BLOOD LACTATE AND LACTATE CLEARANCE: REFINED BIOMARKER AND PROGNOSTIC MARKER IN BURN RESUSCITATION

LACTATES SANGUINS ET LEUR ÉLIMINATION: UN BIOMARQUEUR PRONOSTIQUE PRÉCOCE CHEZ LE BRÛLÉ

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SUMMARY. Adequate resuscitation of acute burn patients is important to ensure end organ perfusion and oxygenation. The ideal marker to the endpoint of burn resuscitation is still not established. We aimed to evaluate the role of blood lactate and lactate clearance in burn resuscitation and their association with mortality and sepsis in burn patients. The retrospective study included patients (18-50 years) with thermal and scald burns with total body surface area of 30% to 60% over a period of 9 months who had achieved target urine output of at least 0.5ml/kg/hr within 24 hours of resuscitation. Patients were divided based on their admission blood lactate levels (Group A < 2 mmol/L and Group B > 2 mmol/L). Group B was further subdivided into Group B1 in whom blood lactate levels reached less than 2 mmol/L within 24 hours of burn resuscitation and Group B2 in whom it did not. Total patients included were 203. Mortality (M) and sepsis (S) rates in subgroup B2 were higher (M=57.9%; S=43.5%) and rates in subgroup B1 (M=25.8%; S=27.4%) were comparable to Group A (M=27.8%; S=26.4%). Persistent lactic acidosis at 24 hours was independently associated with significantly increased mortality and sepsis. Our data suggests a correlation of blood lactate levels and lactate clearance within 24 hours of admission with mortality and sepsis related to burn injury.

Keywords: burns, blood lactate, lactate clearance, mortality, prognostic biomarker, sepsis

RÉSUMÉ. *Un remplissage vasculaire adapté est nécessaire afin de préserver la perfusion et l'oxygénation tissulaires des brûlés. Le marqueur idéal de sa qualité reste à trouver. Nous avons évalué la lactatémie et l'élimination des lactates dans ce but, ainsi que leur corrélation avec la mortalité et le sepsis. Nous avons étudié rétrospectivement, sur 9 mois, 203 patients de 18 à 50 ans, brûlés sur 30 à 60% de SCT, ayant eu une diurèse horaire de plus de 0,5 mL/kg/h dans les 24 premières heures suivant leur brûlure. Le groupe A avait moins de 2 mmol/L de lactate à l'admission, le groupe B plus. Ce dernier groupe a été subdivisé en B1 (lactate redescendant à moins de 2 mmol/L dans les 24 premières heures) et B2 ne le faisant pas. La mortalité de B2 était plus élevée (57,8%) que A (27,8%) et B1 (25,8%), ces 2 derniers groupes étant comparables. De même, un sepsis survenait chez 43,5% des patients de B2 contre 27,4% pour B1 et 26,4% pour A. Plus que leur valeur initiale, c'est l'absence de décroissance dans les 24 premières heures des lactates qui est un marqueur de mauvais pronostic chez le brûlé.*

Mots-clés : *brûlure, lactates sanguins, élimination des lactates, mortalité, pronostic, sepsis, biomarqueur*

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Introduction

Burn injury results in severe hemodynamic derangements that initially start as rapid depletion of intravascular volume primarily caused by severe capillary leak. Burn shock to begin with is hypovolemic and is manifested by marked hemodynamic changes comprising diminished cardiac output, plasma volume and urinary output with sequentially elevated systemic vascular resistance subsequently leading to reduced peripheral blood flow.[1] To counteract these hemodynamic changes and to restore homeostasis, fluid resuscitation should be initiated at the earliest. Resuscitation of these critical burn patients is targeted by a blend of clinical assessments, blood investigations and invasive monitors. The end point of the exercise of resuscitation is to restore the circulating volume, establish cellular oxygenation, aerobic end organ metabolism and correct the acidosis ensued during the injury.[2] The ideal marker to the endpoint of burn resuscitation is still not established. Blood lactate has been studied as one such end point marker of resuscitation in shock. The correlation between blood lactate and cellular hypoxia has been established in the trauma and burn setting.[3,4] In contrast to the existing evidence, data on blood lactate and lactate clearance in burn shock in the Indian subcontinent is not available and for the rest of the world it is sparse. The aim of this study was to evaluate if blood lactate and lactate clearance is a valuable parameter in the evaluation of mortality and sepsis in burn patients.

Methodology

Study setting

The study was retrospective in design and was conducted from January to September 2019 at the Department of Burns, Plastic & Maxillofacial Surgery, VM Medical College & Safdarjung Hospital, Delhi, a tertiary burn care centre in India.

Study population

Patients who presented to the Department of Burns and Plastic Surgery from January to September 2019 with thermal or scald burns involving total body surface area of 30-60% and who achieved a target urine output of at least 0.5ml/kg/hr within 24 hours of resuscitation were included in the study. The exclusion criteria included associated trauma other than burns, presentation to our burn care facility after 24 hours from time of burn, organ failure, pre-existing comorbidities and documented infection pre burn.

Data and definitions

Data were collected using Microsoft Excel 2010 (Microsoft, USA) for eligible patients at the time of admission.

Fluid resuscitation was done using institutional protocol: first 24 hours: 2ml/kg/% burns (lactated ringer) + 50ml/kg/day (dextrose normal saline) was calculated. Half of the calculated volume was administered in the first 8 hours post-burn injury and the remaining half of the calculated volume was administered in the following 16 hours. For the second 24 hours: 1ml/kg/% burns (lactated ringer) + 50ml/kg/day (dextrose normal saline) was administered. After 48 hours: 40ml/kg/day + (25+body surface area burnt) x body surface area x 24 (dextrose normal saline) was calculated and given.[5]

Blood lactate values were assessed using Radiometer ABL 800 flex analyser every 4 hours in the first 24 hours, every 6 hours in the next 24 hours and every 12 hours in the next 24 hours post burn/normalisation of two consecutive blood lactate values, whichever was earlier.

Sepsis was defined by the presence of 3 or more of the following criteria: 1) tachycardia (heart rate >90 beats/min), 2) tachypnea (respiratory rate >20 breaths/min), 3) fever or hypothermia (temperature >38 or <36 °C), 4) leukocytosis or leukopenia (white blood cells >1,2000/mm3 or <4,000/mm3 respectively) along with documented infection or clinical suspicion of infection.[6]

Statistical analysis

The population was divided based on admission blood lactate levels. Group A consisted of patients with blood lactate levels less than 2 mmol/L and Group B with blood lactate levels more than 2 mmol/L. Group B was further subdivided into Group B1 in whom blood lactate levels reached less than 2 mmol/L within 24 hours of burn resuscitation and

Group B2 in whom blood lactate levels did not fall below 2 mmol/L within 24 hours of burn resuscitation. General population characteristics were analysed between the groups. Data were analysed for any association between the groups and sub groups with mortality and sepsis. Mean and median were used to represent the skewed data. The continuous variables were compared using t test. A p value <0.05 was considered statistically significant.

Results

A total of 203 patients were included in the study. The mean age of the study population was 34.1 years (18-50 years). Fifty-two percent of the patients were in the age group of 20-35 years and 51% of the patients were male. Mean total body surface area (TBSA) involved was 55.9% (30-60%). The mean duration of hospital stay was 21.25 days (11-45 days). Seventy patients had inhalational burns. Sixty-six patients developed sepsis during their hospital stay. Mortality within 30 days post burn was seen in 76 patients (*Table I*).

Table I - Population characteristics

Parameters	Overall	Group A (n=72)	Group B (n=131)	p-value
Age (years)	34.1	35.9	32.3	< 0.0001
Male / Female	104/99	33/39	71/60	
Weight in kg, mean	61.8	62.2	61.5	0.0743
TBSA burnt (%)	55.9	55.6	56.3	0.0514
Length of hospital stay-overall (days)	21.25	24.9	17.6	< 0.0001
Length of hospital stay-non survivors (days)	13.25	18.4	9.5	< 0.0001
Inhalational injury present	70	22	48	0.0643
Full-thickness burn present	72	27	45	0.0516
ABSI, mean	9	8	11	0.0473
Sepsis	66	19	47	0.0358
Mortality (30 day)	76	20	56	0.0411
Blood lactate (on admission)		1.83	4.97	< 0.0001
Blood lactate (24 hours)		1.86	3.88	< 0.0001

Seventy-two patients had blood lactate levels at admission less than 2 mmol/L (Group A) and their mean abbreviated burn severity index (ABSI) was 8. Sepsis was clinically detected in 19 patients and 20 patients expired during the first post burn month. The average duration of hospital stay was 24.9 days. Group B included 131 patients with blood lactate levels at admission greater than 2 mmol/L and their mean ABSI was 11. Sepsis was clinically detected in 47 patients and 56 patients expired during the first post burn month. The average duration of hospital stay was 17.6 days.

Subgroup analysis was done for patients in Group B with relation to blood lactate clearance at 24 hours. In subgroup B1 the blood lactate reached values <2 mmol/L at 24 hours and in subgroup B2 the values persisted to be elevated >2 mmol/L at 24 hours. The mortality rate in subgroup B1 and B2 was 25.8% and 57.9% respectively. The sepsis rate in subgroup B1 and B2 was 27.4% and 43.5% respectively. The mortality and sepsis rates in subgroup B2 were higher and the rates in subgroup B1 were comparable to Group A (*Table II*) (*Fig. 1*). The difference in mortality and sepsis rates in subgroups of group B was statistically significant. Lactic acidosis on admission and at 24 hours was studied for associated mortality and sepsis. Persistent lactic acidosis at 24 hours was independently associated with significantly increased mortality and sepsis (*Figs. 2 and 3*). The overall relative risk of mortality and sepsis in the presence of lactic acidosis at 24 hours was 2.1578 and 1.6184 respectively (*Tables III and IV*). Another subgroup analysis was done to understand the relationship between inhalational burns and lactic acidosis. The overall relative risk of lactic acidosis on ad-

Table II - Relation of blood lactate and lactate clearance on mortality and sepsis

Group	Number of patients	Sepsis	Mortality	Blood lactate (on admission)	Blood lactate (24 hours)
Group A	72	19 (26.4%)	20 (27.8%)	1.83	1.86
Group B	131	47 (35.8%)	56 (42.7%)	4.97	3.6
Group B1	62	17 (27.4%)	16 (25.8%)	4.75	1.91
Group B2	69	30 (43.5%)	40 (57.9%)	5.15	4.97

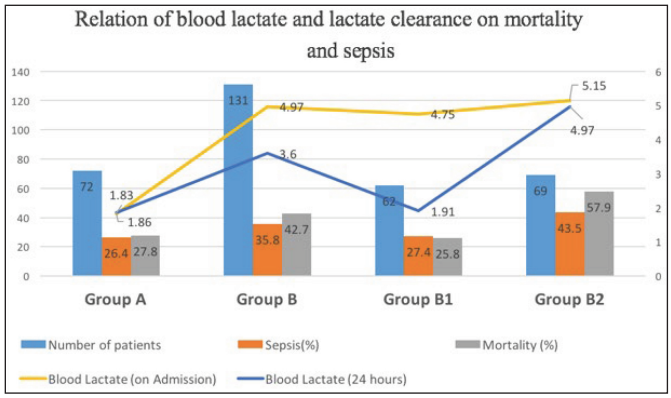

Fig. 1 - Relation of blood lactate and lactate clearance on mortality and sepsis

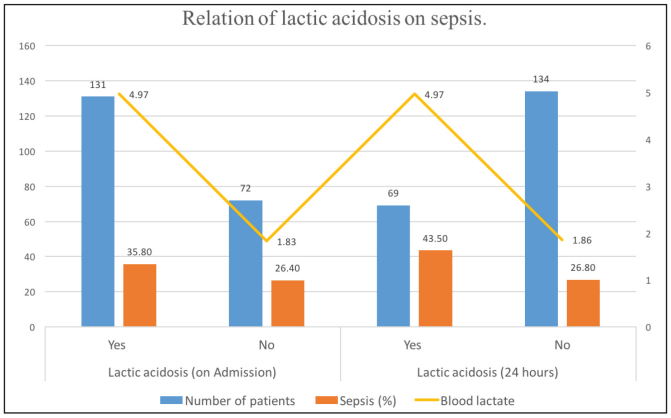

Fig. 2 - Relation of lactic acidosis on sepsis

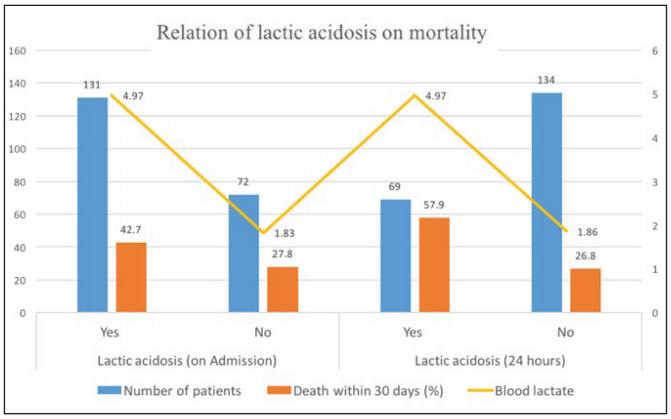

Fig. 3 - Relation of lactic acidosis on mortality

Table III - Relation of lactic acidosis on sepsis

Category	Present	N	Sepsis (%)	p Value	Relative risk
Lactic acidosis (on admission)	Yes	131	47 (37.8)	0.1796	1.3596
	No	72	19 (26.3)		
Lactic acidosis (24 hours)	Yes	69	30 (43.5)	0.0150	1.6184
	No	134	36 (26.8)		

Lactic acidosis - blood lactate levels more than 2 mmol/L

Table IV - Relation of lactic acidosis on mortality

Category	Present	N	Death within 30 days (%)	p Value	Relative risk
Lactic acidosis (on admission)	Yes	131	56 (42.7)	0.0452	1.5389
	No	72	20 (27.7)		
Lactic acidosis (24 hours)	Yes	69	40 (57.9)	< 0.0001	2.1578
	No	134	36 (26.8)		

Lactic acidosis - blood lactate levels more than 2 mmol/L

mission and at 24 hours with inhalational burns was 1.0988 and 0.9748 respectively. The association was not statistically significant (*Tables V and VI*) (*Fig. 4*).

Table V - Relation of lactic acidosis on admission and inhalational burns

Category	Present	Lactic acidosis on admission present	Lactic acidosis on admission absent	p Value	Relative risk
Inhalational burns	Yes	48	22	0.382	1.0988
	No	83	50		

Lactic acidosis - blood lactate levels more than 2 mmol/L

Table VI - Relation of lactic acidosis at 24 hours and inhalational burns

Category	Present	Lactic acidosis at 24 hours present	Lactic acidosis at 24 hours absent	p Value	Relative risk
Inhalational burns	Yes	16	32	0.9128	0.9748
	No	53	102		

Lactic acidosis - blood lactate levels more than 2 mmol/L

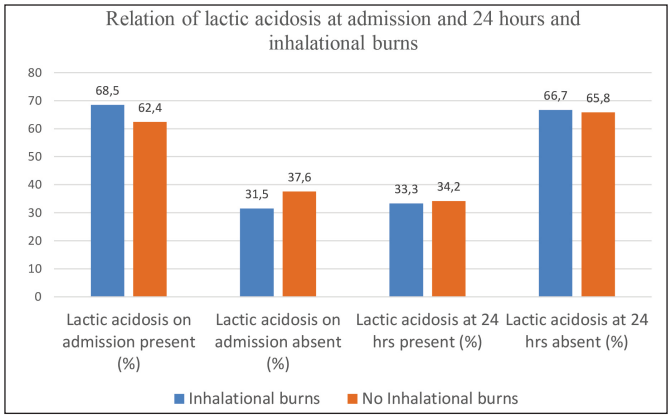

Fig. 4 - Relation of lactic acidosis at admission and 24 hours and inhalational burns

Discussion

Adequate fluid resuscitation has been found to reduce mortality in burn patients. The best marker for monitoring adequacy of burn resuscitation is still under question. An ideal marker would require it to be accurate, reproducible and adequately reflect dynamic changes during resuscitation.[7] In fluid resuscitation of acute burns, conventionally used markers such as blood pressure and urine output, though commonly used, are not reliable.[8] Stress response to catecholamines tends to maintain blood pressure in the face of decreasing circulating volume over variable periods of time.[9] Invasive monitoring often leads to over resuscitation with fluids and is labour intensive.[10] Lactic acidosis in burns occurs as a result of both increased production and decreased clearance of lactate. Anaerobic metabolism induced by cellular hypoxia as a result of hypo-perfusion causes increased production of lactate. Hepatic clearance of lactate is also reduced in shock scenarios.[11] In the setting of septic and hemorrhagic shock, blood lactate has been found to correlate with clinical outcome.[12] Blood lactate levels have been used as an indicator in sepsis.[13] Blood lactate levels are shown to predict microcirculation and global tissue hypoxia. Lactic

acidosis can decrease cardiac contractibility, cardiac output, increase arrhythmogenicity and decrease responsiveness to catecholamines.[14] Lactate levels and base deficit have been found to be associated with burn mortality.[7,15,16]

In this retrospective study of 203 patients, we intended to demonstrate blood lactate as a marker to predict outcomes in burns. Mean ABSI was higher in Group B patients. Overall 30-day mortality was 37.4% in our cohort, which is higher than that reported in other studies.[7,15,16] Inhalational injury was present in 34.4% of cases. The rates of inhalational injury were higher in Group B; the difference was not statistically significant. It is known that the associated mortality rates are higher in inhalational injury; hence a subgroup analysis was done to know the association of lactic acidosis and inhalational injury. In our study, there was no statistically significant increased risk in the inhalational burn subgroup to develop lactic acidosis. In their study, Mokline et al. did not find inhalational injury to be an independent predictor of mortality.[17] In Group B, mean hospital stay was lower, mainly because of the higher mortality rates. These deaths occurred much earlier during their hospital course (9.5 vs 18.4 days).

Group A patients had significantly lower occurrence of sepsis (26.3%) and 30-day mortality (27.7%) than Group B (sepsis - 35.8%, mortality - 42.7%). Cochran et al. demonstrated that burn patients who died had significantly increased lactate levels in the first 48 hours, but they did not find a specific threshold value in their study.[15] Herero et al. showed that there was 31.3% mortality for patients with a blood lactate at admission of ≥2 mmol/l versus 6% in patients with a blood lactate at admission of <2 mmol/L.[18] Average time for lactate clearance in survivors was significantly less than in non survivors (2.02 vs 4.6 days, $p<0.02$). In their study of 80 burn patients Mokline et al. suggested that initial lactate levels provided the best sensitivity (88%) and specificity (79%) for predicting sepsis (ROC- 0.82). Blood lactate for prediction of mortality had a good sensitivity (86%) and specificity (92%) in their study.[17] However, Cochrane et al. found no association between lactate levels on admission with mortality.[15]

In our study we found that patients who cleared lactate within the first 24 hours had significantly lower mortality (25.8%) and sepsis rates (27.4%) than those who did not clear lactate. In fact, the rates of mortality and sepsis in the group who cleared lactate within the first 24 hours was comparable to patients who had baseline lactate levels of <2 mmol/L. Blood lactate levels did not correlate with total burn surface area. Both Groups A and B had similar TBSA. In our study, average total body surface area burned was 55.9%, which is similar to other studies evaluating the role of lactate in burns.[15] Lactate clearance has been demonstrated in a few studies to be a good marker of resuscitation in burns and other types of shock.[12,19] In patients with sepsis and trauma, lactate clearance has shown improved outcomes.[12,19] In addition, it has been proposed as an early predictor of death in patients with burn injuries. Kamolz et al. prospectively evaluated lactate levels in 166 burn patients. They observed that survivors and non survivors could be separated based on initial lactate level. Moreover, patients who cleared lactate within 24 hours had a 68% chance of survival compared to patients who had a lactate of >2mmol/L (27% chance of survival).[7] For each 10% increase in lactate clearance, an 11% decrease in mortality occurs.[19]

In spite of many studies reiterating the importance of blood lactate and lactate clearance in predicting mortality in burn patients, the role of these markers in the titration of therapy is ambiguous. Overzealous fluid resuscitation may cause fluid overload and acute respiratory distress syndrome. Also, there is not much regional data available to establish the importance of blood lactate and lactate clearance. We demonstrated the association of blood lactate level at the time of admission and lactate clearance with mortality and sepsis. However, to establish the causal relationship, further large multicenter prospective studies are required.

Conclusion

Traditional end points of burn resuscitation are being extensively used clinically. However these end points of resuscitation are not the ideal markers. The

high-end resource extensive devices are not easily available in resource-restricted environments. Our data suggest a correlation of blood lactate levels and lactate clearance within 24 hours of admission with mortality and sepsis related to burn injury. Hence directing measures to normalize lactate levels in addition to the traditional resuscitation end points might lead to better outcomes in burn patients. Our study is limited due to its retrospective nature and limited population. Further prospective studies with larger study populations are required to establish blood lactate and lactate clearance as endpoint in resuscitation of burn patients and its clinical application to improve the outcomes in care of burn patients. Although we have studied inhalational injury and its association with lactic acidosis, there could be other confounding variables that have not been extensively studied in this study.

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