ORIGINAL RESEARCH

EVOLUTIVE STANDARD BASE EXCESS AND SERUM LACTATE LEVEL IN SEVERE SEPSIS AND SEPTIC SHOCK PATIENTS RESUSCITATED WITH EARLY GOAL-DIRECTED THERAPY: STILL OUTCOME MARKERS?

Marcelo Park, Luciano Cesar Pontes Azevedo, Alexandre Toledo Maciel, Vladimir Ribeiro Pizzo, Danilo Teixeira Noritomi, and Luiz Monteiro da Cruz Neto

Park M, Azevedo LCP, Maciel AT, Pizzo VR, Noritomi DT, Cruz Neto LM da. Evolutive Standard base excess and serum lactate level in Severe sepsis and septic shock patients resuscitated with early goal-directed therapy: still outcome markers? Clinics. 2006;61(1):47-52.

PURPOSE: To compare the evolution of standard base excess and serum lactate level between surviving and non surviving patients with severe sepsis and septic shock resuscitated with early goal-directed therapy.
METHODS: This is a retrospective study in an intensive care unit of a university tertiary hospital where 65 consecutive severe sepsis and septic shock patients were observed without any intervention in the treatment by the authors of this report.
RESULTS: In our study, the mortality of severe sepsis and septic shock patients was 38%. The central venous oxygen saturation of both groups was above 70% after the resuscitative period, excluding the second day of the non survivors group (69.8%). After the second day, the central venous oxygen saturation was significantly higher in the survivors group ($P < .001$). Standard base excess was initially low in both groups, but from the second day on, the correction of standard base excess was significantly more successful and linear in the survivor group ($P < .001$). Lactate levels were similar during the evolution of both groups.
CONCLUSIONS: Although evolutive standard base excess and serum lactate level are still outcome markers in severe sepsis and septic shock patients resuscitated with early goal-directed therapy, other studies must be performed to clarify if hemodynamic interventions based on standard base excess and serum lactate level could be reliable to improve clinical outcomes in severe sepsis and septic shock patients

KEYWORDS: Severe sepsis. Septic shock. Monitorization. Lactate. Metabolic acidosis.

INTRODUCTION

Severe sepsis and septic shock are the major causes of admission and death in intensive care units (ICUs). This fact has motivated clinical trials aiming the improvement of care for critically ill septic patients.[1] As a result, low dosages of corticosteroids,[2] strict glycemic control,[3] recombinant human activated protein C,[4] protective ventilatory strategies[5,6] and early goal-directed hemodynamic therapy[7] have been associated with improved outcomes. The latter trial found that early aggressive management of hemodynamics targeting a balance of oxygen consumption and delivery is an effective treatment of severe sepsis and septic shock patients.[7] This finding contrasted with other clinical studies in which hemodynamic optimization was not clearly effective.[8,9] In early goal-directed therapy, the precocious match between oxygen consumption and delivery is achieved with central venous oxygen saturation ($ScvO_2$) ≥ 70%. This approach has been respon-

Intensive Care Unit, Emergency Department, São Paulo University Medical School - São Paulo/SP, Brazil.
Email: mpark@uol.com.br
Received for publication on September 13, 2005.
Accepted for publication on November 16, 2005.

sible for significant reductions in in-hospital mortality.[7] As regards the metabolic consequences of shock and hemodynamic management, there are other simple monitoring tools such as serum lactate levels and standard base excess (SBE) that can be used in critical illness.[10-13] When measured at admission and within the first days of ICU stay, these variables are important outcome markers in conventionally resuscitated patients.[10] However, to the best of our knowledge, there are few clinical studies testing interventions based on serum lactate level or SBE, and there are no studies showing evolutive serum lactate level and SBE as outcome markers following early goal-directed therapy.[14-15] The aim of this study was to compare $ScvO_2$, serum lactate levels, and SBE evolution between surviving and non surviving patients with severe sepsis and septic shock who underwent early goal-directed hemodynamic therapy.

METHODS

Data were retrieved from our prospectively collected database for a tertiary teaching 7-bed ICU hospital in São Paulo, Brazil. The period investigated was July 2003 to May 2004. The following data were collected: age, gender, APACHE II score, length of stay in the ICU, clinical outcome, need for mechanical ventilation, diagnosis of acute respiratory distress syndrome (ARDS),[16] need for dialysis, and infection source. These sets of data were collected from the patients as they were admitted with diagnosis of severe sepsis and septic shock according to the consensus conference criteria.[17]

Blood samples were obtained as required; at admission all patients were monitored with an arterial and central venous line; after this initial period every procedure, such as fluid challenges, inotropic agents, and vasopressors, was checked with a new blood samples 10 to 15 minutes after stabilization, as is the standard of care of our unit. The number of patient blood samples was variable as required for additional interventions. After reaching a $ScvO_2$ e•70%, (or in the absence of such response, but with a higher reached $ScvO_2$), new blood samples were collected every 6 hours during the first 24 hours. Data compatible with a fully resuscitated patient retrieved from the database were the establishment of a plateau, that is, a steady level without great variations above or under the current value.

$ScvO_2$ was obtained through the gas analysis of blood drawn from the central venous catheter. The plateau value of $ScvO_2$ was taken to be that collected after the initial resuscitation of patients as the optimized compatible; afterwards, a mean daily value was determined until the fifth day. The SBE and serum lactate levels were obtained through the arterial blood analysis gained from the arterial line at the same time of central venous blood sample collection as described above. Central venous catheter position was previously verified, and possible complications were ruled out with a chest X ray. All blood samples were analyzed in an AVL Omni Roche gas analyzer (Basel, Switzerland), and to determine the SBE value, the Van Slyke method was used.[18]

The $ScvO_2$, serum lactate level, and SBE were compared between the survivor and non survivor groups during the first 5 days of evolution. Data are shown as medians and interquartile range. Single medians between groups were compared using the Mann Whitney U test, and categorical data were compared using Fisher or chi-square analysis as indicated. To show and analyze the evolution during the first 5 days, data were considered normal using the Kolmogorov-Smirnov model, and then shown as mean ± standard deviation and tested with 2-way analysis of variance (ANOVA). The commercially available SPSS 10.0 statistical package was used, taking $P < .05$ as a significant level. Bonferroni's correction for continuity was applied when necessary.

RESULTS

During 10 months, 65 patients were observed, 25 with severe sepsis and 40 with septic shock. The general characteristics and infection source of the whole group (survivors and non survivors) are shown in Table 1. In our study, the mortality of severe sepsis and septic shock patients was 38%. The median of age and APACHE II score were higher in non survivors, as were the number of patients who needed mechanical ventilation. The infection sources were similar between survivors and non survivors. Within the resuscitative period, patients received a median of 5,302 (range, 4,523–7,310) mL of crystalloids resulting in a positive fluid balance of 4,802 (range, 3,548–5,281) mL during those twelve hours. Forty patients needed a median of 0.3 (range, 0.2–0.3) μg/kg/minute of norepinephrine as a vasopressor, and 39 patients needed a median of 13 (range, 10–22) μg/kg/minute of dobutamine as an inotropic agent.

The mean $ScvO_2$ after the initial resuscitation on the first day of ICU stay (Figure 1 - Panel A) was above 70% in both groups. After the second day, the $ScvO_2$ of survivors was significantly higher than that of non survivors, and excluding the second day, the median $ScvO_2$ of both groups was higher than 70%. The SBE was low in both groups after resuscitation; during the following days, there was a linear trend to normalization in the survivor group, with significant differences in individual comparisons of days 3, 4, and 5 with day 1 (Figure 1 - Panel B). In the non survivor group, there was a worsening of SBE on the second

Table 1 - General characteristics of survivors, nonsurvivors, and the whole group

Characteristic	All patients (n = 65)	Survivors (n = 40)	Nonsurvivors (n = 25)	*P* value
Age* - year	54 [33,69]	41 [27,61]	67 [51,63]	<.001
Gender (Females) - no (%)	28 (43)	20 (50)	8 (32)	.24
APACHE II*	24 [16,27]	21 [12,25]	26 [18,30]	.03
Days in ICU*	10 [6,13]	10 [6,13]	9 [7,16]	.91
ARDS - no (%)	25 (38)	16 (40)	9 (36)	.95
MV** - no (%)	57 (88)	32 (80)	25 (100)	.02
Dialysis - no (%)	5 (8)	2 (5)	3 (12)	.37
Septic shock - no (%)	50 (77)	28 (70)	22 (88)	.87
Severe sepsis - no (%)	15 (23)	12 (30)	3 (12)	.13
Sepsis source				
Pneumonia - no (%)	40 (62)	24 (60)	16 (64)	.95
Abdominal - no (%)	10 (16)	6 (14)	4 (16)	>.99
Urinary tract - no (%)	5 (8)	3 (8)	2 (8)	>.99
Soft tissue - no (%)	4 (6)	2 (5)	2 (8)	.64
Catheter - no (%)	3 (4)	3 (8)	0 (0)	.28
Unidentified - no (%)	3 (4)	2 (5)	1 (4)	>.99

* median range; ** MV denotes the number of patients on mechanical ventilation
no denotes the number of patients

day, with a subsequent slow recovery. Serum lactate levels were similar in both groups during the first 5 days of evolution excluding the second day, when the non survivor group had a higher level of serum lactate than the survivor group (Figure 1 - Panel C).

DISCUSSION

The first hours following the diagnosis of severe sepsis and septic shock are known as the "golden hours". In this period, aggressive hemodynamic resuscitation is related to higher survival rates and reduced organ dysfunctions.[7] The match between oxygen delivery/consumption is the rationale for this phenomena.[7,8,19] After the "golden hours", the aggressive hemodynamic resuscitation is no longer efficient in restoring organ function or in decreasing mortality.[19] It may surmised that following this initial period, irreversible endothelial and organ cellular dysfunctions and set in and consequently the benefits of aggressive hemodynamic resuscitation are lost.[19-21]

The $ScvO_2 \geq 70\%$ has been considered a marker of systemic oxygen delivery/consumption matching,[7,8,20] but this

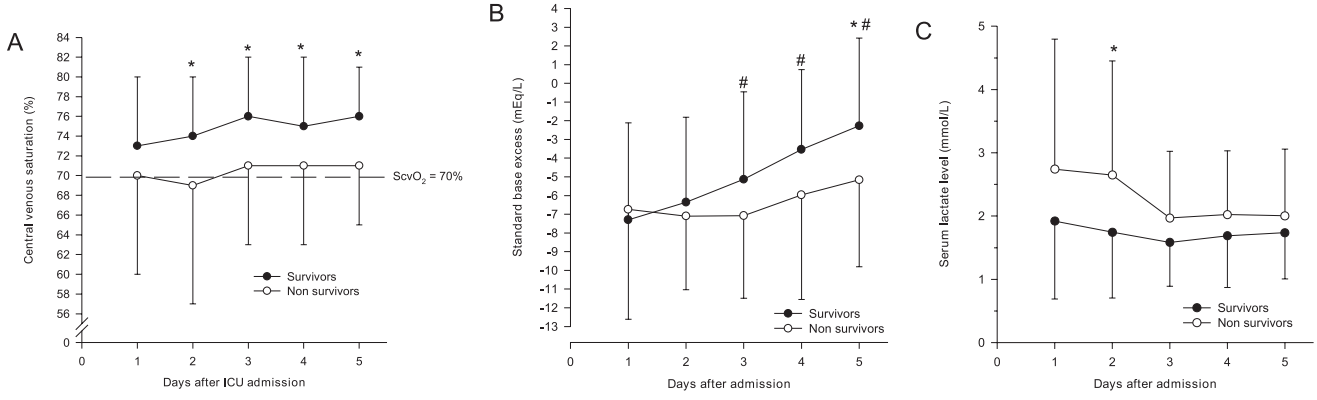

Figure 1 - Panel A. Central venous saturation of survivors and non survivors, the analysis within group did not disclose differences during the evolution (P = 0.358, ANOVA two way). (*) Between groups there were differences in days 2,3,4 and 5 (P < 0.001, ANOVA two way with Tukey post hoc analysis). There was not factor time interaction (P = 0.964, ANOVA two way). **Panel B.** Standard base excess of survivors and non survivors, the analysis within group (#) disclose differences during the evolution (P < 0.001, ANOVA two way, with Tukey post hoc analysis showing differences between the days 3,4 and 5 vs day 1 among the survivors). (*) Between groups there was difference in day 5 (P = 0.008, ANOVA two way with Tukey post hoc analysis). There was not factor time interaction (P = 0.290, ANOVA two way). **Panel C.** Serum lactate levels of survivors and non survivors, the analysis within group did not disclose differences during the evolution (P = 0.555, ANOVA two way). (*) Between groups there was difference in day 2 (P < 0.001, ANOVA two way with Tukey post hoc analysis). There was not factor time interaction (P = 0.430, ANOVA two way).

cut-off value was extrapolated from normal subjects.[22-23] In our study, all patients reached a $ScvO_2 \geq 70\%$, with survivors reaching a higher $ScvO_2$ than non-survivors. This finding can be explained by the greater dysfunctions of the microcirculation,[23 24] heart, [24,25] and cellular metabolism in nonsurvivors.[21] Clinically, it is hard to interpret this fact, but it seems that patients who reach higher $ScvO_2$ levels are more prone to survive. Many ICUs have used the mixed venous saturation (SvO_2) ≥ 70% as a goal of resuscitation in severe sepsis and septic shock patients.[1] We and others have found the $ScvO_2$ values to be higher than SvO_2 values in severe sepsis and septic shock patients.[26,27] Taking all these quoted studies into account, results point out to higher values of $ScvO_2$ as a possible better goal in severe sepsis and septic shock resuscitation.

The SBE can reflect a great amount of disturbances secondary to sepsis and its resuscitation,[18] and low values at admission are associated with higher mortality in the ICU.[10,11] In a previous retrospective study, any improvement of SBE in severe sepsis and septic shock patients on the third day of ICU stay was a strong predictor of better outcome.[28] The evolutive behavior of SBE has not been clinically studied following early goal-directed therapy. [10,11] In our results, faster improvement of SBE occurred in the survivor group. Similarly, in the Rivers study,[7] a faster decrement of base deficit in the early goal-directed therapy group in relation to the control group was observed, with normal base deficit values being achieved by the third day.

High serum lactate values at admission are also associated with worse outcomes.[10] Likewise, the persistence of high values during the ICU stay is a predictor of death and organ failure.[12, 13] In this study, we measured serum lactate levels before and after the early goal-directed hemodynamic therapy. Non survivors had a slightly higher value of serum lactate during the first 2 days after the admission, but we would like to stress that it was far from a clinically significant difference. The evolutive behavior of the serum lactate level of the survivors was static within the group. Our results conflict with those of Rivers et al,[7] which showed a progressive correction of serum lactate level that was more accentuated in the early goal-directed therapy group. The same investigators have shown that in severe sepsis and septic shock patients that are conventionally resuscitated, a serum lactate clearance greater than 10% within 6 hours of admission was associated with better outcomes.[29]

In conclusion, although evolutive SBE and serum lactate level are still considered to be outcome markers in septic patients treated with early goal-directed hemodynamic therapy during their ICU stay, other studies must be performed to clarify if hemodynamic interventions based on SBE and serum lactate level could be reliable to improve clinical outcomes in severe sepsis and septic shock patients.

RESUMO

Park M, Azevedo LCP, Maciel AT, Pizzo VR, Noritomi DT, Cruz Neto LM da. Standard base excess e o nível sérico de lactato evolutivos nos pacientes com sepse grave e choque séptico reanimados com o early goal directed therapy: ainda discriminadores de mortalidade? Clinics. 2006;60(1):47-52.

OBJETIVO: Comparar a evolução do "standard base excess" e o nível de lactato sérico entre pacientes sobreviventes e não sobreviventes com sepse grave ou choque séptico reanimados com o "early goal directed therapy".

MÉTODOS: Estudo retrospectivo em uma unidade de terapia intensiva de um hospital escola onde sessenta e cinco pacientes com sepse grave e choque séptico foram observados sem intervenções.

RESULTADOS: Em nosso estudo, a mortalidade na sepse grave e choque séptico foi de 38%. A saturação venosa central de oxigênio nos dois grupos foi maior que 70% depois da reanimação, exceto no segundo dia no grupo dos pacientes não sobreviventes (69,8%). Depois do segundo dia, a saturação venosa central foi significantemente maior no grupo dos sobreviventes ($p<0.001$). O "standard base excess" foi inicialmente baixo em ambos os grupos, mas a partir do segundo dia a recuperação do "standard base excess" foi significantemente mais importante e linear no grupo dos sobreviventes ($p<0.001$). Os níveis de lactato foram similares na evolução dos dois grupos.

DISCUSSÃO: O "standard base excess" e o lactato são ainda considerados como marcadores prognósticos em pacientes com sepse grave ou choque séptico reanimados de acordo com o "early goal directed therapy". Outros estudos devem ser realizados com a intenção de demonstrar se intervenções hemodinâmicas baseadas no "standard base excess" e nos níveis de lactato podem ser úteis em melhorar desfechos clínicos em pacientes com sepse grave ou choque séptico.

UNITERMOS: Sepse grave. Choque séptico. Monitorização. Lactato. Acidose metabólica.

REFERENCES

1. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004;32:858-73.
2. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862-71.
3. Van den BG, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345:1359-67.
4. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344:699-709.
5. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338:347-54.
6. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301-8.
7. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-77.
8. Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med. 2002;30:1686-92.
9. Mazza BF, Machado FR, Mazza DD, Hassmann V. Evaluation of blood transfusion effects on mixed venous oxygen saturation and lactate levels in patients with SIRS/sepsis. Clinics. 2005;60:311-316.
10. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, et al. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med. 2001;27:74-83.
11. Balasubramanyan N, Havens PL, Hoffman GM. Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. Crit Care Med. 1999;27:1577-81.
12. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg.1996;171:221-6.
13. Marecaux G, Pinsky MR, Dupont E, Kahn RJ, Vincent JL. Blood lactate levels are better prognostic indicators than TNF and IL-6 levels in patients with septic shock. Intensive Care Med. 1996;22:404-8.
14. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg. 2000;90:1052-9.
15. Schultz SC, Hamilton IN, Jr., Malcolm DS. Use of base deficit to compare resuscitation with lactated Ringer's solution, Haemaccel, whole blood, and diaspirin cross-linked hemoglobin following hemorrhage in rats. J Trauma. 1993;35:619-25.
16. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149:818-24.
17. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. Chest. 1992;101:1481-3.
18. Morgan TJ, Clark C, Endre ZH. Accuracy of base excess—an in vitro evaluation of the Van Slyke equation. Crit Care Med. 2000;28:2932-6.
19. Singer M, De S, V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet. 2004;364:545-8.
20. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO_2 Collaborative Group. N Engl J Med. 1995;333:1025-32.

21. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360:219-23.

22. Rivers EP, Ander DS, Powell D. Central venous oxygen saturation monitoring in the critically ill patient. Curr Opin Crit Care. 2001;7:204-11.

23. Rady MY, Rivers EP, Martin GB, Smithline H, Appelton T, Nowak RM. Continuous central venous oximetry and shock index in the emergency department: use in the evaluation of clinical shock. Am J Emerg Med. 1992;10:538-41.

24. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF. Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet. 2002;360:1395-6.

25. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med. 1984;100:483-90.

26. Park M, Amaral ACKB, Matos GFJ. How useful are venous saturations collected from central venous catheters? Am J Respir Crit Care Med. 2004;169:A346.

27. Chawla LS, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M. Lack of equivalence between central and mixed venous oxygen saturation. Chest. 2004;126:1891-6.

28. Palma LC, Ferreira GF, Amaral ACKB, Brauer L, Azevedo LCP, Park M. Acidosis and mortality in severe sepsis and septic shock evaluated by base excess variation. Crit Care 2003;7:39.

29. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004;32:1637-42.