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Research Article

Serial estimations of blood lactate predict postoperative outcome in cancer patients undergoing head and neck surgeries

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KEYWORDS

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Abstract To determine predictability of serial estimations of blood lactate levels for postoperative outcome of head and neck cancer patients and determine validity of single versus serial estimations for accurate prediction of outcome.

The study included 322 cancer patients assigned for major head and neck surgeries and admitted to ICU. Data collection included age, sex, and associated comorbidities, and clinical status was determined using APACHE II score. Arterial lactate was measured at time of admission (T0), and 8-hourly (T8, T16, T24), and percentage of change of blood lactate level was calculated versus T0 level. Patients were categorized as survivor and non-survivors, and among each group, patients were categorized according to estimated level of blood lactate into four categories.

The mean of APACHE score at ICU admission was 16.6 ± 3.1, and mean duration of ICU and hospital stay was 3.2 ± 1.2 and 19.3 ± 5.5 days, respectively. Fifty-two patients died for postoperative mortality rate 16.1%. Non-survivors were significantly older and had significantly higher APACHE score and significantly longer ICU and hospital stay. At admission blood lactate level was significantly higher in non-survivors compared to survivors. All patients showed progressive increase of blood lactate level, but non-survivors showed significantly higher frequency of elevated blood lactate strata compared to survivors with significantly higher difference between both groups at T8, T16, and T24. There was positive significant correlation between high at admission blood lactate level and APACHE score. Regression analysis defined % of change of blood lactate at T16, high APACHE score, high at admission blood lactate and old age as specific predictors for

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postoperative mortality in descending order of specificity. Serial estimations of blood lactate are conclusive test for follow-up of patients undergoing major surgical procedures requiring ICU admission. Combined high APACHE score and percentage of change of blood lactate could discriminate survivors from non-survivors especially 16-h after ICU admission.

1. Introduction

Lactate is formed by reduction in pyruvate and is metabolized by oxidation to pyruvate in a reaction catalyzed by cytosolic NAD-dependent lactate dehydrogenase. Pyruvate is oxidized through the mitochondrial respiratory chain to carbon dioxide and water with accompanying energy production. Mitochondrial fate of pyruvate is oxygen demanding and so if oxygen supply is insufficient or compromised or if pyruvate production exceeds the capacity of oxidative metabolism, pyruvate will be diverted to lactate leading to increased blood lactate levels. Such increase in blood lactate if accompanied by decreased clearance through the liver and heart hyperlactataemia results. Excessive lactate production may give rise to lactic acidosis [1–4].

Measurement of blood lactate to monitor critically ill patients for risk assessment remains under research. An elevated serum lactate level was found to be associated with high morbidity in patients with severe sepsis and septic shock with a possible role for hepatic dysfunction for augmenting serum lactate level due to either impaired lactate clearance or excessive production [5].

The point of controversy is whether to perform a single or serial lactate measurements and the appropriate reference interval. Hyperlactataemia is common at admission in a general ICU and is associated with increased mortality, irrespective of presence of hypotension.

Shock was the commonest cause for hyperlactataemia followed by respiratory and renal failures [6] Jat et al. [7] reported that among pediatric septic shock patients; non-survivors had higher blood lactate levels at admission as well as at 12 and 24 h.

The current prospective study aimed to determine the predictability of serial estimations of blood lactate levels for postoperative outcome of head and neck cancer patients and to determine the validity of single versus serial estimations for accurate prediction of outcome.

2. Patients and methods

The present study was conducted at Department of Anesthesia and Intensive Care; National Cancer Institute From January 2009 till October 2011. After approval of the Study protocol by the Local Ethical Committee and obtaining fully informed written Consents. The study involved 322 cancer patients who underwent major head and neck surgeries and admitted to the ICU. The cases were total laryngo-pharyngectomies, total laryngectomies, commando operations, total thyroidectomies, and maxillectomies.

Associated comorbidities were found as diabetes mellitus, cardiac insufficiency, liver cirrhosis, and chest troubles.

All cases received general anesthesia, after proper assessment of the airway. In the form of IV induction with propofol 1–2 mg/kg followed by suxamethonium 1 mg/kg then intubation with Armord tube was done. Few cases need Fibreoptic Intubation. Maintenance was carried with Isoflurane 1–1.5 MAC and Oxygen. Fentanyl was used as narcotic intraoperative. Mechanical ventilation was facilitated by Atracurium. Arterial canula was inserted for all cases. Invasive monitoring was used in the form of CVP and ABP &Temperature monitoring. Most cases were extubated postoperatively, except few cases who need postoperative ventilation. The patients were followed in the ICU. Serial ABGs were done. Vital signs were followed regularly.

Data collection included age, sex, and associated comorbidities. Clinical status was determined using Acute Physiology and Chronic Health Evaluation (APACHE) II score [8]. Arterial lactate was measured by blood gas analyzer (Rapilab, Bayer Australia, Sydney, NSW, Australia) with the upper normal limit was considered about 18 mg/dl. Four samples were obtained at time of admission (T0), and 8-hourly, there after (T8, T16, T24), and percentage of change of blood lactate level was calculated versus T0 level.

Patients were categorized according to the outcome as regards survival into survivor and non-survivor groups and among each group patients were categorized According to estimated level of blood lactate into four categories: <18 mg/dl, 18–36 mg/dl, 36–54 mg/dl and >54 mg/dl with regard to this study, and after power analysis, the sample size chosen was considered adequate to detect a significant change.

Obtained data were presented as mean ± SD, ranges, numbers and ratios and median values. Results were analyzed using paired t-test, Wilcoxon test for unrelated data (Z test) and Chi-square test. Possible correlation was investigated using Pearson linear regression. Specificity of evaluated parameters as predictors for mortality was evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) and was stratified using Regression analysis (Stepwise method). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. p value <0.05 was considered statistically significant.

3. Results

The study included 322 cancer patients who underwent major head and neck surgeries. Mean age of enrolled patients was 64.4 ± 9.2; range: 44–84.

There were 187 males (58.1%) and 135 females (49.1%). Two hundred and thirteen patients (66.1%) had additional comorbidities in varied combinations; but diabetes mellitus, history of cardiac affection are the commonest. All patients passed smooth intraoperative course, and all admitted immediately to ICU with a mean APACHE Score of 16.6 ± 3.1; range: 6–24. Mean duration of ICU stay was 3.2 ± 1.2; range: 2–7 days, and mean total hospital stay was 19.3 ± 5.5; range:

Table 1 Patients' characteristics and hospital data.

	Survivors	Non-survivors	Total
Number			
	270 (83.9%)	52 (16.1%)	322 (100%)
Age (years)	63.8 ± 9.4 (44–82)	67.7 ± 7.5 (56–84)*	64.4 ± 9.2 (44–84)
Gender			
Males	156 (57.8%)	31 (59.6%)	187 (58.1%)
Females	114 (42.2%)	21 (40.4%)	135 (41.9%)
Co-morbidities			
Diabetes mellitus	198 (73.3%)	34 (65.4%)	232 (72%)
History of cardiac disease	67 (24.8%)	17 (32.7%)	84 (26.1%)
Hypertension	103 (38.1%)	19 (36.5%)	122 (37.9%)
Renal impairment	45 (16.7%0	9 (17.3%)	54 (16.8%)
APACHE score			
	16.3 ± 2.9 (6–19)	18.2 ± 3.4 (10–24)*	16.6 ± 3.1 (6–24)
Hospital stay data			
ICU (days)	2.9 ± 0.9 (2–5)	4.5 ± 1.5 (2–7)*	3.2 ± 1.2 (2–7)
Total (days)	18.7 ± 4.8 (7–26)	22.6 ± 7.3 (10–36)*	19.3 ± 5.5 (7–36)

Data are presented as mean ± SD and numbers; ranges and percentages are in parenthesis.
Percentages were calculated in relation to the corresponding total group number.
* Significant versus survivors.

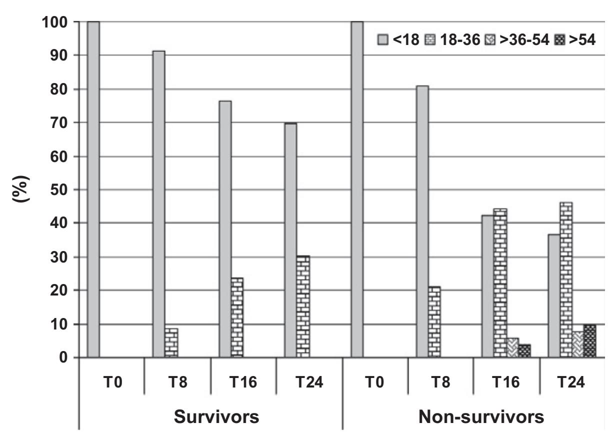

Figure 1 Patients distribution according to survival outcome and blood lactate level strata.

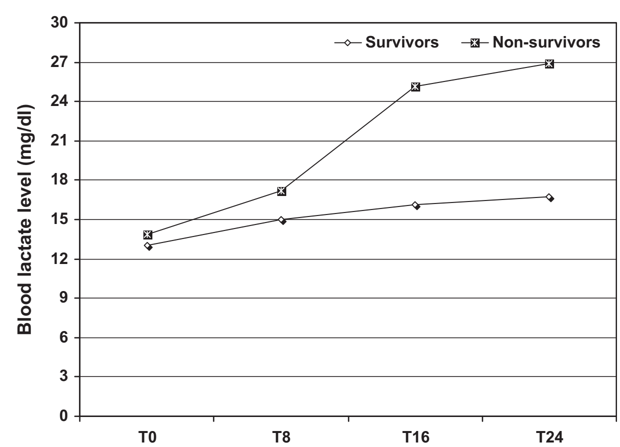

Figure 2 Mean blood lactate levels estimated in studied patients categorized according to survival outcome throughout 24-h ICU stay.

7–36 days. Throughout hospital stay, two hundred and seventy patients were discharged alive from the hospital. The survival rate was 83.9%. There was nonsignificant difference between survivors and non-survivors as regards gender distribution and frequency of co-morbidities. However, non-survivors were significantly older and had significantly higher APACHE score at time of admission to ICU with significantly longer ICU and hospital stay, (Table 1).

The underlying causes of death were mainly the associated morbidities, sepsis, and postoperative surgical complications. Mean blood lactate level estimated at time of admission to ICU was significantly ($p < 0.05$) higher in non-survivors compared to survivors. However, throughout 24-h ICU stay, all patients showed progressive increase in mean blood lactate level, irrespective of survival outcome. At 24-h after ICU admission, 207 patients (64.3%) had blood lactate level below the maximum of normal blood lactate level (< 18 mg/dl), while 115 patients (35.7%) had blood lactate level exceeding the maximum of normal blood lactate level (18 mg/dl); five patients (1.6%) had blood lactate level of > 54 mg/dl, four patients (1.2%) had blood lactate level > 36 mg/dl but < 54 mg/dl, and 106 patients (32.9%) had blood lactate level in range of 18–36 mg/dl (see Fig. 1).

Non-survivors showed significantly higher frequency of elevated blood lactate strata compared to survivors, ($X2 = 6.6$ at T8, 10.456 at T16 and 11.215 at T24, $p < 0.05$ for all). Moreover, mean blood lactate level showed significantly higher difference between both groups at T8, T16, and T24, (Table 1, Figs. 2 and 3). There was a positive significant correlation between high at admission blood lactate level and APACHE score, ($r = 0.178$, $p = 0.001$) (see Table 2).

Considering the significant difference between survivors and non-survivors as regards age, APACHE score and at admission blood lactate level; ROC curve analysis graded

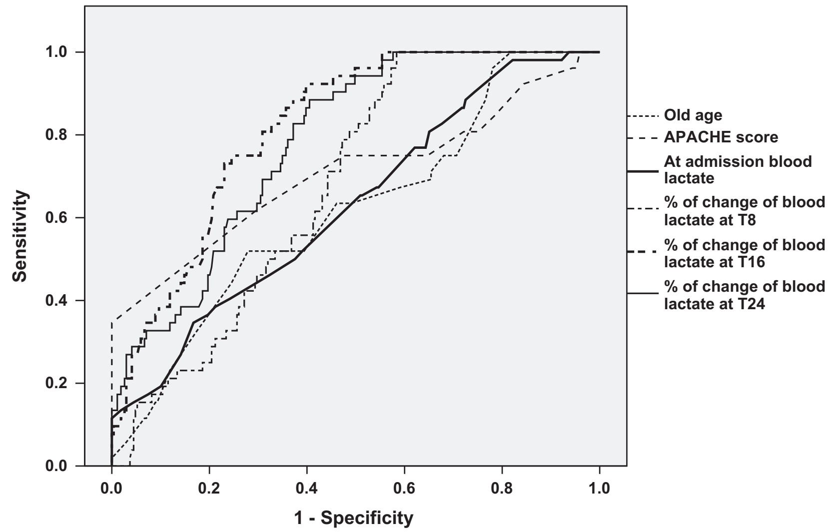

Figure 3 ROC curve analysis of the evaluated parameters as predictors for mortality.

Table 2 Blood lactate levels estimated in studied patients categorized according to survival and blood lactate strata.

Time	Data	Survivors	Non-survivors	Total	
Admission	Frequency	< 18 mg/dl	270 (83.9%)	52 (16.1%)	322 (100%)
		18–36 mg/dl	0	0	0
		> 36–54 mg/dl	0	0	0
		> 54 mg/dl	0	0	0
	Levels (mg/dl)		13 ± 1.88 (9.2–16.2)	13.9 ± 1.9* (10.3–17.8)	13.12 ± 1.9 (9.2–17.8)
8-h after ICU admission (T8)	Frequency	< 18 mg/dl	247 (91.5%)	41 (78.5%)	288 (89.4%)
		18–36 mg/dl	23 (8.5%)	11 (21.2%)	34 (10.6%)
		> 36–54 mg/dl	0	0	0
		> 54 mg/dl	0	0	0
	Levels (mg/dl)		15 ± 3.48 (9.2–23.4)	17.23 ± 4.1* (11.6–29.6)	15.33 ± 3.67 (9.2–29.6)
16-h after ICU admission (T16)	Frequency	< 18 mg/dl	206 (76.3%)	22 (42.3%)	228 (70.9%)
		18–36 mg/dl	64 (23.7%)	25 (44.2%)	89 (27.6%)
		> 36–54 mg/dl	0	3 (5.7%)	3 (0.9%)
		> 54 mg/dl	0	2 (3.8%)	2 (0.6%)
	Levels (mg/dl)		16.1 ± 5 (9.2–27.6)	25.17 ± 11.64* (12.3–50.5)	18.42 ± 7.61 (9.2–50.5)
24-h after ICU admission (T24)	Frequency	< 18 mg/dl	188 (69.6%)	19 (36.5%)	207 (64.3%)
		18–36 mg/dl	82 (30.4%)	24 (46.2%)	106 (32.9%)
		> 36–54 mg/dl	0	4 (7.7%)	4 (1.2%)
		> 54 mg/dl	0	5 (9.6%)	5 (1.6%)
	Levels (mg/dl)		16.74 ± 5.38 (9.2–29.6)	26.91 ± 13.36* (12.3–60.4)	18.38 ± 8.17 (12.3–60.4)

Data are presented as mean ± SD and numbers; ranges and percentages are in parenthesis.
* Significant versus survivors.

these three parameters in addition to the percentage of change of blood lactate level at T8, T16, and T24, according to AUC for each as specific predictor for mortality in the following descending order: percentage of change of blood lactate at T16 (AUC = 0.818), percentage of change of blood lactate at T24 (AUC = 0.783), high APACHE score (AUC = 0.706), percentage of change of blood lactate at T8 (AUC = 0.678), high at admission blood lactate (AUC = 0.629), and lastly, older age (AUC = 0.617) (Table 3, Fig. 3).

Regression analysis defined percentage of change of blood lactate at T16 as specific predictor in four models, high APACHE score in three models, followed by high at admission blood lactate in two models followed by old age in one model (Table 4).

Table 3 Specificity of evaluated parameters as predictors for mortality as judged by ROC curve analysis.

Test parameter	AUC	Std. error	Significance	95% Confidence interval	
				Lower bound	Upper bound
Old age	0.617	0.042	0.007	0.535	0.700
High APACHE	0.706	0.047	<0.001	0.614	0.798
High admission blood lactate	0.629	0.041	0.003	0.548	0.710
Percentage of change versus T0 lactate level					
T8	0.678	0.032	<0.001	0.614	0.741
T16	0.818	0.026	<0.001	0.766	0.869
T24	0.783	0.029	<0.001	0.726	0.839

AUC: area under curve, Std. error: standard error.

Table 4 Predictability of evaluated parameters for mortality as judged by Regression analysis.

Model	Variable	β	Std. error	t	Sig.
Model I	Percentage of change of blood lactate at T16	0.420	0.001	8.278	<0.001
Model II	Percentage of change of blood lactate at T16	0.443	0.001	9.045	<0.001
	High APACHE	0.261	0.006	5.327	<0.001
Model III	Percentage of change of blood lactate at T16	0.465	0.001	9.672	$=0.003$
	High APACHE	0.227	0.006	4.689	$=0.008$
	High at admission blood lactate level	0.198	0.009	4.060	$=0.040$
Model IV	Percentage of change of blood lactate at T16	0.470	0.001	9.858	<0.001
	High APACHE	0.195	0.006	3.954	<0.001
	High at admission blood lactate level	0.202	0.009	4.192	<0.001
	Old age	0.131	0.002	2.703	$=0.007$

β: Standardized coefficient, Std error: standard error, t: paired t-test.
% of change was calculated as follows: $([(T8)-(T0)]/[T0])\times(100))$.

4. Discussion

The prognostic yield of estimation of serum levels of biomarkers for prediction of outcome of critically ill patients admitted to ICU is still a matter of controversy despite the settled advantages. These advantages involve that it spares the need for patients transfer, easiness of repetition and interpretation, instrumental availability, and low cost.

Disturbed redox milieu is one of overwhelmed events that if misdiagnosed could induce critical situation in an already critically ill patient. Additionally, cancer is one of the diseases that depend on disturbed redox milieu for its pathogenesis and/or induces such disturbance. Disturbed mitochondrial respiratory chain cascades affect cellular redox state with subsequent reduction of cellular energetic sources and accumulation of unwanted intermediate reactants that may be harmful to the body function [9–11].

Elevated blood lactate is one example for such events; the current study reported steadily increasing postoperative blood lactate levels in studied patients admitted to ICU with significantly higher levels in those died during their ICU or hospital stay compared to those discharged alive in all examined samples with a positive significant correlation between high at admission blood lactate level and APACHE score. These data points to a correlation between clinical evaluation of disturbed patients' physiological status and disturbed respiratory chain function manifested as shift of pyruvate metabolism to lactate as end product. Both APACHE score and blood lactate level, at ICU admission, were significantly higher in non-survivors compared to survivors indicating a close relation with bad prognosis. ROC curve analysis documented this relation considering both in addition to old age as predictors for bad outcome.

These finding supported that previously reported in literature; Cheung et al. [12] reported that non-survivors had higher lactate concentrations at admission to pediatric ICU than survivors. Singhal et al. [13] found lactate and base deficit were significantly higher in non-survivors compared with survivors, and both were independently significant for predicting mortality. Li et al. [14] reported that blood lactate level >2.7 mmol/L was associated with 9.3-fold-higher odds for postoperative complications and concluded that initial serum lactate level is significantly associated with postoperative complications and can independently predict in-hospital morbidity after major abdominal surgery. Alves et al. [15] detected that after cardiac surgeries, higher levels of arterial lactate upon ICU admission were observed in patients who had renal complications and for surgeries with CPB and in those patients who died.

Through the current study, serial blood lactate levels at 8, 16, and 24-h after admission to ICU were significantly higher in non-survivors compared to survivors with progressive significant elevations till 24-h sample. Moreover, the percentage of change of blood lactate levels showed progressive increase and Regression analysis defined increased percentage of change at T16 as the specific predictor which maintained its significance in four models of analysis. These data indicated a fact that serial estimations and calculation of difference between blood levels is a more accurate and specific predictor for mortality.

In hand with these data, Cheung et al. [12] reported that serial lactate determination accurately predicts survival and may help differentiate survivors with adverse outcome from those with intact neurodevelopment in early childhood. Rocha et al. [16] assessed the preoperative, immediate, 3, 6-h, and 1st day postoperative serum lactate and found increased levels in immediate postoperative estimates but returning to baseline at 24 h, and patients who died had raised and maintained immediate postoperative lactate. Higher immediate and 3-h postoperative serum lactate level best discriminated mortality with area under the curve of 0.68. Hajjar et al. [17] suggested that lactate and standard base deficit measurement should be included in the routine assessment of patients with cancer admitted to ICU with sepsis, septic shock, or after high-risk surgery; these markers may be useful in the adequate allocation of resources in this population.

Combined high APACHE score, high serial changes of blood lactate and old age were found to be the significant specific predictors for mortality among patients enrolled in the current study. In support of these data, Basile-Filho et al. [18] found the differences in blood lactate levels were statistically significant between survivors and non-survivors at the end of the surgery and concluded that determination of the data was effective in predicting early mortality after orthotopic liver transplantation.

Murtuza et al. [19] identified minimum blood lactate level within the first 24-h after the Sano-Norwood procedure as a highly discriminatory predictor of perioperative mortality.

Allen [20] reported that although the presence of hyperlactataemia upon ICU admission appears to be associated with high mortality and morbidity, significant overlap between survivors and non-survivors means that non-survivors cannot be predicted from at admission lactate measurement but persistently elevated postoperative lactate is associated with increased morbidity and mortality in the pediatric cardiac population.

It could be concluded that serial estimations of blood lactate is a conclusive test for follow-up of cancer patients undergoing major surgical procedures requiring ICU admission and combined high APACHI score and percentage of change of blood lactate level could discriminate survivors from non-survivors with high specificity especially at 16-h after ICU admission.

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