ORIGNAL 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?

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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


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. As a result, low dosages of corticosteroids, strict glycemic control, recombinant human activated protein C, protective ventilatory strategies and early goal-directed hemodynamic therapy 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. This finding contrasted with other clinical studies in which hemodynamic optimization was not clearly effective. In early goal-directed therapy, the precocious match between oxygen consumption and delivery is achieved with central venous oxygen saturation (ScvO₂) ≥ 70%. This approach has been respon-
sible for significant reductions in in-hospital mortality. 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. When measured at admission and within the first days of ICU stay, these variables are important outcome markers in conventionally resuscitated patients. 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.

The aim of this study was to compare ScvO2, 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), 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.

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 ScvO2 > 70%, (or in the absence of such response, but with a higher reached ScvO2), 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.

ScvO2 was obtained through the gas analysis of blood drawn from the central venous catheter. The plateau value of ScvO2 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.

The ScvO2, 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 ScvO2 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 ScvO2 of survivors was significantly higher than that of non survivors, and excluding the second day, the median ScvO2 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
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. The match between oxygen delivery/consumption is the rationale for this phenomena. After the “golden hours”, the aggressive hemodynamic resuscitation is no longer efficient in restoring organ function or in decreasing mortality. 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.

The ScvO2 ≥ 70% has been considered a marker of systemic oxygen delivery/consumption matching, but this

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

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

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

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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.\textsuperscript{22-23} In our study, all patients reached a ScvO\textsubscript{2} $\geq$ 70\%, with survivors reaching a higher ScvO\textsubscript{2} than non-survivors. This finding can be explained by the greater dysfunctions of the microcirculation,\textsuperscript{23 24} heart, \textsuperscript{24,25} and cellular metabolism in nonsurvivors.\textsuperscript{21} Clinically, it is hard to interpret this fact, but it seems that patients who reach higher ScvO\textsubscript{2} levels are more prone to survive. Many ICUs have used the mixed venous saturation (SvO\textsubscript{2}) $\geq$ 70\% as a goal of resuscitation in severe sepsis and septic shock patients.\textsuperscript{1} We and others have found the ScvO\textsubscript{2} values to be higher than SvO\textsubscript{2} values in severe sepsis and septic shock patients.\textsuperscript{26,27} Taking all these quoted studies into account, results point out to higher values of ScvO\textsubscript{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,\textsuperscript{18} and low values at admission are associated with higher mortality in the ICU.\textsuperscript{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.\textsuperscript{28} The evolutive behavior of SBE has not been clinically studied following early goal-directed therapy.\textsuperscript{10,11} In our results, faster improvement of SBE occurred in the survivor group. Similarly, in the Rivers study,\textsuperscript{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.\textsuperscript{10} Likewise, the persistence of high values during the ICU stay is a predictor of death and organ failure.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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


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 significativamente 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 significativamente 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.


REFERENCES


