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Original Article

The handheld blood lactate analyser versus the blood gas based analyser for measurement of serum lactate and its prognostic significance in severe sepsis

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ABSTRACT

Background: This study was done to compare the accuracy of the Lactate Pro LT 1710 (Arkray Inc., Kyoto, Japan) with the Combiline Plus (Eschweiler GmbH & Co. KG Holzkoppelweg, Kiel, Germany), and also, to analyze the prognostic significance of serum lactates and Simplified Acute Physiology Score 3 (SAPS 3) in patients of severe sepsis.

Methods: 106 patients of severe sepsis admitted to the ICU were screened. The serum lactate from an arterial sample analyzed in both the machines was recorded at admission and at 48 h. These patients were then followed up to the 28th day for mortality.

Results: The Lactate Pro LT 1710 handheld point of care lactate meter provides consistent results comparable to the Eschweiler Combiline blood gas analyser. Serum lactate concentration was significantly higher in nonsurvivors at the time of admission (3.30 ± 1.26) and at 48 h (4.34 ± 1.73). Lactate clearance at 48 h appears to be a better predictor of mortality than the lactate levels at 0 h and 48 h. The mean SAPS 3 at admission amongst survivors was significantly less as compared to nonsurvivors. The SAPS 3 had improved to $47.44 (\pm 11.79)$ in survivors at 48 h, while in nonsurvivors it had worsened to $81.98 (\pm 12.32)$ ($p = 0.00$); thus, a worsening SAPS 3 at 48 h had a poorer prognosis.

Conclusions: The Lactate Pro LT 1710 provides similar results to the Combiline Eschweiler blood gas analyser and is a cheaper alternative. It would prove to be a boon in peripheral hospitals in the aggressive management of critically ill patients.

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Introduction

The sepsis syndrome accounts for about 40% of ICU expenditure and a mortality of nearly 60%.¹ The incidence of sepsis in the USA has increased at an annual rate of 8.7%, from 82.7 cases per 100,000 population in 1979 to 240.4 per 100,000 population in 2000.²

Timely fluid resuscitation, source control, early appropriate antibiotics, and bundled care have improved morbidity and mortality in patients of the sepsis syndrome.^{3–6} A raised prehospital blood lactate level has been shown to be associated with inhospital mortality and gave prognostic information superior to that provided by the patient's vital signs.⁷ International guidelines recommend the use of serum lactate levels at the outset to guide therapy.⁶ Also, lactate clearance during resuscitation has been found to be a better prognostic indicator than an isolated elevated lactate reading.^{7–9} In the service setting, however, lactate measurement is only available at centers where arterial blood gas (ABG) analysers with a lactate sensor are available; by the time these patients reach a tertiary center, vital time for goal-directed intervention has already been lost; thus, there is a need to search for a simpler point of care lactate analyser.

The Lactate Pro LT 1710 is the only strip-based lactate analyser approved by the FDA for medical use.¹⁰ Since the start of this study, Arkay Inc. has come up with an advanced model; however, the technique remains the same. The Lactate Pro2 LT 1730 uses 0.3 mL of volume as against 5.0 mL, and provides results in 15 s as against 60 s for the LT 1710 and does not need to be calibrated. There are very few studies that have compared the results of strip-based lactate analysers against blood gas based analysers. The purpose of this study was to compare the accuracy of the lactate levels obtained from the Lactate Pro LT 1710 (Arkay Inc., Kyoto, Japan) handheld lactate analyser compared with the Comiline Plus (Eschweiler GmbH & Co. KG Holzkoppelweg, Kiel, Germany), and also, to analyze the prognostic significance of serum lactate measurement obtained from the handheld point of care analyser in patients of severe sepsis.

Methods

Following approval of the institutional ethical committee, this simple prospective observational study was performed in the ICU of a 1200-bedded tertiary health facility. The study group was of 106 patients admitted to the surgical and medical ICU. All patients who were designated as severe sepsis or septic shock (6) were screened irrespective of cause and underlying condition. Informed consent was taken from the patients or next of kin if patient was not in a state to give informed consent.

All patients underwent ABG analysis at admission, and at 48 h, the samples were analyzed with the ABG machine Eschweiler Combi Line installed in the ICU and using the Lactate Pro LT 1710. All ABG samples were drawn preferably from the radial or femoral arteries, which were cannulated in preheparinized syringes. Preheparinized syringes 3 cc BD™ were used. These syringes contained 80 I.U. of heparin as

lyophilized lithium heparin. After the ABG sample was taken in a heparinized syringe, another sample was taken in a plain syringe and introduced into the lactate pro strip.

The Lactate Pro LT 1710 is a handheld portable analyser. A small blood sample size of only 5 mL is required. The reagent strip fills by capillary action. Lactate in the sample reacts with potassium ferricyanide and lactate oxidase to form potassium ferrocyanide and pyruvate. Upon the application of a given voltage, ferrocyanide is oxidized, releasing electrons and creating a current. This current is measured amperometrically and is directly proportional to the lactate concentration of the blood sample. Its measuring range is from 0.8 to 23.3 mmol/l and it takes 60 s.

The Eschweiler Comiline Plus is a blood gas analyser that incorporates electrolyte and metabolite measurement. This analyser is designed for laboratory use only and is not a portable serum lactate measurement, and requires a 75 mL blood sample. It combines an enzymatic receptor and an amperometric detector. Inside the lactate biosensor, blood lactate passes across the outer layer of a multilayered membrane and reacts with lactate oxidase that has been immobilized between the layers, to form pyruvate and H₂O₂. The H₂O₂ passes across the inner membrane, where it is subjected to a given potential and oxidized, creating a current that is measured amperometrically. The size of the current is directly proportional to the lactate concentration of the sample. The Comiline carries out sensor calibrations automatically in a preprogrammed cycle of 90 min, but in economy mode in a cycle of 240 min. A daily quality control check was done. The range of the lactate biosensor was 0–20 mmol/l with a resolution of 0.1 mmol/l and a precision of LAC: 0.0–10.0 mmol/l = 5%, 10.0–20.0 mmol/l = 10–15%.

These patients were then followed up for up to the 28th day of their diagnosis of severe sepsis for mortality. The reliability of the blood lactate values obtained from the two different analysers was first analyzed using Bland–Altman plots. Thereafter, the values obtained from the Lactate Pro LT 1710 analyser were used for the study. Inclusion criteria were as follows: age >18 yrs, patients with a diagnosis of severe sepsis, patients with septic shock where systolic blood pressure was <90 mmHg, and/or mean blood pressure 60 mmHg in spite of adequate fluid resuscitation. Exclusion criteria were as follows: age <18 years, patients in sepsis with trauma, discharge against medical advice, serum lactate not measured before institution of any treatment, and patients given Metformin in the last 48 h of diagnosis of severe sepsis/septic shock.

Sample information

It included age, gender, contact details, comorbidities, initial vital parameters, and serum lactate level at admission and at 48 h. Simplified Acute Physiology Score 3 (SAPS 3)¹¹ score was recorded at admission and at 48 h. Laboratory reports at the time of diagnosis of severe sepsis and treatment given to the patient, including any vasoactive support if required, were also recorded. Body fluids were sent for culture and sensitivity. The prognostic significance of serum lactate levels at admission and at 48 h along with the SAPS 3 scores was analyzed and compared between the patients who survived and those who died at 28 days.

Statistical analysis

The information was collected using a structured questionnaire. Cross-checking and data cleaning were done. Nominal data were presented as number (N) and percentage (%). Continuous variables were expressed as mean and standard deviation (SD). Chi-square test was applied to compare nominal data. For parametric data, Unpaired *t* test was applied to compare two groups (between group comparison). Paired *t* test was applied to compare within group findings (*pre* versus *post*). For nonparametric variables, Mann–Whitney *U* test was applied to compare two groups (between group comparison). Receiver-operating characteristics (ROC) curves and area under the curve (AUC) were calculated. Cut-off values for the parameters were chosen to correspond to the best respective Youden's index for mortality prediction. Youden's index = sensitivity + specificity – 1. For area under the ROC curves (AUC), results are expressed as mean (95% confidence interval). A regression analysis was performed to discriminate if any parameter was independently correlated to the survival status. The comparison of reliability of results of serum lactate levels from the Eschweiler ABG analyser and the Lactate Pro LT 1710 was done using Bland–Altman plots.¹²

Additional parametric as well as nonparametric analysis of the data was performed as deemed essential. *p* value of <0.05 was considered as statistically significant. The analysis of the data was performed using Microsoft Excel and SPSS 17.

Sample

The study was carried out over a period of 18 months and all patients of severe sepsis and septic shock were screened. As per the above criteria, out of 106 patients, 60 patients were included for analysis in our study. 46 patients were excluded from the study as per exclusion criteria. Out of the 60 patients included, 34 died at 28 days, while 26 were alive.

We analyzed the data of the 60 patients who were admitted in the ICU and diagnosed as suffering from severe sepsis and septic shock.

Their breakup is shown below in the diagram.

Results

Demographic data are provided in Table 1. Fifty-eight (58%) patients died in the first 28 days. The mean SAPS 3 was 53 ± 16 in survivors versus 69 ± 15 in nonsurvivor patients ($p < 0.01$).

The mean ($\pm$ SD) age among the survivors was $50.28 (\pm 19.39)$ yrs, while that among the nonsurvivors was $56.34 (\pm 18.33)$ yrs. This difference was statistically insignificant ($p = 0.22$). The male:female ratio was 02.53:1. The mean ($\pm$ SD) number of days of ICU stay among the survivors was $11.68 (\pm 9.64)$ days, while that of nonsurvivors was $13.65 (\pm 4.87)$ days (Table 1).

Bland–Altman plots comparing the Eschweiler Combiline Plus and the Lactate Pro LT 1710 showed a clinically insignificant discrepancy between the two methods with a lower limit of agreement being -0.80 and an upper limit of agreement of 1.22 and a R^2 value of 0.05 (Fig. 1). Paired lactate levels from both the monitors also showed a good agreement of lactate values (Fig. 2) by both the methods with a consistent variability without any scatter in the values as the values increased from low to high lactate levels.

Mann–Whitney *U* test was applied for comparison of survivors and nonsurvivors data. Serum lactate concentration was significantly higher in nonsurvivors as compared to survivors at the time of admission (0 h) and at 48 h post-admission ($p = 0.001$), as is depicted in Table 2.

The mean lactate clearance ($\pm$ SD) among the survivors was $11.64 (\pm 55.63\%)$, while that among the nonsurvivors was $-37.88 (\pm 62.95\%)$. This difference was statistically significant ($p = 0.003$), where lactate clearance = $[(\text{lactate initial} - \text{lactate delayed}) / \text{lactate initial}] \times 100\%$. Results are depicted in Fig. 3.

The AUC at 0 h was 0.734 (95%CI = $0.607-0.860$), with a sensitivity of 65% and specificity of 76%. Similarly, the AUC at 48 h was 0.897 (95%CI = $0.897-0.981$), with a sensitivity of 91.4% and specificity of 84%. For lactate clearance the AUC at 48 h was 0.910 (95%CI = $0.823-0.997$), with a sensitivity of 97% and specificity of 80%, as shown in Table 3 and Figs. 4 and 5.

Among all the three parameters, serum lactate clearance at 48 h post-admission is the best predictor of the mortality at Day 28. Serum lactate at admission has a comparatively poor ability to predict day-28 mortality (Table 4).

Table 1 – Demographic profile of sepsis patients admitted in ICU.

Parameter	Mortality			p value
	Survivors Mean $\pm$ SD	Nonsurvivors Mean $\pm$ SD	All Mean $\pm$ SD	
Age (years)	50.28 $\pm$ 19.39	56.34 $\pm$ 18.33	53.81 $\pm$ 18.86	0.22
Male	16 (64%)	27 (77.1%)	43 (71.7%)	
Female	9 (36%)	8 (22.9%)	17 (28.3%)	
ICU stay (days)	11.68 $\pm$ 9.64	13.65 $\pm$ 4.87	12.83 $\pm$ 7.24	0.30

Unpaired t test is applied; p value is significant if <0.05.

Table 2 – Serum lactate concentrations in survivors and nonsurvivors during first 48 h in ICU.

Parameter	Mortality			p value
	Survivors Mean $\pm$ SD	Nonsurvivors Mean $\pm$ SD	All Mean $\pm$ SD	
Serum lactate at 0 h	2.27 $\pm$ 0.98	3.30 $\pm$ 1.26	2.87 $\pm$ 1.25	0.001
Serum lactate at 48 h	1.88 $\pm$ 1.12	4.34 $\pm$ 1.73	3.32 $\pm$ 1.93	0.001
Lactate clearance at 48 h	11.64 $\pm$ 55.63	-37.88 $\pm$ 62.95	-17.24 $\pm$ 64.41	0.003

Table 3 – Area under receiver operating characteristics (ROC) curve for static rates and lactate clearance.

Parameter	AUC	p value	95%CI AUC lower	95%CI AUC upper	Threshold	Sensitivity	Specificity
Serum lactate at 0 h	0.734	0.002	0.607	0.860	2.85	65%	76%
Serum lactate at 48 h	0.897	0.001	0.813	0.981	2.3	91.4	84%
Lactate clearance	0.910	0.001	0.823	0.997	2.03	97%	80%

Fig. 1 – Bland–Altman plot showing reliability of the values obtained from both the analysers.

Fig. 2 – Paired lactate levels from both the monitors showing a good agreement of lactate values by both the methods without any scatter in the values as the values increase from low to high lactate levels.

Fig. 3 – Serum lactate clearance during the first 48 h.

Logistic regression found that individually the serum lactate at 0 h, at 48 h, and lactate clearance are independently correlated to a survival status with a $p = 0.001$.

At 0 h, the mean ($\pm$ SD) SAPS 3 among the survivors was 51.24 ($\pm$ 12.03), while that among the nonsurvivors was 72.28

($\pm$ 12.47). This difference was statistically significant ($p = 0.00$). At 48 h, SAPS 3 among the survivors was 47.44 ($\pm$ 11.79), while that among the nonsurvivors was 81.98 ($\pm$ 12.32). This difference was statistically highly significant ($p = 0.00$). The same has been depicted in [Tables 5 and 6](#).

Fig. 4 – Area under receiver operating characteristics (ROC) curve for lactates at admission and at 48 h.

Discussion

In the service setting, blood gas and metabolite analysers are used in ICUs for determination of blood lactate levels. These analysers are not portable and the cost of one sample works out to be approximately Rs 300. In contrast, the Lactate Pro LT

Table 4 – Multivariate analysis between the deceased and the survivors.

Parameter	<i>p</i> value	Odd's ratio	95%CI lower	95%CI upper
Serum lactate at 0 h	0.01	2.2	1.31	3.87
Serum lactate at 48 h	0.01	3.7	1.94	7.07
Lactate clearance	0.01	0.96	0.93	0.98

Fig. 5 – Receiver operating characteristics (ROC) curve lactate clearance.

1710 costs Rs 186 per test, and being a handheld portable lactate analyser, it has the flexibility of point of care use. To confirm that the Lactate Pro is operating correctly, it has a check strip. A calibration strip is also supplied to provide a nonquantitative indication of instrument accuracy.¹³ The level of agreement between the Lactate Pro and other monitors was generally less than ± 2.0 mM over the physiological range of 1.0–18.0 mM. Thus, the Lactate Pro has been found to be accurate and reliable.¹⁴ In humans, in reports on precision of measurements, Lactate Pro had a low interassay coefficient of variance of 1.1–4.7%.¹⁵ The findings of the present study were similar with the Bland–Altman plots comparing the two machines showing a clinically insignificant discrepancy between the two methods with a lower limit of agreement

being -0.80 and an upper limit of agreement being 1.22 and a R^2 value of 0.05 . Paired lactate levels from both the monitors also showed a good agreement with a consistent variability without any scatter in the values, as the values increased from low to high lactate levels.

The surviving sepsis campaign has used lactate levels as a parameter indicating sepsis-induced hypoperfusion to guide early goal-directed therapy.⁶ Landmark studies have advocated use of serum lactate in both the diagnostic and treatment phases for septic shock.^{5,16,17} The present study also further reiterates this view, thus showing that the results obtained from the Lactate Pro LT 1710 are comparable to the results of earlier studies on prognosis of sepsis using lactate as a biomarker. Varpula et al.¹⁶ concluded that nonsurvivors had higher lactate levels than those of survivors at the outset (3.4 versus 2.1 mmol/l respectively, $p < 0.005$). In the present study, serum lactate concentration was significantly higher in nonsurvivors at the time of diagnosis (3.30 ± 1.26 mmol/l) versus (2.27 ± 0.98 mmol/l) in survivors. At 48 h, nonsurvivors had a lactate level of (4.34 ± 1.73 mmol/l) versus (1.88 ± 1.12 mmol/l) in survivors; both these differences were highly significant statistically.

The mortality rate was found to have decreased once therapy was targeted to a 20% decrease in lactate levels every 2 h for the first 8 h,¹⁸ and it has been demonstrated that nonsurvivors compared with survivors had a lactate clearance of $-38.1 \pm 34.6\%$ versus $12.0 \pm 51.6\%$, respectively ($p = 0.005$).¹¹ In our study, lactate clearance was similar i.e., nonsurvivors ($-37.88 \pm 62.9\%$) and survivors ($11.64 \pm 55.63\%$) (negative value indicates rise in serum lactate levels). Even in patients who could achieve hemodynamic targets in the first 48 h, the absence of lactate clearance during this time is a pointer for aggressive therapy, as mortality was found to be higher, thus underlining the need to target lactate clearance.¹⁹

The SAPS 3 score uses information available within 1 h of admission to the ICU.²⁰ Interestingly, about half of the predictive power of the original SAPS 3 score is derived from

Table 5 – Simplified Acute Physiology Score 3 (SAPS 3) in survivors and nonsurvivors during first 48 h in ICU.

Parameter	Mortality			p value
	Survivors Mean $\pm$ SD	Nonsurvivors Mean $\pm$ SD	All Mean $\pm$ SD	
SAPS 3 at 0 h	51.24 $\pm$ 12.03	72.28 $\pm$ 12.47	63.51 $\pm$ 16.06	0.00
SAPS 3 at 48 h	47.44 $\pm$ 11.79	81.98 $\pm$ 12.32	64.71 $\pm$ 19.96	0.00
Unpaired t test is applied; p value is significant if < 0.05 .				

Table 6 – Correlation between the prognostic factors and Simplified Acute Physiology Score 3 (SAPS 3) in survivors and nonsurvivors during first 48 h in ICU.

	SAPS 3 at 0 h		SAPS 3 at 48 h	
	Pearson correlation	Sig. (2-tailed)	Pearson correlation	Sig. (2-tailed)
ICU stay	0.084	0.524	0.176	0.180
Serum lactate at 0 h	0.319*	0.013	–	–
Serum lactate at 48 h	–	–	0.558**	0.000
Lactate clearance	–	–	-0.325*	0.011
* Correlation is significant at the 0.05 level.				
** Correlation is significant at the 0.01 level.				

information available before ICU admission.¹⁹ Prognostic scoring systems that are meant to include measurements over the first 24 h period in the ICU are not valid for use in ICU triage. However, we calculated the SAPS 3 at 48 h too and found that the mean SAPS 3 at admission amongst survivors was 51.24 (± 12.03), while in nonsurvivors it was 72.28 (± 12.47); this difference was statistically significant ($p = 0.00$); also, the SAPS 3 had improved to 47.44 (± 11.79) in survivors at 48 h, while in nonsurvivors it had worsened to 81.98 (± 12.32) ($p = 0.00$) (Table 5); thus, a worsening SAPS 3 at 48 h had a poorer prognosis.

We also found a highly significant correlation between serum lactate levels at 48 h and SAPS 3 at 48 h in survivors and nonsurvivors, while lactate clearance had a significant correlation (Table 6). There was a significant correlation between serum lactates at 0 h and SAPS 3 at admission in survivors and nonsurvivors (Table 6).

In the present study, lactate clearance at 48 h appears to be a better predictor of mortality than the lactate levels at 0 h and 48 h. Previous studies have observed that the trend of blood lactate concentrations may provide more information than a single value when analyzing the response to therapy.^{21,22}

Conclusions

The results obtained from the Lactate Pro LT 1710 point of care lactate analyser were consistent with the results obtained from the Eschweiler Combiline Plus blood gas analyser. Moreover, the prognostic value of the absolute results, and the values of lactate clearance obtained in the first 48 h using the Lactate Pro LT 1710, predicted mortality at 28 days as accurately as has already been established in literature.

There was a highly significant correlation between SAPS 3 and serum lactate levels at 48 h in survivors and nonsurvivors at 28 days.

Conflicts of interest

The authors have none to declare.

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