were collected prospectively and prespecified as an efficacy outcome.

RESULTS

25 eligible randomised controlled trials (total 11 321 respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001). In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses (adjusted odds ratio 0.81, 0.72 to 0.91) but not in those receiving one or more bolus doses (adjusted odds ratio 0.97, 0.86 to 1.10; P for interaction=0.05). Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L (adjusted odds ratio 0.30, 0.17 to 0.53) than in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (adjusted odds ratio 0.75, 0.60 to 0.95; P for interaction=0.006). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (adjusted odds ratio 0.98, 0.80 to 1.20, P=0.83). The body of evidence contributing to these analyses was assessed as being of high quality.

CONCLUSIONS

Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.