DOMINGOS DIAS CICARELLI

Tratamento precoce do choque séptico com dexametasona: monitorização comparativa com proteína C-reativa e proteína amilóide A sérica

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Área de concentração: Anestesiologia

Orientador: Dr. Fábio Ely Martins Benseñor

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“Os deuses percebem coisas no futuro, as pessoas comuns no presente, mas os sábios percebem as coisas que estão prestes a acontecer”

Filostrato

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Sumário

LISTA DE ABREVIATURAS

Dr.	Doutor
et al.	e outros

LISTA DE SÍMBOLOS

bpm	batimentos por minuto
μg/kg/min	micrograma por kilograma por minuto
μg/dl	micrograma por decilitro
μg	micrograma
mEq/l	miliequivalente por litro
mg/kg	miligrama por kilograma
mg	miligrama
mg/dl	miligrama por decilitro
mmHg	milímetro de mercúrio
mmol/l	milimol por litro
°C	grau centígrado

LISTA DE SIGLAS

ANOVA	analysis of variance
APACHE	acute physiology and chronic health evaluation
CV	coeficiente de variação
$D_{(A-a)}O_2$	diferença artério-alveolar de oxigênio
DP	desvio-padrão
DPOC	doença pulmonar obstrutiva crônica
FC	freqüência cardíaca
FiO_2	fração inspirada de oxigênio
FMUSP	Faculdade de Medicina da USP
FR	freqüência respiratória
GCS	Glasgow Coma Scale
HCFMUSP	Hospital das Clínicas da FMUSP
HDL	high density lipoprotein
IC	intervalo de confiança
NNT	número necessário para tratar
NYHA	New York Heart Association
PAM	pressão arterial média
PaO_2	pressão arterial de oxigênio
PCR	proteína C-reativa
RR	risco relativo
SAA	serum amyloid A

SDMO	síndrome de disfunção de múltiplos órgãos
SDRA	síndrome do desconforto respiratório agudo
SOFA	sequencial organ failure assessment
SRIS	síndrome da resposta inflamatória sistêmica
USP	Universidade de São Paulo
UTI	Unidade de Terapia Intensiva

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RESUMO

Cicarelli DD. *Tratamento precoce do choque séptico com dexametasona: monitorização comparativa com proteína C-reativa e proteína amilóide A sérica* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2008.

INTRODUÇÃO: Sepse e choque séptico são doenças comuns em pacientes gravemente enfermos, evoluindo muitas vezes com síndrome de disfunção de múltiplos órgãos (SDMO) e morte. Este trabalho investiga a eficácia da administração precoce de dexametasona em evitar a progressão do choque séptico para SDMO e morte e o comportamento da proteína amilóide A sérica (SAA) e da proteína C-reativa (PCR) como marcadores da evolução e gravidade dos pacientes em choque séptico no período pós-operatório. MÉTODOS: Estudo prospectivo, aleatório, duplamente encoberto, realizado na Unidade de Terapia Intensiva pós-operatória do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, com 29 pacientes que no período pós-operatório evoluíram com choque séptico. Os participantes foram divididos de forma aleatória em dois grupos, de acordo com a solução administrada: dexametasona 0,2 mg/kg (grupo D) ou placebo (grupo P), repetidas a cada 36 horas. Os pacientes foram acompanhados durante sete dias de internação na UTI através do escore SOFA (*Sequential Organ Failure Assessment*) e dosagens séricas diárias de PCR, SAA e lactato. RESULTADOS: Os pacientes do grupo D, quando comparados aos pacientes do grupo P, permaneceram mais dias sem necessidade do uso do vasopressor (respectivamente 2,9±2,7 e 0,7±0,6, p=0,01) e mais tempo livre de ventilação mecânica (respectivamente 2,6±2,5 e 0,6±0,5, p=0,03). A mortalidade no

grupo P foi de 67% (10 em 15) e no grupo D foi de 21% (3 em 14) (Risco Relativo=0,31, IC95% 0,11-0,88). Os valores de PCR e SAA apresentaram forte correlação durante o período de observação (R=0,91/p=0,002). PCR e SAA não tiveram correlação com o escore SOFA (respectivamente R=0,71/p=0,05 e R=0,52/p=0,18), nem com o lactato (p=0,88 e p=0,67). CONCLUSÕES: O tratamento precoce com dexametasona nos pacientes com choque séptico reduziu a mortalidade em 7 dias de acompanhamento. Os níveis séricos de PCR e SAA apresentaram-se elevados nos pacientes em choque séptico e tiveram forte correlação, porém não foram preditores de disfunção orgânica nem de mortalidade.

Descritores: Choque séptico. Dexametasona. Corticoesteróides. Proteína C-reativa. Proteína amilóide A sérica.

SUMMARY

Cicarelli DD. *Septic shock early treatment with dexamethasone: comparative study with C-reactive protein and serum amyloid A protein* [thesis]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2008.

INTRODUCTION: Sepsis and septic shock are a very common condition in critically ill patients, leading to multiple organ dysfunction syndrome (MODS) and death. This study aimed at investigating the efficacy of early administration of dexamethasone in patients with septic shock in order to block the evolution to MODS and death. It also evaluated serum amyloid A protein (SAA) and C-reactive protein (CRP) as evolution and organ dysfunction markers in postoperative septic shock patients. METHODS: Prospective, randomized, double-blind study, developed in a surgical intensive care unit of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo that involved 29 patients with septic shock. All eligible patients were prospectively randomized to receive either a dose of 0.2 mg/kg of dexamethasone (group D) or placebo (group P), repeated every 36 hours intervals. Patients were monitored over a 7-day period by Sequential Organ Failure Assessment score (SOFA) and daily measurements of CRP, SAA and lactate. RESULTS: Patients treated with dexamethasone had more vasopressor therapy-free days (2.9±2.7 versus 0.7±0.6, p=0.01) and more mechanical ventilation-free days (2.6±2.5 e 0.6±0.5, p=0.03). Mortality in group P was 67% (10 in 15) and in group D was 21% (3 in 14) (Relative Risk=0.31, 95%CI 0.11 to 0.88). CRP and SAA were strongly correlated during the 7 day period of observation (R=0.91/p=0.002). CRP and SAA did not correlate with

SOFA (respectively R=0.71/p=0.05 and R=0.52/p=0.18) and lactate (p=0.88 and p=0.67). CONCLUSIONS: Early treatment with dexamethasone reduced 7-day mortality in septic shock patients. CRP and SAA levels were significantly elevated in septic shock and were strongly correlated to each other, but did neither correlate with organ dysfunction nor predict mortality.

Descriptors: Septic shock. Dexamethasone. Adrenal cortex hormones. C-reactive protein. Serum amyloid A protein.

INTRODUÇÃO

A Síndrome da Resposta Inflamatória Sistêmica (SRIS) é o resultado da liberação de mediadores inflamatórios desencadeada por um agente causal, infeccioso ou não.[1] Quando a causa da SRIS é uma infecção, definimos o quadro como sepse.[1] A sepse pode ser classificada como grave quando evolui com disfunção orgânica.[1] O choque séptico é definido como sepse grave evoluindo com hipotensão a despeito de adequada ressuscitação volêmica, necessitando do uso de vasopressores.[1] A Síndrome de Disfunção de Múltiplos Órgãos (SDMO) é definida como disfunção orgânica em pacientes críticos que necessitam intervenção para manutenção da homeostasia.[2]

Sepse é a principal causa de mortalidade em unidades de terapia intensiva não cardiológicas em todo o mundo, principalmente em decorrência da SDMO.[3] Estima-se uma taxa de mortalidade que varia de 20% a 80%, sendo que em nosso país a taxa de mortalidade atinge 65% nos pacientes com choque séptico.[4] Aproximadamente metade dos pacientes em choque séptico morre por disfunção de múltiplos órgãos.[1] A importância epidemiológica da sepse levou à criação de um comitê internacional em 2002, capitaneado por três sociedades médicas (*Society of Critical Care Medicine*, *European Society of Intensive Care Medicine* e *International Sepsis Fórum*), que vem desenvolvendo uma campanha mundial denominada *Surviving Sepsis Campaign* (Campanha Sobrevivendo à Sepse) com o objetivo de implementar protocolos de tratamento baseados nas melhores evidências científicas disponíveis, visando reduzir a mortalidade desta doença.[5] Um dos tratamentos recomendados para os pacientes com choque séptico baseia-se no uso de glicocorticóides.[5]

Os glicocorticóides têm efeito imunossupressor, reduzindo a transcrição de genes pró-inflamatórios pela inibição do fator nuclear kappa B.[6,7] Estudos têm utilizado corticóides para reduzir o processo inflamatório sistêmico associado à sepse e ao choque séptico.[8] Alguns destes, publicados recentemente, utilizaram baixas doses de hidrocortisona, demonstrando melhora na evolução dos pacientes em choque séptico, bem como usando metilprednisolona para resolução de pacientes com Síndrome do Desconforto Respiratório Agudo (SDRA).[9] As recomendações atuais para o uso de corticóides restringem-se aos pacientes com choque séptico refratário às drogas vasoativas.[10]

Além do uso precoce da hidrocortisona, questiona-se a respeito do melhor corticóide a ser utilizado, e pode-se supor que a dexametasona seria uma opção melhor.[11] A dexametasona, comparada à hidrocortisona, apresenta maior potência e duração de ação (36-48 horas), com maior efeito antiinflamatório (vinte e cinco vezes maior) e menor efeito mineralocorticóide (desprezível). Alterações clinicamente significativas podem ocorrer no manejo de fluidos e eletrólitos resultantes dos efeitos mineralocorticóides dos glicocorticóides. A dexametasona não interfere com a reabsorção de sódio e água, evitando desta forma hipervolemia e distúrbios iônicos.[12] O tratamento com dexametasona é indicado em casos de suspeita não confirmada de insuficiência adrenal aguda, pois substitui a hidrocortisona na terapia destes pacientes, com a vantagem de não interferir no teste diagnóstico com corticotropina que é realizado para confirmar a insuficiência adrenal.[12]

O choque séptico tem como característica a diminuição da perfusão e oxigenação tecidual. O lactato plasmático, que se encontra com níveis elevados em situações de perfusão tecidual inadequada, é um bom marcador da evolução dos

pacientes sépticos, sendo muito bem correlacionado com a mortalidade dos mesmos.[13,14] Pacientes que evoluem com diminuição precoce dos níveis de lactato após a instituição da terapêutica para o choque séptico, têm menor mortalidade do que os pacientes que evoluem com lactato elevado.[15]

A resposta inflamatória à infecção envolve a liberação de mediadores que podem ser usados como marcadores de gravidade da sepse.[16] Entre estas proteínas de fase aguda que participam da resposta inflamatória, a proteína C-reativa (PCR) é um componente inato do sistema imunológico, que se liga com a fosfocolina e reconhece alguns patógenos e constituintes fosfolipídicos de células danificadas. A proteína amilóide A sérica (SAA) é uma apolipoproteína que se liga rapidamente à lipoproteína de alta densidade (HDL) após sua síntese, influenciando o metabolismo do colesterol durante inflamações, causando adesão e quimiotaxia de células fagocitárias e linfócitos. [17,18] Em alguns pacientes com inflamação crônica, o aumento da produção de SAA pode ser deletério por ocorrer deposição tecidual dos seus fragmentos e desenvolvimento de amiloidose sistêmica.[17,19]

A PCR e a SAA têm padrão semelhante na maioria das doenças inflamatórias, atingindo uma concentração plasmática máxima em torno de 24 horas após o início do processo inflamatório e decaindo lentamente.[20] A PCR é comumente utilizada como marcador de estado inflamatório agudo, sendo sua produção hepática iniciada após uma lesão tecidual ou infecção.[21] Sua concentração plasmática tem sido descrita como paralela ao curso clínico da infecção, sendo que sua queda indicaria a resolução do processo infeccioso.[1] A SAA é a outra grande proteína de fase aguda presente nos seres humanos, com a taxa de aumento mais precoce e de maior intensidade dentre todas as proteínas de fase aguda, incluindo a PCR.[18,22] As

concentrações plasmáticas de SAA são habitualmente paralelas às da PCR. Alguns autores têm descrito a SAA como um marcador clínico útil de inflamação em infecções bacterianas ou virais, como a PCR.[23] Embora estudos sugiram que a SAA seja um marcador mais sensível de doença inflamatória, poucos ensaios sobre a SAA estão publicados até o momento.[18]

OBJETIVOS

1. Avaliar os efeitos do tratamento precoce com dexametasona sobre a evolução de pacientes que desenvolveram choque séptico no período pós-operatório.

2. Comparar as concentrações plasmáticas de PCR e SAA em pacientes com diagnóstico de choque séptico no período pós-operatório, tratados precocemente com dexametasona, correlacionando-as com indicadores de gravidade.

MÉTODOS

Este estudo foi prospectivo, duplamente encoberto, aleatório, com grupo controle. Após aprovação pela Comissão de Avaliação de Protocolos de Pesquisa do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), foram obtidos os consentimentos informados dos pacientes ou parentes mais próximos antes da inclusão no estudo.[24] Foram incluídos 34 pacientes admitidos na Unidade de Terapia Intensiva Cirúrgica do HCFMUSP entre novembro de 2003 e dezembro de 2004.

Pacientes que tiveram diagnóstico de choque séptico após sua admissão na UTI, foram considerados aptos a participar do estudo. Foram usados os critérios de diagnóstico de choque séptico estabelecidos pelo consenso entre o *American College of Chest Physicians* e a *Society of Critical Care Medicine*.[25] Pacientes com menos de 18 anos, com histórico de terapia imunossupressora, uso anterior à internação na UTI de corticóides por mais de 2 semanas no último ano ou durante esta internação no hospital, com diagnóstico de pancreatite aguda ou crônica, doença terminal (estágio final de neoplasia com expectativa de vida inferior a 3 meses) ou sangramento gastrointestinal recente foram excluídos do estudo.[9] Pacientes com diagnóstico de choque séptico prévio à internação na UTI também foram excluídos. Uma tabela de randomização determinou a ordem de inclusão dos pacientes para receberem placebo ou dexametasona. Todos os pacientes participantes foram randomizados em dois grupos: Grupo D, composto de 14 pacientes e Grupo P, com 15 pacientes. Os pacientes do Grupo D receberam dexametasona por via venosa na dose de 0,2mg/kg (três doses

com intervalo de 36 horas entre cada dose), enquanto os pacientes do Grupo P receberam placebo (solução salina 0,9% em três doses com intervalos de 36 horas entre cada dose).

A gravidade da doença após a admissão na UTI foi avaliada com base no escore APACHE II (*Acute Physiology And Chronic Health Evaluation II*) (Anexo A).[26] Os pacientes foram avaliados diariamente através do escore SOFA (*Sequential Organ Failure Assessment)*[27,28,29] por no máximo sete dias consecutivos (Anexo B). As concentrações plasmáticas de lactato, PCR e SAA foram medidas diariamente.[30]

As amostras de sangue para as dosagens de PCR e SAA foram centrifugadas e analisadas em aparelho automatizado (Behring Nephelometer Analyzer II, Dade Behring, Marburg, Denmark) por imunonefelometria usando kits comerciais. A sensibilidade analítica para PCR era de 0,0175mg/l com coeficiente de variação (CV) de 7,6%. A sensibilidade analítica para SAA foi determinada pelo limite inferior da curva de referência, sendo dependente da concentração da SAA do padrão utilizado (CV entre 5,4% e 6,4%).

Os pacientes foram tratados de acordo com os protocolos da UTI com relação aos antibióticos, culturas e critérios de alta. Exames laboratoriais e clínicos relevantes foram realizados durante o estudo, também de acordo com os critérios da unidade. Os pacientes foram avaliados durante sua internação na UTI com relação à duração da terapia com vasopressores (escore SOFA cardiovascular com 2 pontos ou mais), duração da ventilação mecânica e mortalidade. Acompanhou-se a incidência de efeitos colaterais como o aumento da glicemia, infecções secundárias e hemorragia gastrointestinal, secundários ao uso da dexametasona.

Os pacientes que evoluíram com choque séptico refratário, a despeito do uso de altas doses de norepinefrina (>0,5μg/kg/minuto) e dobutamina (≥20μg/kg/minuto) foram excluídos do estudo e receberam hidrocortisona por via venosa na dose de 100mg a cada 8 horas.[31,32]

A análise estatística utilizou o programa *Sigma Stat for Windows*, versão 2.03 (*SPSS Inc*.). Para variáveis contínuas, o tratamento foi comparado com base no teste *t* de *Student*, teste U Mann-Whitney e ANOVA bicaudal para tratamento e evolução. Regressão logística múltipla foi realizada para determinar o risco relativo (RR) de morte e o intervalo de confiança (IC) em 7 dias e 28 dias.[33] Os coeficientes de correlação de Pearson foram calculados para as proteínas. Um valor de $p<0,05$ foi considerado significativo.

RESULTADOS

Dos 34 pacientes incluídos inicialmente, três foram excluídos após desistência dos parentes em participar do estudo e 2 pacientes foram excluídos após perda de dados. Foram então, efetivamente, avaliados 29 pacientes.

Os dados são apresentados como média ± desvio padrão (DP). A idade dos pacientes foi 65 ± 14 anos (variando entre 34 a 88 anos). O estudo envolveu 13 homens (45%) e 16 mulheres (55%). A idade do Grupo D foi de 69 ± 11 anos enquanto a do Grupo P foi de 61 ± 15 anos (p=0,12). Não houve diferença entre os grupos quanto ao escore APACHE II (20 ± 5 para o Grupo D e 19 ± 4 para o Grupo P, p=0,53). Na admissão dos pacientes, as características da população estudada e a gravidade da doença foram semelhantes nos grupos Placebo e Dexametasona (Tabela 1).

Tabela 1 – Características dos pacientes quando admitidos na UTI.

Características	Grupo P (n = 15)	Grupo D (n = 14)	p
Idade (anos)	61 ± 15	69 ± 11	0,12
Gênero masculino (%)	47%	43%	0,59
Peso (kg)	63,5 ± 11,7	68,5 ± 15,0	0,32
Escore APACHE II	19 ± 4	20 ± 5	0,53
Escore SOFA	10 ± 2	9 ± 3	0,44
Doenças pré-existentes (%)			
Hipertensão	28,6	33,3	
Infarto do miocárdio	14,3	13,3	
Diabetes	14,3	13,3	
Doença hepática	7,1	-	
DPOC	7,1	6,7	
Câncer	21,4	20	
Trauma	35,7	20	
Outros indicadores de gravidade			
Tempo livre de ventilação mecânica (dias)	0,6 ± 0,5	2,6 ± 2,5	0,03
Tempo sem uso de vasopressor (dias)	0,7 ± 0,6	2,9 ± 2,7	0,01
Tempo livre de diálise (dias)	4,7 ± 2,6	5,4 ± 2,5	0,66
Cirurgia	**N=29 (grupo P+D)**		
Politrauma (excluindo trauma craniano)	3,4%		
Gastrointestinal	75,9%		
Correção de aneurisma abdominal	6,9%		
Torácica	3,4%		
Urológica	10,4%		

Grupo P – placebo, grupo D – dexametasona, APACHE – acute physiology and chronic health evaluation, SOFA – sequential organ failure assessment, DPOC –doença pulmonar obstrutiva crônica.

Na tabela 2 observamos os procedimentos cirúrgicos a que os pacientes foram submetidos, a antibioticoterapia utilizada durante sua internação na UTI e as culturas e respectivos microorganismos isolados.

Tabela 2 – Microbiologia dos pacientes.

Paciente	Grupo	Cirurgia/doença	Antibiótico	Microorganismo	Culturas
1	D	Colecistectomia/abscesso VB	Vancomicina+cefepime	*S. aureus*	Cultura do abscesso
2	D	Drenagem de empiema pleural	Ceftriaxone+clindamicina	*S. pyogenes*	Cultura do empiema
3	D	Colecistectomia/abscesso VB	Ceftriaxone+metronidazol	-	Negativas
4	D	Cistectomia/piúria	Ceftriaxone+metronidazol	-	Negativas
5	D	Correção AAA/amput. de perna	Ceftazidime+clindamicina	*P. aeruginosa*	Cultura de ferida perna
6	P	Colectomia/cont. cavidade	Ceftriaxone+metronidazol	-	Negativas
7	D	Fratura exposta de calcâneo	Ciprofloxacina	*E. faecalis*	Cultura do sítio cirúrgico
8	D	Duplo J/pionefrose	Ceftriaxone	*K. pneumoniae*	Urocultura
9	D	Sigmoidectomia	Ceftriaxone+metronidazol	*A. baumanii*	Hemocultura
10	D	Hemicolectomia	Ceftriaxone+metronidazol	*Candida albicans*	Hemocultura
11	P	Enterectomia/isquemia mesentérica	Ceftriaxone+metronidazol	-	Negativas
12	D	GDP	Ceftriaxone	*Serratia marcesens*	LBA
13	D	GDP	Ceftriaxone+metronidazol	*S. coag negativa*	Hemocultura
14	D	Abscesso retroperitoneal	Cefepime+vanco+imipenem	*P. aeruginosa*	Hemocultura
15	P	Correção AAA	Vancomicina+imipenem	*S. aureus*	Hemocultura
16	P	Sigmoidectomia/perfuração	Ceftriaxone+metronidazol	*Serratia marcesens*	Cultura ascite
17	P	Colectomia	Cefepime+vancomicina	*S. aureus*	Hemocultura
18	P	Gastrectomia parcial	Ceftriaxone+metronidazol	-	Negativas
19	P	Colecistectomia	Cipro+metronidazol	*Escherichia coli*	Urocultura
20	P	Hemicolectomia	Cefepime+vanco+metro	*E. cloacae*	Hemocultura
21	P	Enterectomia/cont. cavidade	Vanco+imipenem	-	Negativas
22	D	Colectomia	Ceftriaxone+metronidazol	*A. baumanii*	Hemocultura
23	P	Colectomia	Ceftriaxone+metronidazol	*P. aeruginosa*	Hemocultura
24	D	Enterectomia/cont. cavidade	Ceftriaxone+metronidazol	-	Negativas
25	P	Abscesso cervical	Imipenem+vanco+metro	*K. pneumoniae*	Hemocultura
26	P	Sigmoidectomia/perfuração	Ceftriaxone+metronidazol	*P. aeruginosa*	Hemocultura
27	P	Sigmoidectomia	Cefepime+metronidazol	*S. aureus*	Hemocultura
28	P	Duplo J/pionefrose	Cefepime+metronidazol	-	Negativas
29	P	Colectomia	Ceftriaxone+metronidazol	*P. aeruginosa*	LBA

VB – vias biliares, AAA – aneurisma de aorta abdominal, amput – amputação, cont – contaminação, GDP – gastroduodenopancreatectomia, Vanco – vancomicina, Cipro – ciprofloxacina, Metro – metronidazol, S. aureus – Staphylococcus aureus, S. pyogenes –Streptococcus pyogenes,P. aeruginosa – Pseudomonas aeruginosa, E. faecalis – Enterobacter faecalis, K. pneumoniae – Klebsiella pneumoniae, A. baumanii – Acinetobacter baumanii, S. coag negative – Staphylococcus coagulase negative, E. cloacae – Enterobacter cloacae, LBA – lavado broncoalveolar.

A mortalidade em 7 dias do Grupo P foi de 67% (10 em 15), e a do Grupo D foi de 21% (3 em 14) (RR=0,31; IC 95% de 0,11 a 0,88). O número necessário para tratar (NNT) foi de 2,17. A mortalidade em 28 dias no grupo P foi de 80% (12 em 15) e no grupo D foi de 50% (7 em 14) (RR=0,63; IC 95% de 0,31 a 1,29) (Figura 1). Com relação aos efeitos colaterais da dexametasona (aumento da glicemia, infecções secundárias ou hemorragia gastrintestinal), somente um paciente no grupo P desenvolveu pneumonia no 4° dia de pós-operatório de correção de aneurisma de aorta.

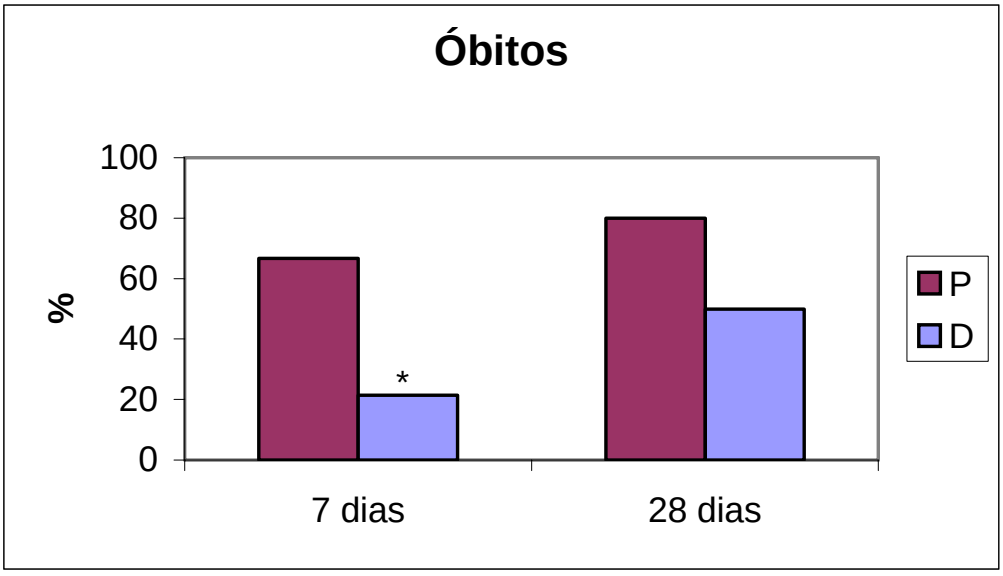

Figura 1. Mortalidade do Grupo D comparada à do Grupo P em 7 dias (* - RR=0,31; IC 95% 0,11-0,88) e em 28 dias (RR=0,63; IC 95% 0,31-1,29).

Os dois grupos diferiram com relação ao escore SOFA durante o estudo (Figura 2). O Grupo D evoluiu com valores menores de escore SOFA em relação ao Grupo P (p=0,0002), porém não foram evidenciadas diferenças com relação à coagulação avaliada pelo SOFA através da contagem de plaquetas, ao sistema hepático avaliado pela dosagem de bilirrubina sérica, ao sistema renal avaliado pela dosagem plasmática de creatinina ou com relação ao sistema nervoso central avaliado pela escala de coma de Glasgow.

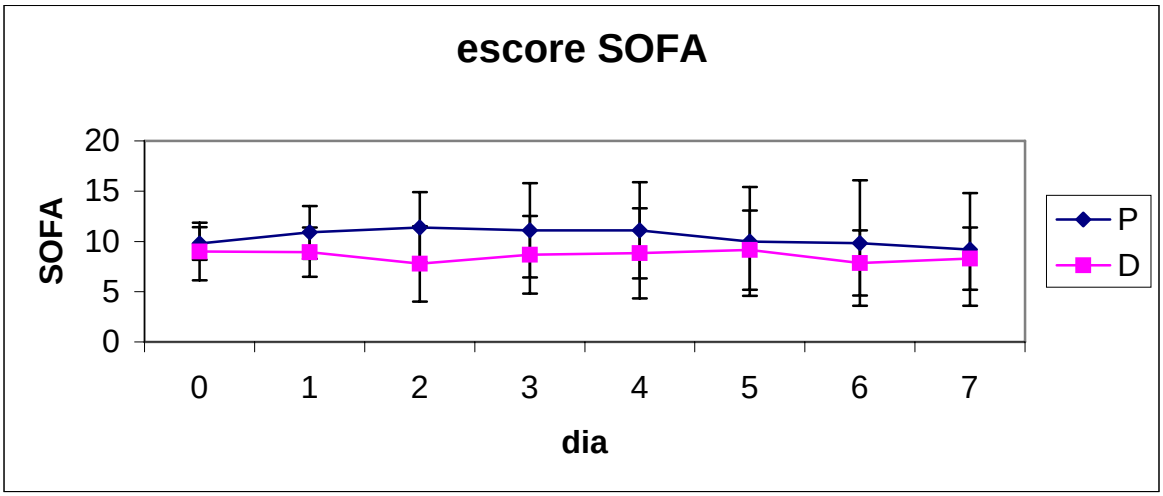

Figura 2. Evolução do escore SOFA dos grupos P e D (p=0,0002).

O sistema respiratório, após 24 horas da administração da medicação, evoluiu com melhor relação PaO_2/FiO_2 no Grupo D, indo de 267±109 para 292±101, em comparação ao Grupo P, de 209±90,1 para 203±84,7 (teste de Mann-Whitney com p = 0,041). Contudo, esta melhora não persistiu durante o restante do período avaliado no estudo (Figura 3).

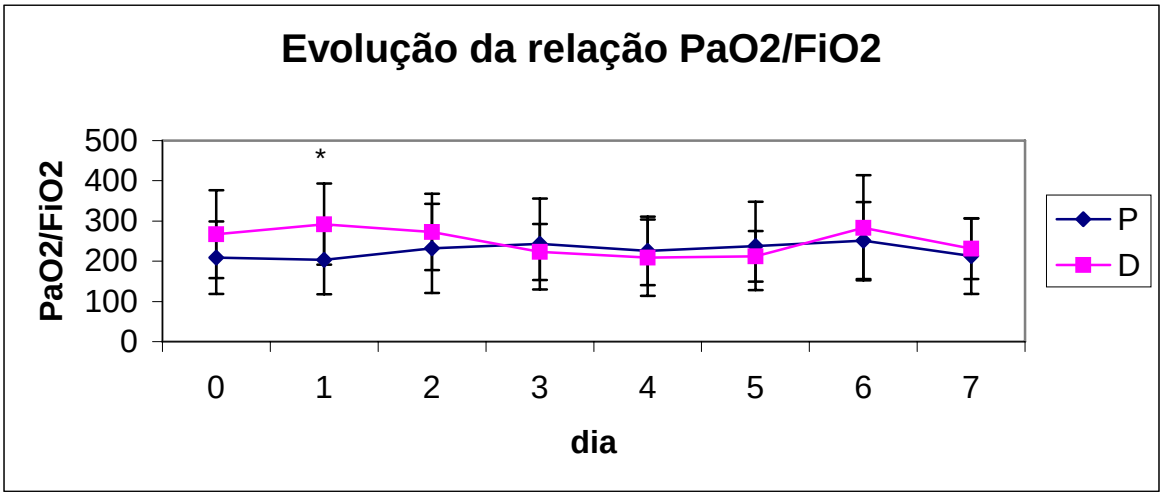

Figura 3. Evolução da relação PaO_2/FiO_2 durante o estudo (* - p=0,041).

O tempo livre de ventilação mecânica em 7 dias foi estatisticamente diferente entre os grupos: 2,6 ± 2,5 dias por paciente do grupo D e 0,6 ± 0,5 dias no grupo P (p = 0,03) (Figura 4).

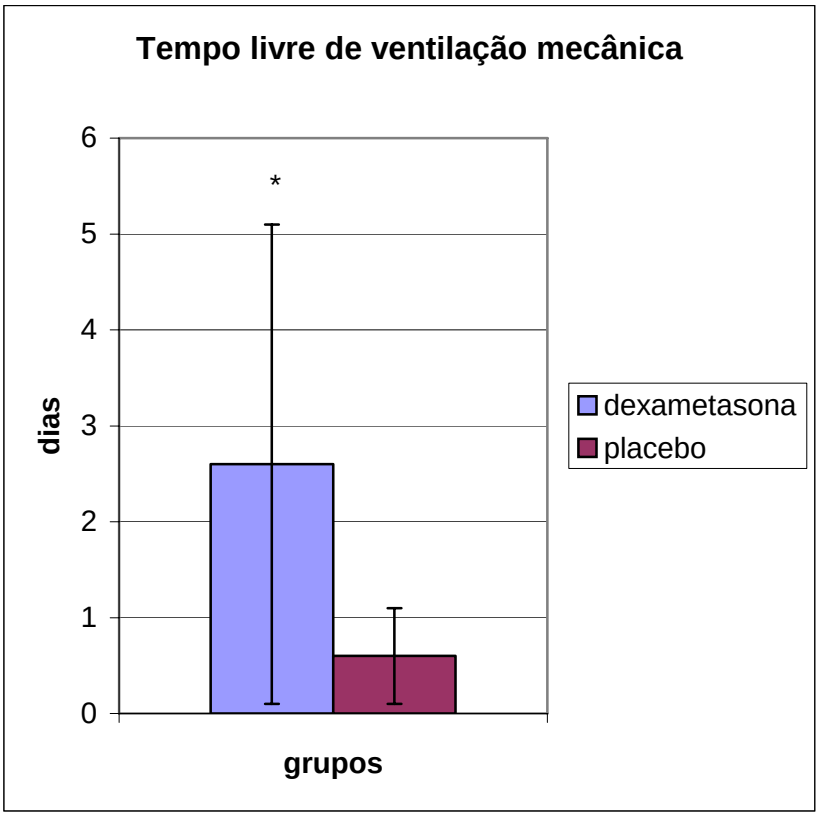

Figura 4. Tempo livre de ventilação mecânica nos grupos (em dias) (* - p=0,03).

O tempo sem uso da terapia com vasopressores em 7 dias foi estatisticamente diferente entre os grupos: 2,9 ± 2,7 dias por paciente do grupo D e 0,7 ± 0,6 dias no grupo P (p = 0,01) (Figura 5).

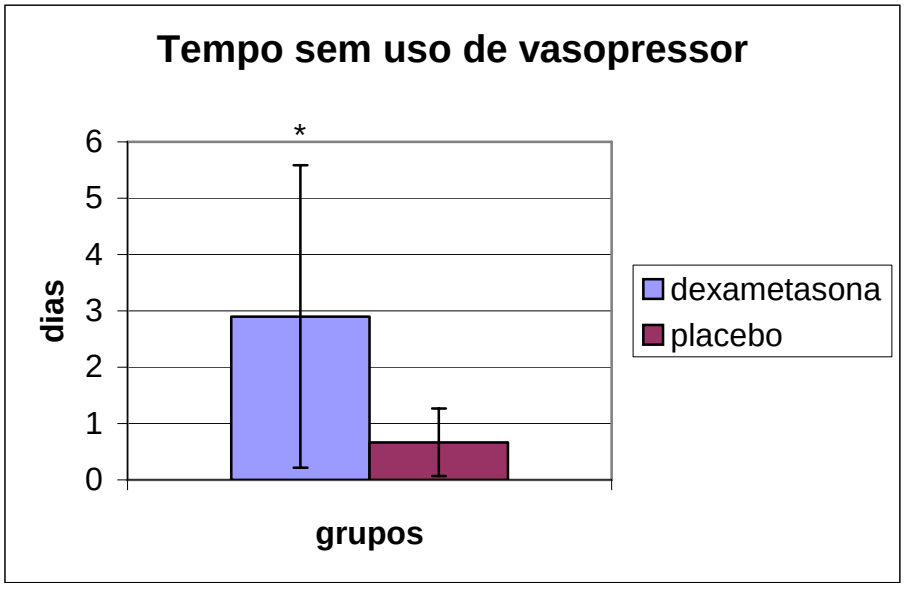

Figura 5. Dias sem necessidade da terapia com vasopressores nos grupos (* - p=0,01).

Os dois grupos também diferiram com relação à dosagem plasmática de lactato durante o período de sete dias (Figura 6).

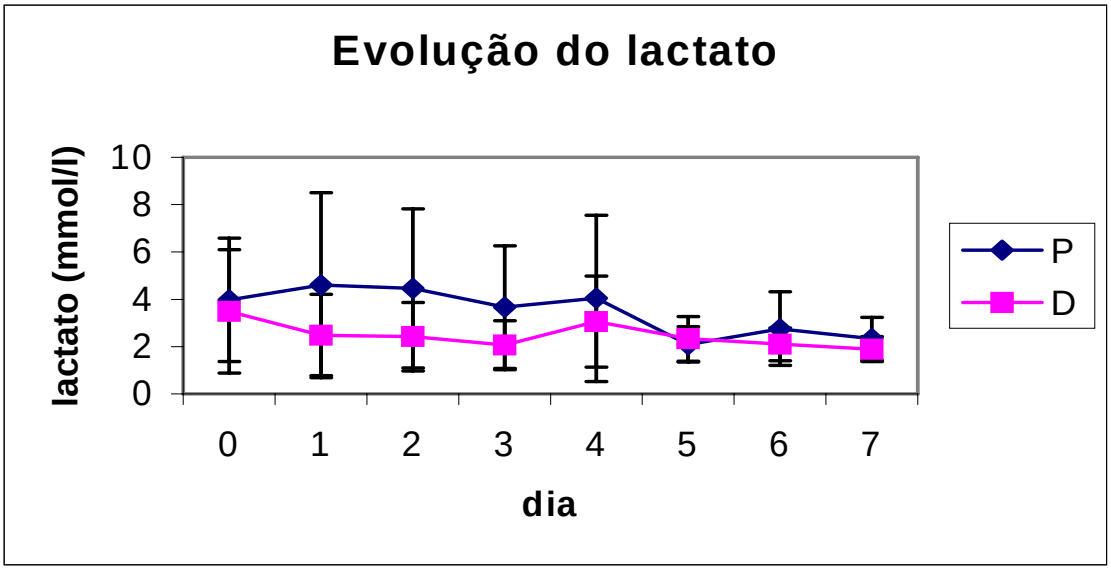

Figura 6. Evolução do lactato (mmol/l) nos grupos (p=0,02).

As evoluções do escore SOFA, do lactato plasmático, da dosagem plasmática de PCR e SAA dos pacientes estudados de ambos os grupos durante o período de sete dias são mostradas na Tabela 3 e na Figura 7.

O escore SOFA e o lactato mostraram pequena variação, enquanto a SAA diminuiu até o dia 4 atingindo estabilidade assim como a PCR permaneceu com valores baixos.

Tabela 3 – Evolução do SOFA, lactato, PCR e SAA durante o período de 7 dias.

Parâmetros (média±DP)	Dia 0	Dia 1	Dia 2	Dia 3	Dia 4	Dia 5	Dia 6	Dia 7
SOFA	9,6±2,3	10,0±2,7	9,3±4,2	9,7±4,5	9,3±4,3	9,6±3,8	8,7±4,2	8,6±3,5
Lactato(mmol/l)	3,9±2,6	3,4±2,9	3,1±2,7	2,3±1,1	2,9±2,5	2,4±0,8	2,6±1,2	2,1±0,8
PCR (mg/dl)	19,4±8,3	20,6±9,2	16,6±6,3	13,4±6,0	12,0±7,9	13,4±11,4	11,9±8,3	10,0±4,4
SAA (mg/dl)	46,8±40,7	36,6±28,6	28,8±21,9	23,0±18,9	21,3±19,4	26,4±26,2	22,2±20,5	21,7±16,8

SOFA – sequential organ failure assessment, PCR – proteína C-reactiva, SAA – proteína amilóide A sérica.

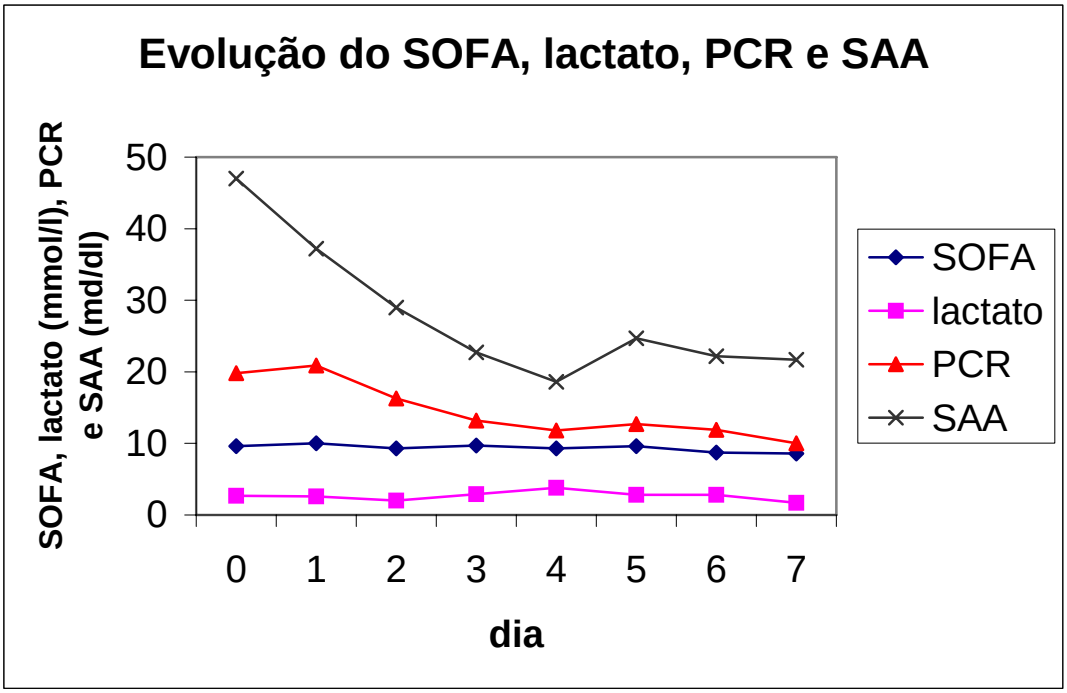

Figura 7. Evolução diária do escore SOFA, lactato (mmol/l), PCR e SAA (mg/dl).

As dosagens de PCR evoluíram com maior queda no grupo tratado (grupo D) apresentando diferença significativa entre os grupos. A proteína SAA não apresentou diferença entre os grupos (Figura 8 e 9).

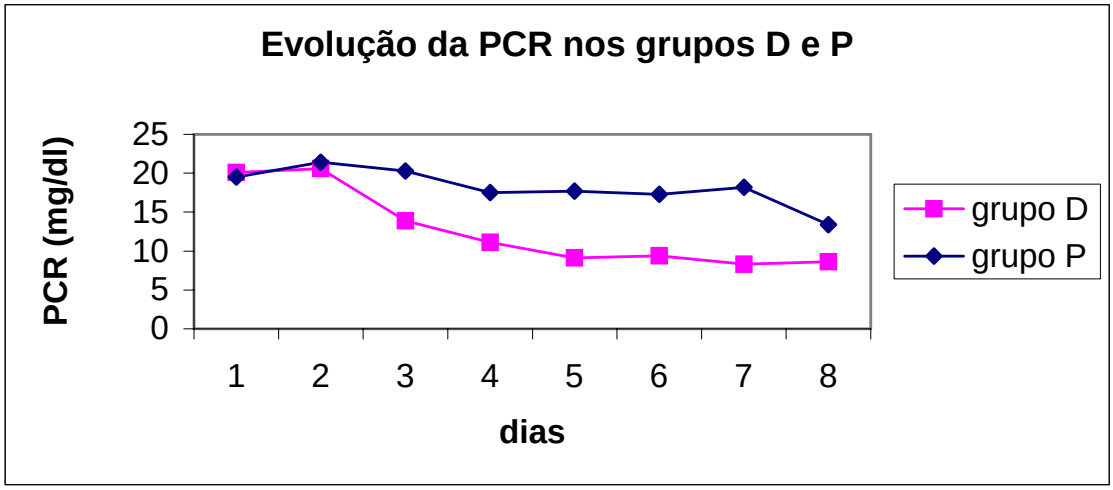

Figura 8. Evolução da PCR entre os grupos D e P (p=0,006).

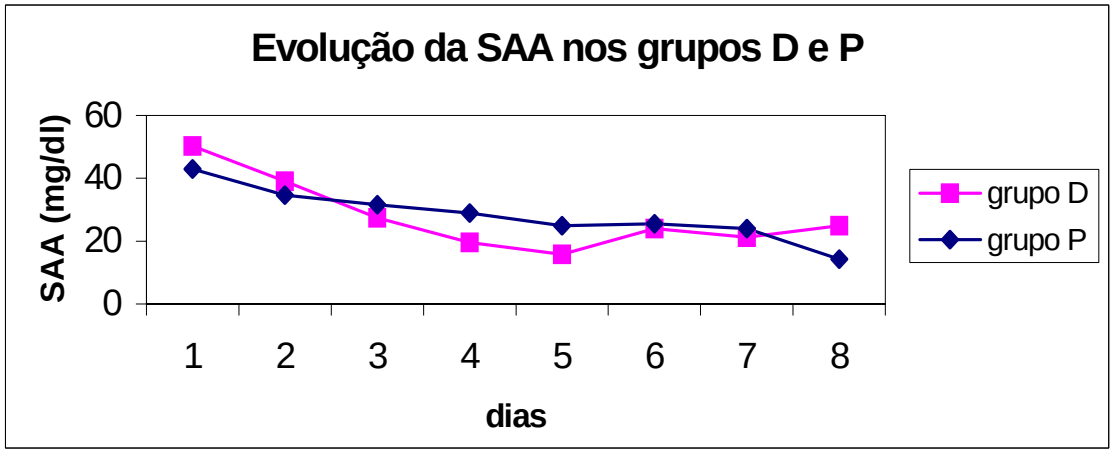

Figura 9. Evolução da SAA entre os grupos D e P (p=0,66).

A análise da dosagem plasmática de PCR e de SAA mostrou que ambas tiveram boa correlação com o SOFA, porém sem significância estatística. A correlação dos níveis de PCR e SOFA foi de 0,51 (R=0,71/p=0,05). A correlação dos níveis de SAA e SOFA foi de 0,27 (R=0,52/p=0,18). As correlações podem ser vistas nas Figuras 10 e 11.

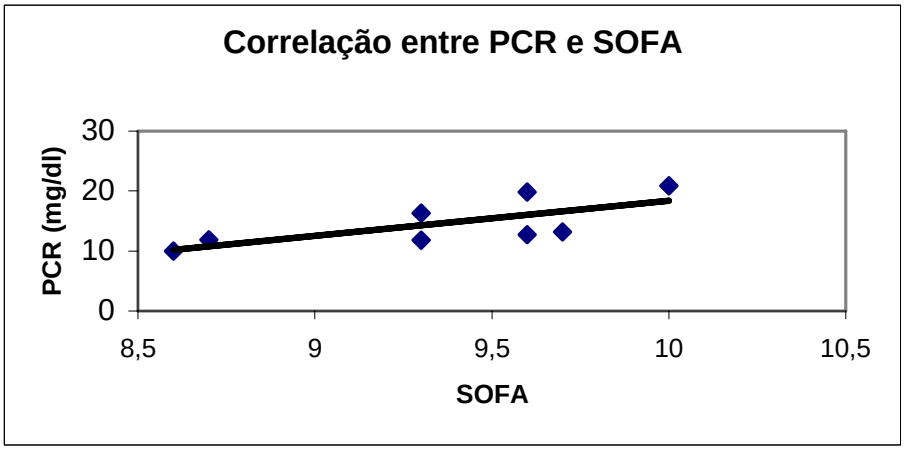

Figura 10. Correlação entre PCR e SOFA (R=0,71/p=0,05).

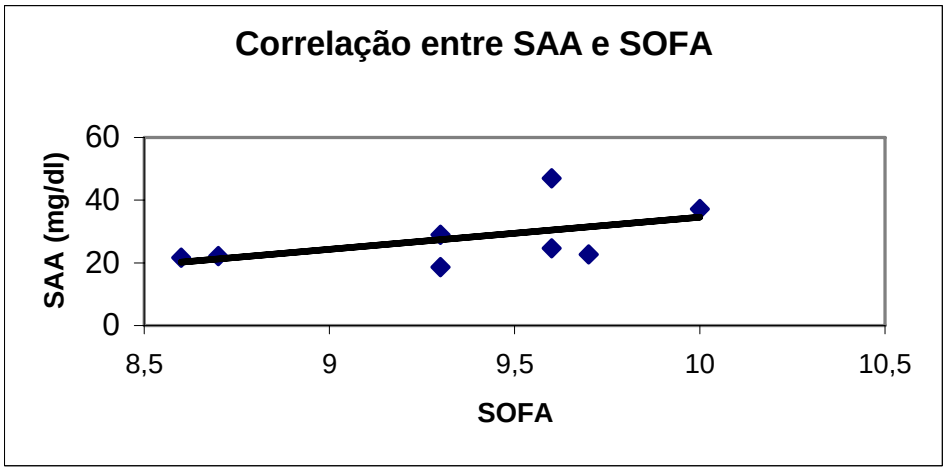

Figura 11 – Correlação entre SAA e SOFA (R=0,52/p=0,18).

Quando as concentrações plasmáticas de PCR e SAA foram analisadas comparativamente às dosagens diárias de lactato, ambas, PCR e SAA, apresentaram uma discreta correlação negativa. A correlação entre os níveis de PCR e lactato foi de 0,004 (R=0,06, p=0,88). A correlação dos níveis de SAA e lactato foi de 0,03 (R=0,18, p=0,67).

As dosagens de SAA apresentaram alta correlação com as da PCR, de 0,81 (R=0,91, p=0,002). Pode-se observar esta correlação na Figura 12.

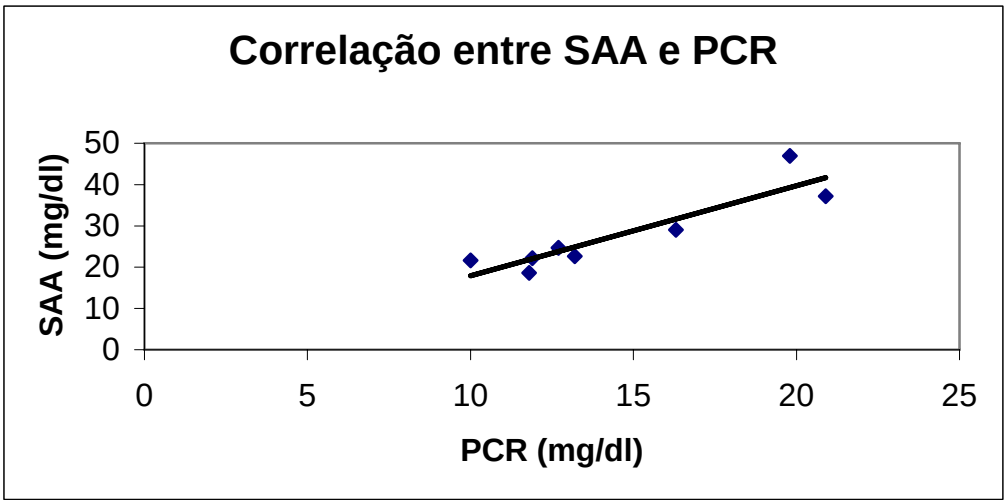

Figura 12. Correlação entre SAA (mg/dl) e PCR (mg/dl) (R=0,91/p=0,002).

Por outro lado, as dosagens diárias de lactato apresentaram fraca correlação com os valores do escore SOFA. A correlação do lactato com o SOFA foi de 0,11 (R=0,32, p=0,43).

A mortalidade destes pacientes em sete dias foi de 44,8% (13 em 29) e em 28 dias foi de 65,5% (19 em 29). A concentração plasmática das proteínas não se correlacionou à mortalidade (Tabela 4).

Tabela 4 – Valor prognóstico de PCR e SAA (mg/dl) em pacientes em choque séptico.

	óbito	Sobrevivente	P
PCR			
Dia 0	9,9 (9,9)	19,4 (4,7-37)	NS
Dia 1	17,6 (16,1-19)	20,6 (4,8-40)	NS
Dia 2	27 (16,1-40)	15,9 (4,7-29,6)	NS
Dia 3	17,9 (17,9)	12,9 (5-27,7)	NS
Dia 4	9,9 (4,8-15)	12 (4,3-34,3)	NS
Dia 5	4,3 (4,3)	13,4 (2,3-40,8)	NS
Dia 6	33,3 (33,3)	9,8 (2,9-33,3)	NS
Dia 7	-	10 (3,1-16,9)	NS
SAA			
Dia 0	34,1 (34,1)	46,8 (9-160)	NS
Dia 1	11,9 (0,7-16,8)	36,6 (7-115,1)	NS
Dia 2	33,2 (17,6-63,5)	28,9 (4,7-96,8)	NS
Dia 3	39,5 (39,5)	21,7 (3,1-77,7)	NS
Dia 4	3,2 (2,1-4,2)	21,3 (2,1-82,4)	NS
Dia 5	7,8 (7,8)	26,4 (0,9-89,2)	NS
Dia 6	68,7 (68,7)	17,6 (0,3-68,7)	NS
Dia 7	-	21,7 (0,5-51,8)	NS

NS – não significativo, dados expressos como média (variação).

DISCUSSÃO

A dexametasona diminuiu o tempo de uso de medicações vasopressoras e levou à melhora da função respiratória caracterizada por aumento da relação PaO_2/FiO_2 no primeiro dia após sua administração e por maior tempo livre de ventilação mecânica. O uso precoce de dexametasona em pacientes em choque séptico no período pós-operatório diminuiu a disfunção orgânica e a mortalidade em sete dias.

Este estudo revelou também correlação significativa entre a SAA e a PCR em pacientes no período pós-operatório em choque séptico, evidenciando a PCR como melhor marcadora da evolução dos pacientes tratados.

A escolha pela dexametasona deveu-se à sua potência e maior duração de ação (36-48 horas) e por sua ação ser predominantemente antiinflamatória, com mínimos efeitos mineralocorticóides. Quando comparada à hidrocortisona, a dexametasona não interfere com o estado volêmico do paciente, particularmente por não causar distúrbios do metabolismo de sódio.[26] A dexametasona também não interfere com testes diagnósticos para insuficiência adrenal aguda.[12] A dexametasona foi testada inicialmente em pacientes com SRIS, mostrando alguns benefícios sem causar efeitos adversos.[11] Desta forma, decidiu-se estender o estudo aos pacientes sépticos para investigar os benefícios e os possíveis efeitos colaterais.

A explicação atual para o uso dos corticóides seria a potencialização dos efeitos dos vasopressores através do restabelecimento da sensibilidade dos receptores, permitindo melhores efeitos com menores doses.[34] Como 30 a 70% dos pacientes em sepse ou choque séptico apresentam insuficiência adrenal, a reposição de corticóides nestes pacientes seria obrigatória.[34-38] Ainda não está definido qual o melhor método

para o diagnóstico da insuficiência adrenal nestes pacientes. Vários estudos utilizam a hidrocortisona após a realização de um teste de estimulação adrenal com corticotropina.[36] A definição de insuficiência adrenal seria um aumento no cortisol total menor ou igual a 9μg/dl em resposta a um estímulo de 250μg de corticotropina.[37,38] Lipiner-Friedman et al observam que quanto maior a variação do cortisol (valor de pico menos o valor basal) melhor é a evolução clínica do paciente. Portanto, só seria necessária reposição de corticóide nos pacientes com pouca variação do cortisol após o estímulo. Porém, concluem que outros estudos são necessários para otimizar o diagnóstico de insuficiência adrenal em pacientes em choque séptico ou sepse grave.[39]

Administrou-se dexametasona mais precocemente nos pacientes ora estudados, logo após o diagnóstico de choque séptico, assim como Annane et al [36], porém diferentemente deste, não se descontinuou a terapêutica, pois não foi realizado o teste para diagnóstico de insuficiência adrenal relativa. Acredita-se que caso 50% dos pacientes estudados não tivessem insuficiência adrenal, não seriam encontrados os resultados positivos apresentados. Portanto, entende-se que o principal mecanismo de ação dos corticóides não foi o tratamento da insuficiência adrenal, mas sim seu efeito antiinflamatório. Questiona-se se este teste é realmente necessário. A maioria dos locais de atendimento de pacientes sépticos não tem disponibilidade de realizar o teste, seja pelo custo, seja pela incerteza do diagnóstico, e alguns relatos publicados mostram que mesmo pacientes em choque séptico sem insuficiência adrenal, apresentam melhor evolução após a terapia com corticóide.[2,40] Os resultados ora apresentados estão em concordância com estes autores, pois a dexametasona foi administrada independente do

diagnóstico de insuficiência adrenal, e resultou na descontinuação precoce dos medicamentos vasopressores e diminuição da mortalidade destes pacientes.[41]

Sprung et al (Estudo Corticus), em publicação recente, confirmam esta observação, pois não encontram diferença entre pacientes tratados com hidrocortisona que apresentam ou não resposta ao teste com corticotropina.[42] Estes autores confirmam com seus resultados a pouca importância do diagnóstico de insuficiência adrenal para os pacientes em choque séptico.

Porém, Sprung et al também não observam benefício do uso da hidrocortisona no choque séptico para redução da mortalidade em 28 dias, apesar da hidrocortisona apressar a reversão do choque.[42] O resultado obtido por eles difere do resultado deste estudo, porém, o momento do início da terapia com corticóide também difere, sendo que o estudo de Sprung et al apresenta janela terapêutica de 72 horas entre o diagnóstico de choque séptico e o início da terapia, e este estudo iniciou a terapêutica com corticóide imediatamente após o diagnóstico de choque séptico.

As recomendações atuais da *Surviving Sepsis Campaign* (2008) para o uso de corticóides na sepse incluem apenas pacientes em choque séptico refratário à ressuscitação com fluidos e drogas vasoativas.[43] O teste com corticotropina para diagnóstico de insuficiência adrenal não é recomendado. A hidrocortisona é preferível em relação à dexametasona, pois a dexametasona pode causar supressão prolongada do eixo hipotalâmico-hipofisário-adrenal após sua administração.[43] Esta última recomendação é baseada no estudo de Reincke et al que observaram supressão do eixo hipotalâmico-hipofisário-adrenal após administração de dexametasona em pacientes do grupo controle. Os pacientes gravemente enfermos do outro grupo, que também receberam a mesma dose de dexametasona, não responderam com supressão do eixo.[44]

Logo, esta recomendação feita não tem embasamento nos resultados de Reincke et al. Outros autores também questionam algumas das recomendações da *Surviving Sepsis Campaign* desde 2004, apontando hierarquização equivocada das evidências disponíveis e presença de vieses nas recomendações feitas.[45]

Se a sepse pode ser considerada a resposta inflamatória sistêmica à infecção, sepse, sepse grave e choque séptico constituiriam gradações diferentes de uma mesma doença e a continuidade deste processo correlacionar-se-ia a um aumento da disfunção orgânica e da mortalidade. A administração precoce de corticóides para bloquear o processo que se inicia pela resposta inflamatória avaliada neste estudo é válida. Evidenciou-se este fato observando a diminuição do escore SOFA nos pacientes tratados, bem como a diminuição dos níveis de lactato e da mortalidade. Acredita-se que o principal mecanismo de ação dos corticóides nestes pacientes seja simplesmente devido à sua ação antiinflamatória. Neste estudo, usou-se dexametasona na dose de 0,2 mg/kg em pacientes com diagnóstico de choque séptico e não foram observados efeitos adversos que pudessem ser atribuídos à medicação. Em estudo anterior, a mesma dose de dexametasona administrada a pacientes com diagnóstico de SRIS também não causou efeitos adversos.[11] Sprung et al observaram aumento do risco relativo de superinfecção nos pacientes do grupo da hidrocortisona.[42] Todos os eventos relacionados à nova infecção relatados naquele estudo estão aumentados no grupo hidrocortisona, porém o intervalo de confiança de 95% para os dados apresentados inclui o valor nulo de 1,0, não havendo portanto diferença estatística do risco nos grupos estudados.[46] Portanto, a afirmação do aumento do risco de superinfecção dos pacientes estudados por ele não pode ser feita. Logo, mesmo em pacientes que tenham reserva adrenal adequada, o uso de corticóides em doses consideradas fisiológicas não

causa efeitos adversos graves como infecções secundárias ou sangramentos gastrointestinais.[11,41]

Meduri et al, em estudo experimental, concluem que os corticóides diminuem o edema pulmonar e a formação de colágeno.[47] Thompson demonstra melhora dos pacientes com diagnóstico de SDRA após terapia com corticóides, provavelmente devido à inibição da fibroproliferação pulmonar.[9,48] Estes estudos apóiam a observação feita de que pacientes tratados com dexametasona evoluíram com melhora da relação PaO_2/FiO_2 no primeiro dia após o início da terapia e maior tempo livre de ventilação mecânica. A despeito do uso de corticóides para tratamento da fase aguda da SDRA não ser aconselhado até então, pois as recomendações incluíam o uso do corticóide somente na fase crônica ou fibroproliferativa, Meduri et al encontraram melhora dos pacientes que fizeram uso de metilprednisolona por sete dias na fase aguda da SDRA, com redução da duração da ventilação mecânica.[49,50] Neste estudo, mesmo os pacientes que receberam dexametasona durante a fase exsudativa da doença, ou seja, nos primeiros 5 dias, evoluíram com melhora da relação PaO_2/FiO_2 nas primeiras 24 horas, e aumento do tempo livre de ventilação mecânica. A explicação para este fato pode ser a de que a manutenção da integridade da barreira epitelial na resolução do edema alveolar parece ser fator determinante para a evolução favorável dos pacientes com SDRA. Pacientes que concentram proteína no fluido edematoso nas primeiras 12 horas do início da doença parecem se recuperar mais rápido. Por fim, desde que a mudança na relação PaO_2/FiO_2 após o tratamento inicial da SDRA pode discriminar entre sobreviventes e não sobreviventes, o uso de corticóides nas fases iniciais parece ser uma terapêutica útil.[49,50]

A SAA tem sido considerada por alguns autores como equivalente à PCR como marcador de pacientes com infecção bacteriana na prática clínica.[51] Outros autores sugerem que a SAA seria um marcador mais sensível do que a PCR em infecções com baixa atividade inflamatória, incluindo infecções virais, e em outras condições clínicas, especialmente naquelas envolvendo os pulmões. [51,52] Estudos ainda confirmaram o papel da SAA e da PCR no diagnóstico e manuseio de infecções neonatais.[16,53]

Os padrões de produção de citocinas e da resposta de fase aguda diferem de acordo com a resposta inflamatória. As respostas de fase aguda refletem a presença e a intensidade da inflamação e têm sido usadas como guia clínico para o diagnóstico e tratamento.[18] Póvoa et al acreditam que valores absolutos de PCR maiores que 8,7mg/dl predizem infecção em 88% dos pacientes.[54,55] Porém, outros autores defendem que 80 a 85% dos pacientes com concentrações plasmáticas de PCR superiores a 10mg/dl têm infecções bacterianas.[18,56] Neste estudo, todos os pacientes estavam em choque séptico, e portanto, tinham infecção documentada. Pôde-se observar que todos os pacientes apresentaram concentrações plasmáticas de PCR maiores que 10mg/dl durante o período de estudo, confirmando os resultados de Gabay et al.[18] Em relação às concentrações plasmáticas de SAA, nenhum valor de corte foi determinado em estudos prévios. Observou-se que todos os pacientes estudados apresentaram concentrações maiores do que 20mg/dl. É possível aventar a hipótese de que este seja um valor sugestivo de corte para o diagnóstico de infecção nos pacientes, embora outros estudos sejam necessários para confirmar tal dado.

Não foram observadas diferenças entre as dosagens plasmáticas de PCR e SAA em pacientes que foram a óbito comparativamente àqueles que sobreviveram.

Outros autores também relatam que tais proteínas não foram marcadores com valor prognóstico em pacientes em choque séptico.[21,56] Este fato está em concordância com os resultados aqui apresentados, visto que as proteínas não se correlacionaram com a dosagem plasmática de lactato, que é sabidamente um marcador eficiente da evolução destes pacientes.[13-15] Em contraste com estes resultados, alguns autores têm observado que as dosagens de PCR estão associadas com a mortalidade e falência orgânica em pacientes criticamente enfermos, embora não especificamente com choque séptico.[57]

Não foi encontrada correlação significativa entre as dosagens de PCR e SAA e o escore SOFA, dado que está em concordância com os achados de Castelli et al e Luzzani et al em relação à PCR.[1,58] Castelli et al definem a PCR como bom marcador de atividade inflamatória, porém não de disfunção orgânica. Os resultados encontrados estão em concordância com Castelli em caracterizar a PCR como marcadora da da resposta inflamatória, visto que apresentou queda significativa nos pacientes tratados com dexametasona, e concordam também com este autor ao não caracterizá-las (PCR e SAA) como marcadoras de disfunção orgânica.

Gabay et al ressaltam a possibilidade do uso dos glicocorticóides aumentarem os efeitos estimulantes das citocinas na produção das proteínas de fase aguda.[18] Desta forma, os pacientes que recebem dexametasona podem evoluir com valores mais altos da PCR e SAA. Os resultados encontrados evidenciam que apenas a SAA não se comportou de forma diferente entre os pacientes tratados e não. Ë possível que os glicocorticóides influenciem mais a SAA que a PCR, mascarando seu valor como marcador da melhora dos pacientes, ou simplesmente que esta seja pior marcador da evolução dos pacientes em relação à PCR.

CONCLUSÕES

A dexametasona diminuiu o tempo de uso de medicações vasopressoras e o tempo de ventilação mecânica e seu uso precoce diminuiu a disfunção orgânica e a mortalidade em 7 dias de pacientes com choque séptico em período pós-operatório.

Tanto PCR quanto SAA apresentaram concentrações plasmáticas elevadas nestes pacientes; a PCR foi marcadora da evolução dos pacientes tratados com dexametasona, porém nem PCR nem SAA foram preditoras de disfunção orgânica ou mortalidade.

ANEXOS

Anexo A – Escore APACHE II

Escore Fisiológico Agudo

Pontos	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperatura(°C)	≥41	39-40,9		38,5-38,9	36-38,4	34-35,9	32-33,9	30-31,9	≤29,9
PAM(mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
FC(bpm)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
FR	≥50	35-49		25-34	12-24	10-11	6-9		≤5
$D_{(A-a)}O_2/PaO_2$	≥500	350-499	200-349		<200/>70	61-70		55-60	<55
PH arterial	≥7,7	7,6-7,69		7,5-7,59	7,33-7,49		7,25-7,32	7,15-7,24	<7,15
Sódio(mEq/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Potássio(mEq/l)	≥7	6-6,9		5,5-5,9	3,5-5,4	3-3,4	2,5-2,9		<2,5
Creatinina(mg/dl)	≥3,5		1,5-1,9		0,6-1,4		<0,6		
Hematócrito	≥60		50-59,9	46-49,9	30-45,9		20-29,9		<20
Leucócitos	≥40		20-39,9	15-19,9	3-14,9		1-2,9		<1
GCS	15-valor observado								

PAM: pressão arterial média, FC: freqüência cardíaca, FR: freqüência respiratória, $D_{(A-a)}O_2/PaO_2$: diferença alvéolo-arterial de oxigênio / pressão arterial de oxigênio, pH arterial: pH da gasometria arterial, GCS: escala de coma de Glasgow.

Ajuste para a idade

Idade (anos)	Pontos
<44	**0**
45-54	**2**
55-64	**3**
65-74	**5**
>75	**6**

Ajuste para o estado prévio de saúde

Para qualquer um dos seguintes:
1. Hepática: cirrose comprovada por biópsia
2. Cardiovascular: grupo IV da classificação da NYHA
3. Respiratório: DPOC (hipercarbia, oxigênio domiciliar)
4. Diálise crônica
5. Imunocomprometimento
Acrescente 2 pontos para cirurgia eletiva ou neurocirurgia, 5 pontos para cirurgia de urgência.

NYHA: New York Heart Association, DPOC: doença pulmonar obstrutiva crônica.

Escore APACHE II=escore fisiológico agudo+idade+estado prévio de saúde.

Anexo B - ESCORE SOFA

SOFA (pontos)	**1**	**2**	**3**	**4**
Respiratório PaO_2/FiO_2 (mmHg)	< 400	< 300	< 200 (com suporte respiratório)	< 100 (com suporte respiratório)
Coagulação Número de plaquetas	< 150.000	< 100.000	< 50.000	< 20.000
Hepático (Bilirrubinas mg/dl)	1,2 – 1,9	2,0 -5,9	6,0 – 11,9	> 12
Cardiovascular Hipotensão (mmHg / mcg/Kg/min)	PAM<70 mmHg	Dopamina=5 ou dobutamina (qualquer dose)	dopamina>5 ou adrenalina=0,1 ou noradrenalina≤0,1	dopamina>15 ou adrenalina>0,1 ou noradrenalina>0,1
SNC Escala de Glasgow	13 –14	10 –12	6 -9	< 6
Renal Creatinina (mg/dl)	1,2 – 1,9	2,0 – 3,4	3,5 – 4,9	> 5,0

Anexo C – ARTIGOS RELACIONADOS À TESE PUBLICADOS EM PERIÓDICOS

ORIGINAL ARTICLE

Domingos Dias Cicarelli
Fábio Ely Martins Benseñor
Joaquim Edson Vieira

Effects of single dose of dexamethasone on patients with systemic inflammatory response

Surgical Support Unit, Anesthesia Division, Department of Surgery, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil

ABSTRACT

CONTEXT AND OBJECTIVE: Systemic inflammatory response syndrome (SIRS) is a very common condition among critically ill patients. SIRS, sepsis, septic shock and multiple organ dysfunction syndrome (MODS) can lead to death. Our aim was to investigate the efficacy of a single dose of dexamethasone for blocking the progression of systemic inflammatory response syndrome.

DESIGN AND SETTING: Prospective, randomized, double-blind, single-center study in a postoperative intensive care unit (Surgical Support Unit) at Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo.

METHODS: The study involved 29 patients with SIRS. All eligible patients were prospectively randomized to receive either a single dose of 0.2 mg/kg of dexamethasone or placebo, after SIRS was diagnosed. The patients were monitored over a seven-day period using Sequential Organ Failure Assessment score (SOFA).

RESULTS: The respiratory system showed an improvement on the first day after dexamethasone was administered, demonstrated by the improved PaO_2/FIO_2 ratio ($p < 0.05$). The cardiovascular system of patients requiring vasopressor therapy also improved over the first two days, with a better evolution in the dexamethasone group ($p < 0.05$). Non-surviving patients presented higher lactate assays than did survivors ($p < 0.05$) during this period.

CONCLUSIONS: Dexamethasone enhanced the effects of vasopressor drugs and evaluation of the respiratory system showed improvements (better PaO_2/FIO_2 ratio), one day after its administration. Despite these improvements, the single dose of dexamethasone did not block the evolution of SIRS.

KEY WORDS: Sepsis syndrome. Sepsis. Inflammation. Adrenal cortex hormones. Dexamethasone.

INTRODUCTION

Systemic inflammatory response syndrome (SIRS) is a very common condition among critically ill patients. It occurs frequently in the postoperative period, with or without infection. SIRS may be related to trauma, burns, pancreatitis or pulmonary diseases, leading to acute lung injury (ALI) and acute distress respiratory syndrome (ARDS).[1] SIRS can be defined by two or more symptoms such as fever (body temperature > 38°C) or hypothermia (< 36°C), tachycardia (> 90 beats/min), tachypnea (> 20 breaths/min) or hyperventilation ($PaCO_2$ < 32 torr), and abnormal white blood cell counts (> 12,000 cells/µl or < 4,000 cells/µl) or immature neutrophils (bands > 10%).[1,2]

SIRS, sepsis, septic shock and multiple organ dysfunction syndrome (MODS) are strongly related. The patient's progression through this sequence often leads to death. However, some patients with SIRS develop MODS without diagnosed infection or sepsis.[3] Sepsis is defined as a condition in which the patient displays the SIRS criteria as well as a documented or a suspected infection. Severe sepsis is defined as sepsis with organ dysfunction, inadequate perfusion or hypotension (systolic blood pressure < 90 mmHg or a reduction ≥ 40 mmHg from the baseline). Septic shock is defined as severe sepsis with hypotension despite adequate fluid resuscitation, which requires vasopressor support. MODS is defined as organ dysfunction in critically ill patients who require intervention to reach homeostasis.[1]

Activation of the inflammatory cascade by a new agent, with or without infection, seems to be self-sustained.[3] However, resolution of the inducing agent cannot be the only treatment for SIRS and cannot break the progression of the inflammatory response that leads to MODS and death. Despite early administration of antibiotics, the progression of SIRS to sepsis, septic shock, MODS and death is sometimes unavoidable.

To lessen the progression of SIRS and improve the outcome, drugs such as glucocorticoids and anti-inflammatory nonsteroids have been used, albeit unsuccessfully. More recently, specific monoclonal antibodies against inflammatory cytokines such as tumor necrosis factor (TNF) have been tested.[4]

Glucocorticoids have an important immunosuppressive effect, in which they reduce the transcription of pro-inflammatory genes by inhibiting the nuclear factor kappa B.[4-8] Several studies have involved the use of corticosteroids to reduce the systemic inflammatory process associated with the host response to sepsis and septic shock.[9-21] However, most of these studies involved extremely high doses over short periods (< 24 hours), and no diagnostic criteria for sepsis were applied, because such criteria were not yet well-established at that time. The results were controversial, although some authors believed in the benefit of corticosteroids after observing early shock reversal or blood pressure elevation in treated patients.[11,13,14,17,19,20,22,23]

Some of these studies have not been confirmed by other groups.[15] The results from two meta-analyses indicated no survival benefit when supraphysiological doses of corticosteroids were administered for short-term treatment of sepsis, and higher infection rates were associated with corticosteroids.[12,18] Some authors[16,24,25] believe that more careful, broader-scope studies are needed to conclusively identify the real benefits from these drugs.

Several reports have been published recently, from studies involving lower doses of hydrocortisone. These showed improved outcomes for patients with septic shock, and also showed that methylprednisolone could be used to obtain ARDS resolution.[10,21,26,27] These recent results, as well as the unfavor-

able results from using specific monoclonal antibodies, rekindle hope for the efficacy of corticosteroids in treating SIRS.

OBJECTIVE

This study aimed to evaluate the effectiveness of a single dose of dexamethasone in blocking the progression of SIRS.

METHODS

This study was prospective, randomized, double-blind and placebo-controlled. After approval by a local ethics committee, informed consent was obtained from patients or from their next of kin prior to enrollment.[28] Twenty-nine patients admitted into the postoperative intensive care unit (Surgical Support Unit, SSU) of Hospital das Clínicas, Universidade de São Paulo, took part in the study. Apart from these patients, one other patient was excluded after his next of kin withdrew their consent.

Patients with SIRS diagnosed 12 hours after SSU admission,[1,29] with or without sepsis, were eligible for the study. Patients were excluded if they were under 18; had a history of immunosuppression therapy or a history of glucocorticoid use for over two weeks within the last year or upon admission to this hospital; were suffering from active pancreatitis; had a terminal illness (end-stage neoplasm with a life expectancy of less than three months); or had recently suffered gastrointestinal hemorrhage.[27] After SIRS diagnosis, blood, urinary and catheter-tip cultures (if infection was suspected) were obtained in accordance with the SSU hospital routine. A randomization table determined the order of inclusion for the patients to receive placebo, among the expected 30 admissions. All the eligible patients were prospectively randomized into two groups: Group D comprising 15 patients and Group P with 14 patients. Group D patients were given intravenous dexamethasone 0.2 mg/kg (in a single dose),[30] while Group P patients received placebo (0.9% physiological saline solution).

Baseline severity of illness was assessed by means of the Acute Physiology and Chronic Health Evaluation II score (APACHE II).[31,32] After SIRS diagnosis, the patients were assessed daily for seven consecutive days using the Sequential Organ Failure Assessment score (SOFA),[33-37] or until their discharge from the SSU. Lactate and C-reactive protein plasma concentrations were also measured daily.[38]

The patients received conventional therapy regarding antibiotic regimens, serial blood cultures (whenever their body temperature was > 38° C) and discharge criteria. Appropriate clinical and laboratory tests were conducted daily throughout the study. The subjects were evaluated during their stay in the SSU on the basis of the duration of vasopressor support (SOFA score of two or more for the cardiovascular system), mechanical ventilation and mortality.

Statistical analysis was performed using the Sigma Stat for Windows software, 2.03 version (SPSS Inc.). For continuous variables, the treatments were compared using the Student t test, Mann-Whitney U test and two-way ANOVA (analysis of variance) for treatment and outcome conditions.

RESULTS

The mean age (± standard deviation, SD) of the 29 patients was 53 ± 19 years (range: 18 to 77 years). The study involved 19 males and 10 females (66% versus 34%). The mean age (± SD) for Group D was 51 ± 22 years, while the mean age for Group P was 54 ± 14 years. There was no difference between these groups in relation to APACHE II (15 ± 5 for Group D and 16 ± 4 for Group P). At the baseline, the demographic characteristics and severity of disease were similar in the two groups (Table 1).

No statistical difference was found in either the mortality rates for the groups during the seven-day follow-up period (five deaths in Group D and three deaths in Group P; p = 0.682; Fisher exact test), or in the blood, urinary or catheter-tip cultures. With regard to collateral effects from dexamethasone (increased glucose, secondary infections or gastrointestinal hemorrhage), only one patient in Group P developed gastrointestinal hemorrhage (patient 7, with enterectomy due to intestinal perforation) while two patients in Group P developed pneumonia (patient 6, with colectomy due to neoplasia, and patient 7, with aneurysm repair).

Among the 29 patients with SIRS, 14 failed to reach the SIRS criteria on the second day of their stay at the SSU. Eleven patients showed positive blood cultures, suggesting that these 38% of the patients had sepsis. Nine patients (31%) had septic shock and the remaining 10 patients required vasopressor therapy during their SSU stay.

The two groups showed similar SOFA scores during the study. No differences were found in coagulation disorders (platelet counts), hepatic dysfunction (serum bilirubin), renal dysfunction (serum creatinine), or central nervous system dysfunction according to the Glasgow scale (Figure 1).

The respiratory system 24 hours after dexamethasone administration showed an improved PaO_2/FiO_2 ratio (Mann-Whitney test; p = 0.017). However, this improvement did not persist throughout the study (Figure 2). The duration of mechanical ventilation was the same in the two groups (3.26 ± 2.46 days for Group D and 3.64 ± 3.15 days for Group P).

Table 1. Baseline characteristics of the 29 patients with diagnosed systemic inflammatory response syndrome

Characteristics	Placebo Group (n = 14)	Dexamethasone Group (n = 15)
Age (years)	54 ± 14	51 ± 22
Male sex (%)	64.3	66.7
Weight (kg)	67.2	69.3
APACHE II score	16 ± 4	15 ± 5
SOFA score	6.9	7.1
Prior or preexisting conditions (%)		
Hypertension	28.6	33.3
Myocardial infarction	14.3	13.3
Diabetes	14.3	13.3
Liver disease	7.1	-
COPD	7.1	6.7
Cancer	21.4	20
Recent trauma	35.7	20
Mechanical ventilation	64.3	60
Shock (use of any vasopressor)	50	60

APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = sequential organ failure assessment; COPD = chronic obstructive pulmonary disease.

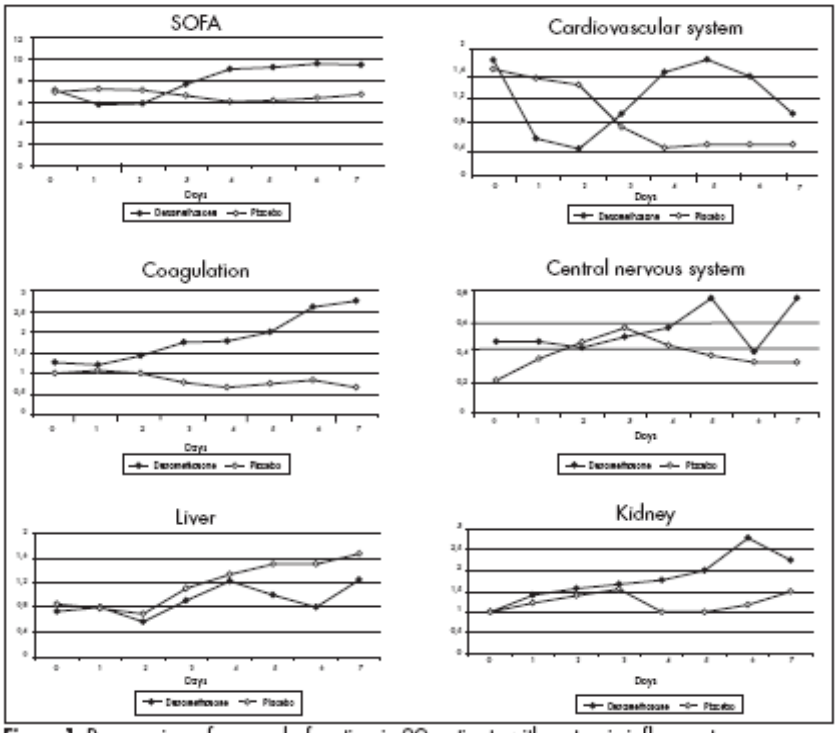

Figure 1. Progression of organ dysfunction in 29 patients with systemic inflammatory response syndrome, as assessed using the different components of the Sequential Organ Failure Assessment score (SOFA).

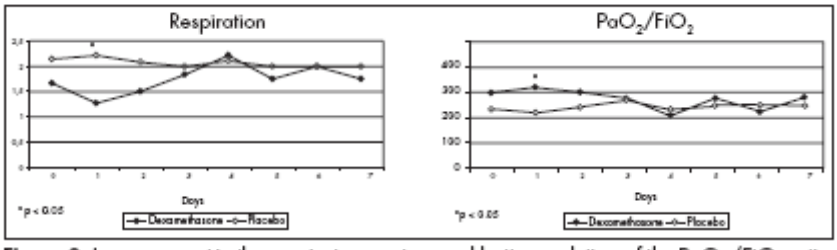

Figure 2. Improvement in the respiratory system and better evolution of the PaO_2/FiO_2 ratio in the first day after diagnosis of systemic inflammatory response syndrome in patients that received a single dose of dexamethasone, compared with those who received placebo.

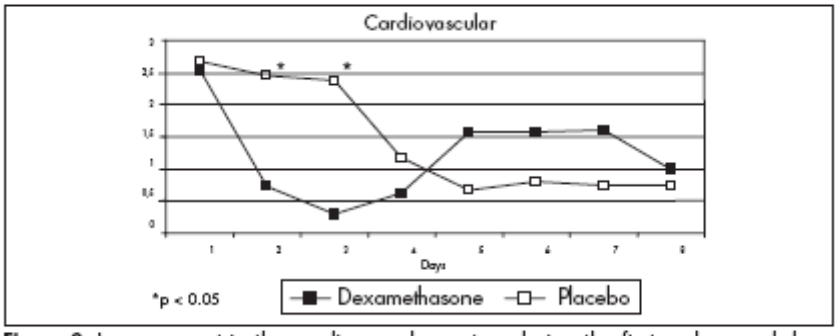

Figure 3. Improvement in the cardiovascular system during the first and second days after diagnosis of systemic inflammatory response syndrome in the group of patients that received a single dose of dexamethasone, compared with placebo, including only the patients that received vasopressor therapy.

The cardiovascular system score showed a trend towards improvement in Group D over the first two days (Figure 1). The better evolution in Group D, when the patients who did not receive vasopressor therapy were excluded (Mann-Whitney test; p = 0.007 and p = 0.018 on days 1 and 2, respectively) (Figure 3), was noteworthy. However the duration of vasopressor therapy was statistically similar for the two groups (2.2 ± 2.1 days for Group D and 2.8 ± 1.9 days for Group P).

All the 29 patients were also divided into two additional groups: survivors and non-survivors, in relation to the treatment. Eight patients (27.6%) died during the seven-day period (SSU mortality). After using two-way ANOVA (analysis of variance) for the treatment, the cardiovascular system score was high for 48 hours among the non-survivors of Group P. In fact, these measurements displayed a significant difference (p = 0.028 on day one; p = 0.003 on day two). The respiratory system score showed the same pattern, i.e. it was low for 48 hours among survivors of Group D, with a significant difference (p = 0.0038 on day one; p = 0.008 on day two).

Compared with the survivor group (21 patients), the non-survivors presented higher lactate assays (Mann-Whitney test; p = 0.002) for four days during the study (Figure 4).

C-reactive protein was higher in the non-survivor group, starting on day three (p = 0.028) and remaining high throughout (Figure 4). There was no difference between Groups D and P relating to C-reactive protein.

Among the 29 patients studied, 17 patients (58.6%) had suspected infection (nine patients in Group P and eight patients in Group D), and positive blood cultures were found in 11 (37.9%) (six patients in Group P and five patients in Group D). Of the 29 patients, 12 (41.3%) were given prophylactic antibiotics and five had to receive therapeutic antibiotics; 17 (58.6%) received therapeutic antibiotics and three had to change antibiotics.

DISCUSSION

Despite recent studies in which patients with septic shock were treated with hydrocortisone, the present study has revealed some advantages in the use of dexamethasone[39]. This drug was chosen because of its potency and long-lasting action (36-48 hours), and its higher anti-inflammatory and lower mineralocorticoid effects. In comparison with hydrocortisone, dexamethasone causes no changes in sodium reabsorption and does not interfere in the water balance, thus avoiding

hypervolemia and sodium disturbances.[30] No recent study was found involving the use of dexamethasone in SIRS or septic patients. All things considered, it seemed reasonable to test dexamethasone on the basis of a single dose, to investigate its benefits and observe any possible adverse effects.

The pathophysiology of sepsis includes host inflammatory response, endothelial damage, increased coagulation with decreasing fibrinolysis, fibroproliferation and microclot formation and relative adrenal insufficiency.[40] However, this systemic inflammatory response can lead to organ dysfunction, instead of protecting and regulating homeostasis.[40]

Corticosteroids can improve the effects of vasopressor drugs, thus reestablishing receptor sensitivity, with better effects from the use of lower doses.[23,26] The first explanation for the hemodynamic improvement of patients receiving corticosteroids was based on observations of the relative adrenal insufficiency that they might develop.[23,25,41] In addition, some published reports have shown that patients without relative adrenal insufficiency could display better evolution following corticosteroid therapy.[42,43] These reports may serve as backing for our finding of early discontinuation of vasopressor therapy in patients receiving dexamethasone.

Currently, the recommendations for corticosteroids in relation to sepsis are that this class of drugs should be used during refractory septic shock, but not during severe sepsis in the absence of shock or with mild shock.[44] Whether or not sepsis is the systemic inflammatory response to infection, sepsis, severe sepsis and septic shock constitute different gradations in the continuum of a disease process. As this process continues, it is correlated with increasing organ dysfunction and mortality. Therefore, early infusion of corticosteroids to block this process that began with an inflammatory reaction ought to be tested.

The use of corticosteroids in septic patients can be explained by the relative adrenal insufficiency of these patients. However, it seems to us that the principal mechanism of action of corticosteroids is based on their anti-inflammatory effect.

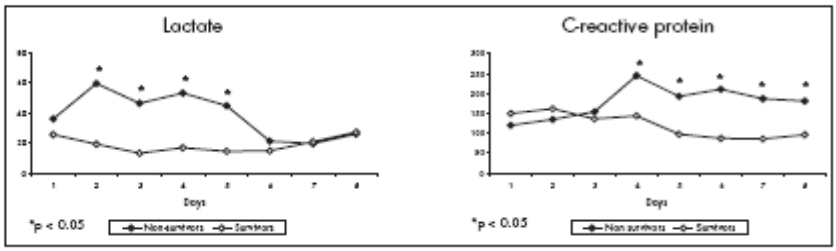

Figure 4. Evolution of lactate (mg/dl) and C-reactive protein (µg/ml) in the survivor and non-survivor groups of patients with systemic response syndrome.

An experimental study revealed that corticosteroids decreased pulmonary edema and collagen formation.[45] Another study demonstrated an improvement in patients with ARDS after corticosteroid therapy, probably because of the inhibition of pulmonary fibroproliferation.[27,46] These previous studies support our observation that patients treated with dexamethasone displayed a better PaO_2/FiO_2 ratio on the first day after therapy. However, the use of corticosteroids for treating the early phase of ALI/ARDS has not been recommended (the recommendations include only the fibroproliferation phase).[47] Nonetheless, even the patients in the present study who received dexamethasone during the early exudative phase (days 1-5) of ALI/ARDS showed an improved PaO_2/FiO_2 ratio. The rationale for this may include the observation that the integrity of the epithelial barrier in relation to the resolution of alveolar edema appears to be a determining factor in the outcome for ARDS patients. Patients who can concentrate the protein in the edematous fluid during the first 12 hours of illness are more likely to recover than those who cannot. Finally, since the change in the PaO_2/FiO_2 ratio following initial treatment of ARDS could pre-discriminate between survivors and non-survivors,[47] the use of corticosteroids in the early phases of ALI/ARDS might be considered a reasonable step.

The arterial lactate assays for the survivor group went on decreasing from the first day of the study onwards. This result confirms previous findings that established that lactate is a good marker for septic patients.[48]

On the other hand, C-reactive protein did not appear to be a good marker for the patients' progression, since the non-survivor group showed higher values only after day 3 of the study. Evaluations of infected patients showed no increased levels of C-reactive protein, contrary to what was suggested by other authors.[38,49-52] Our data cannot support the suggestion that C-reactive protein is a marker for infection. No correlation was observed between C-reactive protein values and the severity of infection or organ dysfunction level.[53]

This study remains part of an ongoing line of research, because of the significant results observed during the first two days after the single dexamethasone dose. Therefore, intravenous dexamethasone will be repeated at 48-hour intervals, to confirm the benefits for patients over a longer period, under closer assessment of their health status.

CONCLUSIONS

Sepsis and acute lung injury can trigger an increased inflammatory response that appears to be attenuated by the administration of dexamethasone. SIRS treatment with corticosteroids may be not a simple resurrection of last rites,[43] but a change in therapy that may have been used incorrectly in the past and may now get a fresh start based on new pathophysiological concepts regarding sepsis.

A single dose of dexamethasone enhanced the effects of vasopressor drugs for an apparently temporary period, and an evaluation of the respiratory system also revealed improvements, but it did not block the evolution of SIRS.

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AUTHOR INFORMATION

Domingos Dias Cicarelli, MD. Attending physician, anesthesiologist in the Surgical Support Unit, Anesthesia Division, Department of Surgery, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

Fábio Ely Martins Benseñor, MD, PhD. Attending physician, anesthesiologist, Supervisor of the Surgical Support Unit, Anesthesia Division, Department of Surgery, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

Joaquim Edson Vieira, MD, PhD. Attending physician, anesthesiologist in the Surgical Support Unit, Anesthesia Division, Department of Surgery, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

Address for correspondence:
Domingos Dias Cicarelli
Av. Piassanguaba, 2933 – Apto. 71
Planalto Paulista
São Paulo (SP) – Brasil
CEP 04060-004
Tel. (+55 11) 275-0569
E-mail: dcicarelli@uol.com.br

RESUMO

Efeitos da dexametasona em dose única em pacientes com síndrome da resposta inflamatória sistêmica

CONTEXTO E OBJETIVO: A síndrome da resposta inflamatória sistêmica (SRIS) acomete muitos pacientes internados em unidades de terapia intensiva. A evolução destes pacientes com SRIS para sepse, choque séptico e síndrome da disfunção de múltiplos órgãos (SDMO) pode conduzi-los rapidamente para o óbito. A proposta do trabalho é avaliar a eficácia da dexametasona em dose única como tratamento da SRIS.

TIPO DE ESTUDO E LOCAL: Estudo prospectivo, aleatório, duplamente encoberto, realizado na Unidade de Terapia Intensiva pós-operatória (Unidade de Apoio Cirúrgico) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

MÉTODOS: Foram estudados 29 pacientes com diagnóstico de SRIS. Os participantes foram aleatoriamente divididos em dois grupos que receberam dexametasona (0,2 mg/kg em dose única) ou placebo após o diagnóstico de SRIS. Os pacientes foram acompanhados durante sete dias de internação na UTI através do escore SOFA *(Sequential Organ Failure Assessment)*.

RESULTADOS: Os pacientes que receberam dexametasona apresentaram melhora do sistema respiratório no primeiro dia, com aumento da relação PaO_2/FIO_2 ($p < 0,05$). Entre os pacientes que faziam uso de vasopressores, os que receberam dexametasona tiveram diminuição da necessidade destas medicações nos primeiros dois dias após a dose de dexametasona ($p < 0,05$).

CONCLUSÃO: A dexametasona diminuiu a necessidade de medicações vasopressoras e causou aumento da relação PaO_2/FIO_2 no primeiro dia após sua administração. Apesar destes efeitos, a dexametasona em dose única não bloqueou a evolução dos pacientes com SRIS.

PALAVRAS-CHAVE: Síndrome séptica. Sepse. Inflamação. Corticosteróides. Dexametasona.

ORIGINAL ARTICLE

Early dexamethasone treatment for septic shock patients: a prospective randomized clinical trial

■ Domingos Dias Cicarelli
■ Joaquim Edson Vieira
■ Fábio Ely Martins Benseñor

Surgical Intensive Care Unit, Anesthesia Division, Department of Surgery, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HC/FMUSP), São Paulo, Brazil

ABSTRACT

CONTEXT AND OBJECTIVE: Sepsis and septic shock are very common conditions among critically ill patients that lead to multiple organ dysfunction syndrome (MODS) and death. Our purpose was to investigate the efficacy of early administration of dexamethasone for patients with septic shock, with the aim of halting the progression towards MODS and death.

DESIGN AND SETTING: Prospective, randomized, double-blind, single-center study, developed in a surgical intensive care unit at Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo.

METHODS: The study involved 29 patients with septic shock. All eligible patients were prospectively randomized to receive either a dose of 0.2 mg/kg of dexamethasone (group D) or placebo (group P), given three times at intervals of 36 hours. The patients were monitored over a seven-day period by means of the sequential organ failure assessment score.

RESULTS: Patients treated with dexamethasone did not require vasopressor therapy for as much time over the seven-day period as did the placebo group ($p = 0.043$). Seven-day mortality was 67% in group P (10 out of 15) and 21% in group D (3 out of 14) (relative risk = 0.31, 95% confidence interval 0.11 to 0.88). Dexamethasone enhanced the effects of vasopressor drugs.

CONCLUSIONS: Early treatment with dexamethasone reduced the seven-day mortality among septic shock patients and showed a trend towards reduction of 28-day mortality.

KEY WORDS: Infection. Septic shock. Sepsis. Glucocorticoids. Dexamethasone.

INTRODUCTION

Septic shock results when infectious or inflammatory agent-induced mediators produce hemodynamic decompensation. Septic shock is defined as severe sepsis with hypotension despite adequate fluid resuscitation that requires vasopressor support. About half of the patients with septic shock die of multiple organ system failure. Multiple organ dysfunction syndrome (MODS) is defined as organ dysfunction in critically ill patients who require intervention to reach homeostasis maintenance.[1]

Glucocorticoids have an important immunosuppressive effect, reducing the transcription of proinflammatory genes by inhibition of the nuclear factor kappa B.[2,3] Several studies have involved the use of corticosteroids to reduce the systemic inflammatory process associated with the host response to sepsis and septic shock.[4] Several reports have been published recently on studies involving lower doses of hydrocortisone, which showed improved outcomes for patients suffering from septic shock. The use of methylprednisolone to obtain resolution of acute respiratory distress syndrome (ARDS) has also been studied.[5]

Currently, the recommendations for using corticosteroids to treat sepsis are that this class of drugs should be used during refractory septic shock, but not during severe sepsis in the absence of shock or when only mild shock is observed.[6] Nonetheless, it needs to be asked why corticosteroids should not be used for septic patients at an early stage, before they evolve to refractory shock.

In a previous study,[7] we used dexamethasone to treat systemic inflammatory response syndrome (SIRS) patients. We observed that a single dose of dexamethasone enhanced the effects of vasopressor drugs for an apparently temporary period, and that the respiratory system also presented improvements. Despite other recent studies[4] in which patients with septic shock were successfully treated with hydrocortisone, our previous study[7] revealed some advantages in using dexamethasone. This drug was chosen because of its potency and long-lasting action (36-48 hours) and its higher anti-inflammatory and lower mineralocorticoidal effects. In comparison with hydrocortisone, dexamethasone causes no changes in sodium reabsorption and does not interfere in the water balance, thus avoiding hypervolemia and sodium disturbances.[8]

OBJECTIVE

This study aimed to evaluate the benefits from early administration of dexamethasone in patients with septic shock.

METHODS

This study was prospective, randomized, double-blind and placebo-controlled. After approval by a local ethics committee, informed consent was obtained from patients or from their next of kin prior to enrollment.[9] Twenty-nine patients admitted into the surgical intensive care unit of Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HC/FMUSP) between November 2004 and December 2005 took part in the study. Three patients were excluded after their next of kin withdrew their consent.

Patients with septic shock diagnosed after admission into the intensive care unit (ICU) were eligible for the study. Patients aged under 18 years, patients with a history of immunosuppression therapy or a history of glucocorticoid use for over two weeks within the last year or upon admission to this hospital, and patients with active pancreatitis, terminal illness (end-stage neoplasm with a life expectancy of less than three months) or recent gastrointestinal hemorrhage were excluded.[5]

A randomization table determined the order of inclusion for the patients to receive placebo among the expected 30 admissions. All the eligible patients were prospectively randomized into two groups: Group D comprising 14 patients and Group P with 15 patients. Group

Table 1. Baseline characteristics of the patients with septic shock studied

Characteristics	Group P (n = 15)	Group D (n = 14)	p
Age (years)	61 ± 15	69 ± 11	0.12
Male Sex (%)	46.7	42.9	0.59
Weight (kg)	63.5 ± 11.7	68.5 ± 15.0	0.32
APACHE II score	19 ± 4	20 ± 5	0.53
SOFA score	10 ± 2	9 ± 3	0.44
Prior or preexisting conditions (%)			
Hypertension	28.6	33.3	
Myocardial infarction	14.3	13.3	
Diabetes	14.3	13.3	
Liver disease	7.1	-	
COPD	7.1	6.7	
Cancer	21.4	20	
Recent trauma	35.7	20	
Other indicators of disease severity			
Mechanical ventilation (days)	4.0 ± 3.2	3.4 ± 2.5	0.22
Shock (days of vasopressor use)	4.2 ± 1.9	3.4 ± 2.1	0.04

Group P = placebo; group D = dexamethasone; APACHE = Acute Physiology and Chronic Health Evaluation; SOFA = sequential organ failure assessment; COPD = chronic obstructive pulmonary disease.

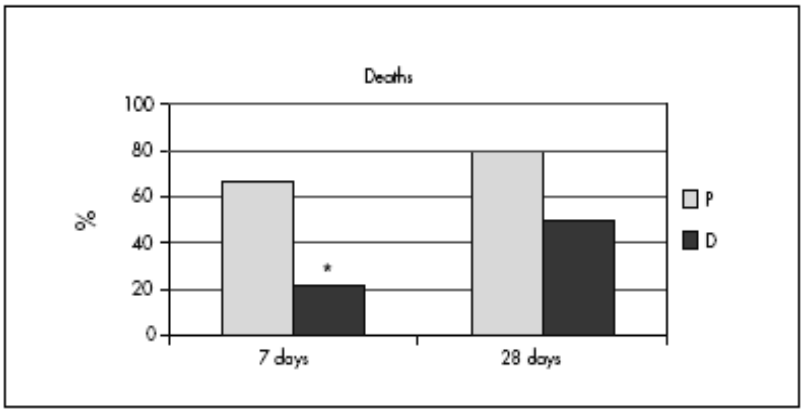

Figure 1. Comparison of mortality in Group D and Group P, for seven-day period (*relative risk, RR = 0.31; 95% confidence interval, CI: 0.11-0.88) and 28-day period (RR = 0.63; 95% CI: 0.31-1.29).

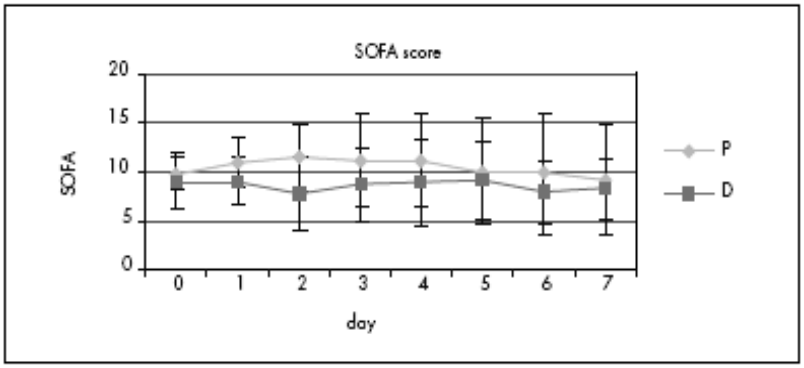

Figure 2. Evolution of sequential organ failure assessment (SOFA) score for group D and group P for a seven-day period.

D patients were given intravenous dexamethasone (0.2 mg/kg, three doses at intervals of 36 hours) while Group P patients received placebo (physiological saline solution 0.9%; three doses at intervals of 36 hours).[10]

The baseline severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II Score (APACHE II).[10] Patients were assessed daily for seven consecutive days using the sequential organ failure assessment score (SOFA),[11-13] or until their discharge from the ICU. Lactate plasma concentrations were also measured daily.[14]

The patients received conventional therapy with regard to antibiotic regimens, serial blood cultures (whenever their body temperature was greater than 38° C) and discharge criteria. Relevant clinical and laboratory tests were conducted daily throughout the study. The subjects were evaluated during their stay in the ICU in relation to the duration of vasopressor support (SOFA score for cardiovascular system of two or more), duration of mechanical ventilation and mortality.

All patients who progressed to refractory septic shock, despite using high doses of norepinephrine (> 0.5 µg/kg/minute) and dobutamine (≥ 20 µg/kg/minute), were excluded from the study and administration of hydrocortisone (100 mg every 8 hours) was started.[6,15]

Statistical analysis was performed using the Sigma Stat for Windows program, version 2.03 (Statistical Package for the Social Sciences, SPSS Inc.). For continuous variables, the treatments were compared using the Student t test, Mann-Whitney U test and two-way analysis of variance (ANOVA) for the treatment and outcome conditions. Relative risk and confidence intervals were calculated for treated patients in relation to seven-day and 28-day mortality.[16]

RESULTS

The mean age (± standard deviation, SD) of the 29 patients was 64 ± 13 years (range: 34 to 88 years). The study involved 13 males and 16 females (45%/55%). The mean age (± SD) of Group D was 69 ± 11 years while for Group P it was 61 ± 15 years (p = 0.12). There was no difference between these groups with regard to APACHE II (20 ± 5 for Group D and 19 ± 4 for Group P; p = 0.53). The baseline demographic characteristics and disease severity were similar in the placebo and dexamethasone groups (Table 1).

The seven-day mortality in Group P was 67% (10 out of 15) and in Group D it was 21% (3 out of 14) (relative risk = 0.31;

95% confidence interval: 0.11 to 0.88); the number needed to treat (NNT) was 2.17. The 28-day mortality in group P was 80% (12 out of 15) and in group D it was 50% (7 out of 14) (relative risk = 0.63; 95% confidence interval: 0.31 to 1.29) (Figure 1). With regard to collateral effects from dexamethasone (increased glucose, secondary infections or gastrointestinal hemorrhage), only one patient in Group P developed pneumonia (on the fourth postoperative day following aneurysm repair).

The two groups showed similar SOFA scores during the study (Figure 2). No differences were found in coagulation disorders (platelet count), liver disorders (serum bilirubin), kidney disorders (serum creatinine) or central nervous system dysfunction (according to the Glasgow scale).

Over the first 24 hours after dexamethasone administration, the respiratory system showed an improved PaO^2/FiO^2 ratio (Mann-Whitney test; p = 0.041). However, this improvement did not persist throughout the study (Figure 3). The duration of mechanical ventilation was 3.4 ± 2.5 days for Group D and 4.0 ± 3.2 days for Group P (p = 0.22).

The duration of vasopressor therapy was statistically different between the groups: 71.9 ± 28.2 hours per patient for Group D and 91.1 ± 18.6 hours for Group P (p = 0.042) (Figure 4).

The two groups were similar in relation to lactate assays during the seven-day period (Figure 5).

DISCUSSION

Dexamethasone enhances the effects of vasopressor drugs and evaluation of the respiratory system showed improvements (better PaO_2/FiO_2 ratio) over the first day after its administration. Early treatment with dexamethasone reduced seven-day mortality among septic shock patients and showed a trend towards reduction of 28-day mortality.

Dexamethasone was chosen because of its potency and long-lasting action (36-48 hours) and its higher anti-inflammatory and lower mineralocorticoidal effects. In comparison with hydrocortisone, dexamethasone causes no changes in sodium reabsorption and does not interfere in the water balance, thus avoiding hypervolemia and sodium disturbances.[10] We had already tested dexamethasone in SIRS patients with some improvements,[7] so we decided to extend that study to septic patients in order to investigate its benefits and observe any possible adverse effects.

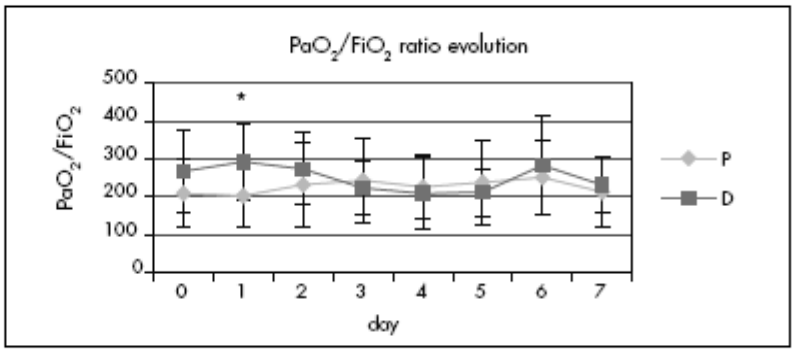

Figure 3. Significant improvement (*) in PaO^2/FiO^2 ratio during the first day in Group D (p = 0.041).

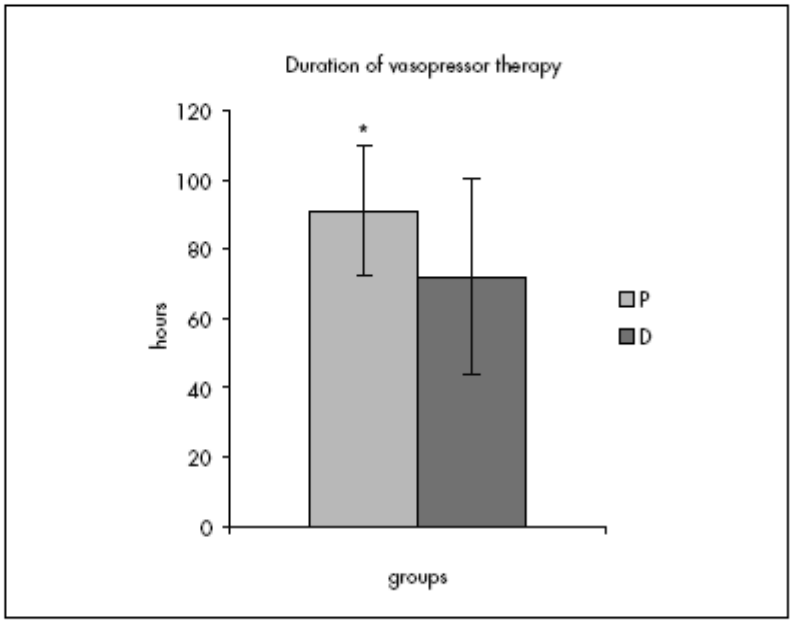

Figure 4. Duration in hours of vasopressor therapy for Group D and Group P (*p = 0.042).

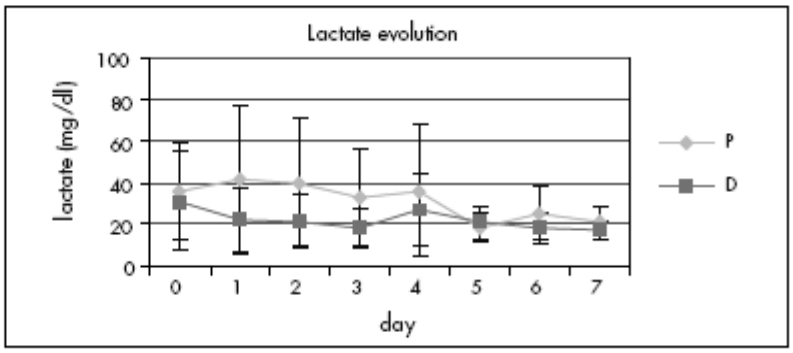

Figure 5. Evolution of lactate concentration (mg/dl) for Group D and Group P over a seven-day period.

The pathophysiology of sepsis includes host inflammatory response, endothelial damage, increased coagulation with decreasing fibrinolysis, fibroproliferation and microclot formation and relative adrenal insufficiency.[17] However, this systemic inflammatory response may lead to organ dysfunction instead of protecting and regulating homeostasis.[17]

Corticosteroids can improve the effects of vasopressor drugs, by reestablishing receptor sensitivity, with better effects using lower doses.[18] The first explanation for the hemodynamic improvement seen in patients receiving corticosteroids was based on observations of the relative adrenal insufficiency that they might develop.[18-20] In addition, some published reports have shown that patients without relative adrenal insufficiency could display better evolution following corticosteroid therapy.[1,21] These reports may serve to support our results of early discontinuation of vasopressor therapy among patients receiving dexamethasone.

Currently, the recommendations for corticosteroids and sepsis are that this class of drugs should be used during refractory septic shock, but not during severe sepsis in the absence of shock or when only mild shock is observed.[6] Whether or not sepsis is the systemic inflammatory response to infection, sepsis, severe sepsis and septic shock constitute different gradations in the continuum of a disease process. Moreover, the continuum of this process is correlated with increasing organ dysfunction and mortality. Early infusion of corticosteroids to block the process that began with an inflammatory reaction deserves to be tested.

The action of corticosteroids in septic patients can be explained by the relative adrenal insufficiency of these patients, but it seems to us that the principal mechanism of action of corticosteroids is based on their anti-inflammatory effect. Several studies have been using hydrocortisone following a corticotropin stimulation test.[20] However, it needs to be asked whether the corticotropin stimulation test is really necessary. We have been using dexamethasone 0.2 mg/kg in SIRS patients and we have not observed any adverse effects at this dose. Therefore, even when including patients with adequate adrenal reserves, the use of corticosteroids at "physiological" doses will not lead to adverse effects like gastrointestinal hemorrhage or secondary infections.

An experimental study showed that corticosteroids decreased pulmonary edema and collagen formation.[22] Another study demonstrated an improvement among patients with ARDS, following corticosteroid therapy, probably because of inhibition of pulmonary fibroproliferation.[5,23] These previous studies support our observation that patients treated with dexamethasone displayed a better PaO_2/FiO_2 ratio on the first day after therapy. However, the use of corticosteroids for treating the early phase of acute lung injury (ALI) and ARDS has not been recommended (the recommendations include only the fibroproliferation phase).[24] Even the patients in this study who received dexamethasone during the early exudative phase (days 1-5) of ALI/ARDS showed an improved PaO_2/FiO_2 ratio. The rationale may include the observation that the integrity of the epithelial barrier in resolving the alveolar edema appears to be a determining factor in the outcome for ARDS patients. Patients who can concentrate the protein in the edematous fluid during the first 12 hours of illness are more likely to recover than those who cannot. Finally, since the change in the PaO_2/FiO_2 ratio following the initial treatment for ARDS could pre-discriminate between survivors and non-survivors,[24] the use of corticosteroids in the early phases of ALI/ARDS might be considered to be a reasonable measure.

CONCLUSION

Dexamethasone enhanced the effects of vasopressor drugs and early treatment with dexamethasone reduced the seven-day mortality among septic shock patients.

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AUTHOR INFORMATION

Domingos Dias Cicarelli, MD. Attending Physician, Anesthesiology in Intensive Care Unit, Anesthesia Division, Department of Surgery, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HC/FMUSP), São Paulo, Brazil.

Joaquim Edson Vieira, MD, PhD. Attending Physician, Anesthesiology, Anesthesia Division, Department of Surgery, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HC/FMUSP), São Paulo, Brazil.

Fábio Ely Martins Bansefior, MD, PhD. Attending Physician, Anesthesiology, Anesthesia Division, Department of Surgery, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (HC/FMUSP), São Paulo, Brazil.

Address for correspondence:
Domingos Dias Cicarelli
Av. Piassanguaba, 2933 — Apto. 71
Planalto Paulista
São Paulo (SP) — Brasil — CEP 04060004
Tel. (+55 11) 2275-0569
E-mail: dcicarelli@uol.com.br

RESUMO

Tratamento precoce com dexametasona em pacientes com choque séptico: ensaio clínico prospectivo e aleatório

CONTEXTO E OBJETIVO: Sepse e choque séptico são doenças muito comuns em pacientes gravemente enfermos, evoluindo muitas vezes com síndrome de disfunção de múltiplos órgãos (SDMO) e morte. A proposta do trabalho foi investigar a eficácia da administração precoce de dexametasona a estes pacientes, tentando evitar a progressão do choque séptico para SDMO e morte.

TIPO DE ESTUDO E LOCAL: Estudo prospectivo, aleatório, duplamente encoberto, monocêntrico, realizado na Unidade de Terapia Intensiva pós-operatória do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

MÉTODOS: Foram estudados 29 pacientes com choque séptico. Os participantes foram aleatoriamente divididos em dois grupos que receberam 0,2 mg/kg de dexametasona (grupo D) ou placebo (grupo P), repetidas a cada 36 horas. Os pacientes foram acompanhados durante sete dias de internação na Unidade de Terapia Intensiva através do escore SOFA (Sequential Organ Failure Assessment).

RESULTADOS: Os pacientes que receberam dexametasona necessitaram de menos tempo de tratamento com vasopressores durante o período de sete dias ($p = 0,043$). A mortalidade em sete dias no grupo P foi de 67% (10 em 15) e no grupo D foi de 21% (3 em 14) (risco relativo = 0.31, intervalo de confiança 95% 0.11-0.88).

CONCLUSÃO: O tratamento precoce com dexametasona dos pacientes com choque séptico reduziu a mortalidade em sete dias de acompanhamento e mostrou tendência de redução da mortalidade em 28 dias.

PALAVRAS-CHAVE: Infecção. Choque séptico. Sepse. Glucocorticóides. Dexametasona.

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Research Article

Comparison of C-Reactive Protein and Serum Amyloid A Protein in Septic Shock Patients

Domingos Dias Cicarelli, Joaquim Edson Vieira, and Fábio Ely Martins Benseñor

Divisão de Anestesia, Departamento de Cirurgia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, 01246-903 São Paulo, SP, Brazil

Correspondence should be addressed to Domingos Dias Cicarelli, dcicarelli@uol.com.br

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Septic shock is a severe inflammatory state caused by an infectious agent. Our purpose was to investigate serum amyloid A (SAA) protein and C-reactive protein (CRP) as inflammatory markers of septic shock patients. Here we evaluate 29 patients in postoperative period, with septic shock, in a prospective study developed in a surgical intensive care unit. All eligible patients were monitored over a 7-day period by sequential organ failure assessment (SOFA) score, daily CRP, SAA, and lactate measurements. CRP and SAA strongly correlated up to the fifth day of observation but were not good predictors of mortality in septic shock.

1. INTRODUCTION

Severe sepsis and septic shocks are a common cause of mortality in intensive care unit (ICU) [1]. They are a state of systemic inflammation in response to infectious agents that can lead to multiple organ system failure and death.

The systemic inflammatory response to infection involves the release of several mediators, which has led to the suggestion that some of these mediators could be used as markers of sepsis severity [2]. Among the acute-phase proteins that participate in the inflammatory response, C-reactive protein (CRP) is a component of the innate immune system that binds phosphocoline and recognizes some foreign pathogens as well as phospholipid constituents of damage cells; serum amyloid A (SAA) protein is an apolipoprotein that rapidly binds to high-density lipoprotein after their synthesis, influencing cholesterol metabolism during inflammatory states, causing adhesion and chemotaxis of phagocitic cells and lymphocytes [3, 4]. In some patients with chronic inflammation, the net effect of increased SAA production may be deleterious due to tissue deposition of its fragments and the development of systemic amyloidosis [3, 5].

CRP and SAA display a similar pattern in most inflammatory diseases, reaching a maximum serum concentration about 24 hours after the inflammatory process sets in and slowly decreasing [6]. CRP is commonly used as a marker of an acute inflammatory state, produced by the liver in response to tissue injury or infection [7]. Its plasma concentration has been reported to parallel the clinical course of infection and the fall of the protein level indicates the resolution of infection [1]. SAA is the other major acute-phase protein in humans, with the earliest and highest increase rate of all acute-phase proteins, including CRP [4, 8]. SAA concentrations usually parallel those of CRP. Some authors have been reported that SAA appears to be a clinically useful marker of inflammation in bacterial or viral infection likewise CRP [9]. Although some studies suggest that SAA is a more sensitive marker of inflammatory disease, assays for SAA are not widely available at present [4].

Until now, no study has compared daily CRP to SAA plasma concentrations in postoperative patients with septic shock, or has correlated them to the severity of patients represented by SOFA score. This study aimed to evaluate CRP and SAA measurements as markers of severity of septic shock patients during postoperative period.

2. METHODS

This study was prospective at a surgical ICU. After approval by a local ethics committee, informed consent was obtained from patients or from their next of kin prior to enrollment

Table 1: Baseline characteristics of the patients.

Characteristics	n = 29
Age (years)	65 ± 13.9
Male sex	45%
Weight (kg)	63.5 ± 11.7
APACHE II score	19.8 ± 4.5
SOFA score	9.6 ± 2.3
Prior or preexisting conditions	(%)
Hypertension	31
Myocardial infarction	13.7
Diabetes	13.7
Liver disease	6.9
COPD	6.9
Cancer	20.7
Surgery	(%)
Multiple trauma (excluding head trauma)	3.4
Gastrointestinal surgery	75.9
Major vascular surgery	6.9
Thoracic surgery	3.4
Urologic surgery	10.4
Other indicators of disease severity	(days)
Mechanical ventilation	4.0 ± 3.2
Shock (use of vasopressor)	4.2 ± 1.9

APACHE: acute physiology and chronic health evaluation, *SOFA*: sequential organ failure assessment, COPD: chronic obstructive pulmonary disease.

[10]. Twenty-nine patients admitted into the surgical ICU of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo had taken part in the study. Additional three patients were excluded after their next of kin gave up the signed consent. Patients with septic shock diagnosed during ICU stay were eligible for the study. We used the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definition of sepsis and septic shock [11]. Patients under 18 were excluded.

Severity of illness at the baseline was assessed based on the *acute physiology and chronic health evaluation II* (APACHE II) score [12]. Patients were assessed daily for 7 consecutive days using the *sequential organ failure assessment* score (SOFA) or until their discharge from the ICU when occurring in less than 7 days [13–15]. C-reactive protein and serum amyloid A protein were also measured daily.

The patients received conventional therapy regarding antibiotic regimens, serial blood cultures (whenever that body temperature >38°C), and discharge criteria. Relevant clinical and laboratory tests were conducted daily throughout the study.

Blood samples for CRP and SAA dosage were thawed and assayed in batches in an automated analyzer (Behring Nephelometer Analyzer II, Dade Behring, Marburg, Denmark) for particle-enhanced immunonephelometry using commercial kits. The analytical sensitivity and accuracy for CRP was 0.0175 mg/L (coefficient of variation (CV) 7,6%). The analytical sensitivity and accuracy for SAA was determined by the lower limit of the reference curve and thus depended on

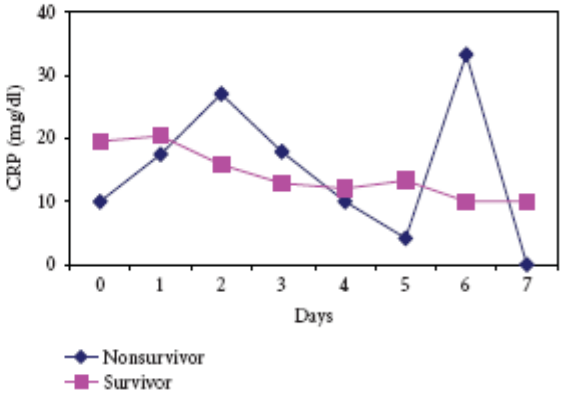

Figure 1: CRP evolution of survivors and nonsurvivors during the first week (NS). NS: not statistically significant.

the concentration of the protein in SAA standard test (CV between 5.4% and 6.4%).

Statistical analysis was performed using commercial available package. Multiple logistic regressions were performed to test mortality of 7 or 28 days follow-up. A distribution analysis was made by the Kolmogorov-Smirnov test, Pearson correlation coefficients were determined, and repeated measures were tested by ANOVA. A P value < .05 was considered significant.

3. RESULTS

The mean (±SD) age of the 29 patients was 65 ± 13.9 years (range, 34 to 88 years). The study involved 13 males and 16 females (45%/55%). The APACHE II score of these patients was 19.8 ± 4.5 (Table 1). Table 2 represents the microbiological characteristics of the studied patients.

SOFA did not show increase from Day 0 to Day 7 of observation (P = .589, ANOVA) while CRP reduced significantly from Day 0 till the end of observation period (P < .001, ANOVA followed by Holm-Sidak test) as well as SAA (P < .001, ANOVA followed by Holm-Sidak test) (Table 3).

CRP and SAA concentrations did not present any correlation with SOFA.

On the other hand, CRP and SAA have shown a good correlation from Day 0 till Day 5 (Table 4).

Mortality of these patients in 7 days was 44.8% (13 in 29) and in 28 days was 65.5% (19 in 29). CRP and SAA concentrations were not associated with Day 7 mortality (Table 5).

CRP and SAA concentrations evolution during the first week comparing survivors and nonsurvivors were not statistically significant (Figures 1 and 2).

4. DISCUSSION

The present study revealed significant positive correlation between SAA and CRP in postoperative septic shock patients. SOFA or APACHE II did not correlate with those serum measurements. Neither marker nor index was associated with mortality rate.

Table 2: Microbiological characteristics of patients.

Patient	Surgery/phatology	Antibiotics	Type of organism	Type of culture
1	Cholecistectomy/biliary abscess	Vanco + cefepime	S. aureus	Abscess culture
2	Empyema pleural drainage	Ceftriaxone + clindamycin	S. pyogenes	Pleural abscess culture
3	Cholecistectomy/biliary abscess	Ceftriaxone + metronidazole	—	Negative cultures
4	Cystectomy/pyuria	Ceftriaxone + metronidazole	—	Negative cultures
5	Aortic bypass/leg amputation	Ceftazidime + clindamycin	P. aeruginosa	Surgical site culture
6	Colectomy/cavity contamination	Ceftriaxone + metronidazole	—	Negative cultures
7	Calcaneal exposure fracture	Ciprofloxacin	E. faecalis	Surgical site culture
8	Pyonephrosis drainage	Ceftriaxone	K. pneumoniae	Urinary culture
9	Sigmoidectomy	Ceftriaxone + metronidazole	A. baumanii	Blood culture
10	Hemicolectomy	Ceftriaxone + metronidazole	Candida albicans	Blood culture
11	Enterectomy/mesenteric ischemia	Ceftriaxone + metronidazole	—	Negative cultures
12	Pancreatic-duodenal resection	Ceftriaxone	Serratia marcesens	BAL
13	Pancreatic-duodenal resection	Ceftriaxone + metronidazole	S. coag negative	Blood culture
14	Retroperitoneal abscess drainage	Cefepime + vanco + imipenem	P. aeruginosa	Blood culture
15	Abdominal aneurysm repair	Vanco + imipenem	S. aureus	Blood culture
16	Sigmoidectomy/perforative lesion	Ceftriaxone + metronidazole	Serratia marcesens	Ascite culture
17	Colectomy	Cefepime + vanco	S. aureus	Blood culture
18	Gastric ulcer	Ceftriaxone + metronidazole	—	Negative cultures
19	Cholecistectomy	Cipro + metronidazole	Escherichia coli	Urinary culture
20	Hemicolectomy	Cefepime + vanco + metro	E. cloacae	Blood culture
21	Enterectomy/cavity contamination	Vanco + imipenem	—	Negative cultures
22	Colectomy	Ceftriaxone + metronidazole	A. baumanii	Blood culture
23	Colectomy	Ceftriaxone + metronidazole	P. aeruginosa	Blood culture
24	Enterectomy/cavity contamination	Ceftriaxone + metronidazole	—	Negative cultures
25	Cervical abscess drainage	Imipenem + vanco + metro	K. pneumoniae	Blood culture
26	Sigmoidectomy/perforative lesion	Ceftriaxone + metronidazole	P. aeruginosa	Blood culture
27	Sigmoidectomy	Cefepime + metronidazole	S. aureus	Blood culture
28	Pyonephrosis drainage	Cefepime + metronidazole	—	Negative cultures
29	Colectomy	Ceftriaxone + metronidazole	P. aeruginosa	BAL

Vanco: vancomycin, Cipro: ciprofloxacin, Metro: metronidazole, S. aureus: Staphylococcus aureus, S. pyogenes: Streptococcus pyogenes, P. aeruginosa: Pseudomonas aeruginosa, E. faecalis: Enterobacter faecalis, K. pneumoniae: Klebsiella pneumoniae, A. baumanii: Acinetobacter baumanii, S. coag negative: Staphylococcus coagulase negative, E. cloacae: Enterobacter cloacae, BAL: bronchoalveolar lavage.

Table 3: SOFA, CRP, and SAA during the study period (mean ± SD).

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
SOFA	9.6 ± 2.3	10 ± 2.6	9.4 ± 4.1	9.8 ± 4.4	9.4 ± 4.2	9.9 ± 3.7	8.7 ± 4.1	8.6 ± 3.5
CRP	19.8 ± 8.4	20.9 ± 9.1	16.3 ± 6.2	13.2 ± 5.9	11.8 ± 7.7	12.7 ± 11.2	11.9 ± 8.3	10.0 ± 4.4
SAA	47 ± 39.8	37.2 ± 28.1	29 ± 21.48	22.7 ± 18.4	18.6 ± 20.8	24.7 ± 25.8	22.2 ± 20.5	21.7 ± 16.8

SOFA: sequential organ failure assessment, CRP: C-reactive protein, SAA: serum amyloid A. ANOVA. Equal variance test: SOFA $P = .956$, CRP $P = .062$, SAA $P = .055$.

SAA has been considered by some authors to be equivalent to CRP in patients with bacterial infectious diseases in clinical practice [16]. Other authors suggest that SAA is a more sensitive marker than CRP in infections with low inflammatory activity (including many viral infections) and in other clinical conditions, especially those involving the lung tissue [16, 17]. Yet other studies have confirmed the role of SAA and CRP in diagnosis and management of neonatal infections [2, 18].

The patterns of cytokine production and the acute-phase response differ for different inflammatory conditions. Acute-phase changes reflect the presence and intensity of inflammation and they have long been used as a clinical guide for diagnosis and management. Among patients with plasma CRP concentrations higher than 10 mg/dL, 80-to-85 percent have bacterial infections [4, 19]. In our study, all the patients were in septic shock with documented infection. We could observe that all patients during the 7-day period of observation presented plasma CRP concentrations greater than 10 mg/dL, according to results that Gabay et al. in a review article cited [4]. This fact could indicate that sepsis is secondary to bacterial infections. In relation to plasma SAA concentrations, a

Table 4: Pearson coefficient for SAA and CPR.

	r	P-value
Day 0	0.682	.0001
Day 1	0.660	.0004
Day 2	0.464	.034
Day 3	0.529	.024
Day 4	0.651	.0062
Day 5	0.778	.0028
Day 6	0.578	.628
Day 7	0.081	.822

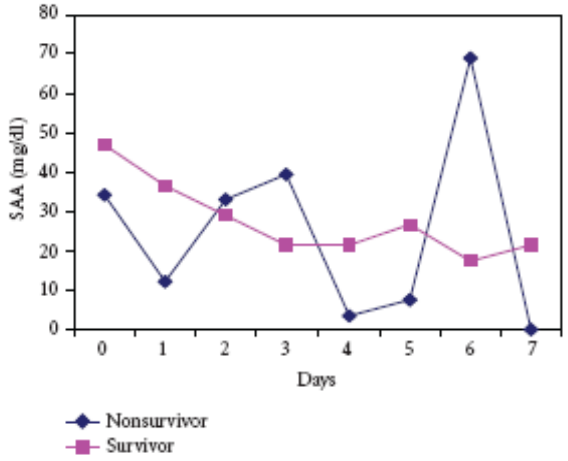

Figure 2: SAA evolution of survivors and nonsurvivors during the first week (NS). NS: not statistically significant.

Table 5: Maximum likelihood, Wald statistic (P-value).

	APACHE II	SOFA	CPR	SAA
Day 0	3.46 (.06)	2.46 (.11)	0.02 (.89)	1.91 (.17)
Day 1	3.06 (.08)	3.50 (.06)	1.01 (.31)	0.03 (.86)
Day 3	0.00 (.98)	0.00 (.98)	0.00 (.98)	0.00 (.98)

cutoff value has not been determined from previous studies. We observed a level higher or closer to 20 mg/dL, but more studies were needed to find a cutoff value for SAA as an early diagnostic tool for patients with infection.

We did not observe difference between CRP and SAA early (Day 1) concentrations in patients who survived compared with those who died. Other authors have found that these proteins were not prognostic markers in patients with septic shock [7, 19]. This fact is in concordance with our results.

Previous reports have observed that CRP level was associated with organ failure in critically ill patients, although not specifically under septic shock [14]. This study could not find any good correlation between CRP or SAA with SOFA, probably not in agreement with other authors [20]. They believe that both CRP and SAA are good markers of organ dysfunction, considering the established diagnostic of septic shock.

Study limitations are attributed primarily to the small sample size and the age of the patients that could influence CRP levels. Some authors believe that the older the patient is, the higher CRP levels that can be observed [21].

In conclusion, SAA protein and CRP are strongly correlated, but were not good predictors of organ dysfunction and mortality in septic shock.

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