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Intraoperative lactate measurements are not predictive of death in high risk surgical patients

A medida do lactato arterial intraoperatório não é determinante de mortalidade em pacientes cirúrgicos de alto risco

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ABSTRACT

Objectives: An increased lactate level is classically considered a marker for poorer prognosis, however little information is available on intraoperative lactate's kinetics and its connection with prognosis. This study aimed to evaluate the time when perioperative lactate is most relevant for prognosis.

Methods: This was an observational prospective study conducted in a tertiary hospital. Patients with requested intensive care unit postoperative stay, aged ≥ 18 years, undergoing major surgery were included. Palliative surgery patients and those with heart and/or severe liver failure were excluded. Arterial lactate levels were measured immediately before the surgery start (T0), after anesthesia induction (T1), 3 hours after the surgery start (T2), intensive care unit admission (T3) and 6 hours after the intensive care unit admission (T4).

Results: Sixty seven patients were included. The mean lactate values for the patients' T0, T1, T2 and T4 were 1.5 ± 0.8 mmol/L, 1.5 ± 0.7 mmol/L, 1.8 ± 1.2 mmol/L, 2.7 ± 1.7 mmol/L and 3.1 ± 2.0 mmol/L, respectively. The hospital mortality rate was 25.8%, and surviving and non-surviving patients lactate values in the intensive care unit were 2.5 ± 1. and 4.8 ± 2.8 mmol/L ($P < 0.0001$), respectively. The other times measurements showed no statistically significant differences between the groups.

Conclusions: In surgical patients, intraoperative arterial lactate levels failed to show a predictive value; however during the postoperative period, this assessment was shown to be useful for hospital mortality prediction.

Keywords: Intraoperative period; Intraoperative care; Perfusion; Lactates/administration & dosage; Prognosis; Time factors

INTRODUCTION

About 234 million surgeries are performed yearly.[1] Major surgeries postoperative complications cause morbidity and mortality.[2,3] The mortality in high risk surgical patients ranges between 9.7% in the USA and 35.9% in the United Kingdom.[4]

Data confirm that unfavorable postoperative outcomes in high risk surgery are a global concern.[5-7] Even in patients who survive beyond hospitalization, complications remain as key determinants for short survival.[7] Therefore, the search for tools able to improve these patients outcome is very relevant.

Several reports indicate that postoperative major and high risk surgery complications are strongly correlated with oxygen supply disorders, which in

230

Silva Junior JM, Oliveira AMRR, Silveira BR,
Ferreira UP, Albretht RN, Gonzaga TB et al.

turn are related to microvascular flow impairment.[8-10]

When cells oxygen availability is limited, anaerobic metabolism takes place, causing metabolic acidosis. This metabolic acidosis may be quantified by means of arterial gas contents assessment, analysis of the base difference and serum lactate concentration.[11]

Therefore, lactate is a key hypoperfusion indicator, and has been studied for several decades,[12] showing increased serum levels to be strongly correlated with poorer patients' prognosis.[11]

In some instances, as during sepsis, trauma, or shock, the use of serum lactate as surrogate of tissue hypoxia is established.[13-15] However, little perioperative arterial lactate kinetics in high risk surgical patients information is available.[16]

Therefore this study was aimed to evaluate the perioperative lactate measurement and to assess its best discriminative time for surviving versus non-surviving patients.

METHODS

After approved by the institution's Ethics Committee, this study was conducted in a tertiary hospital surgical center and intensive care unit (ICU).

This was a prospective study. The inclusion criteria were: ≥18 years-old patients who signed the informed consent form before the surgery, undergoing surgery with requested ICU postoperative stay and at least two of the following:

- severe cardiorespiratory comorbidities (coronary insufficiency, chronic obstructive pulmonary disease, previous stroke),

- surgery scheduled for neoplasm resection (esophagectomy, total gastrectomy) longer than 8 hours,

- above 70 years-old, with evidence of physiological reserve impairment involving at least one vital organ,

- acute renal failure (blood urea nitrogen > 100 mg/dL or creatinine > 3 mg/dL),

- advanced vascular disease, or aortal involvement,

- massive acute intraoperative blood loss predicted and

- severe nutritional disorders patients.

Palliative surgery, low life expectancy, liver failure (Child B or C) and functional class IV or heart failure with less than 30% echocardiogram ejection fraction, were excluded.

The study primary endpoint was to evaluate the intraoperative lactate levels and hospital mortality, while the secondary endpoint was to evaluate postoperative complications such as organ dysfunction, i.e., circulatory shock (vasoactive drugs required for more than 1 hours although volume resuscitation), worsened pulmonary oxygen exchange [oxygen partial pressure/inspired oxygen fraction (PaO_2/FiO_2 < 200) ratio], renal failure (50% creatinine increase or urinary output less than 400 mL in 24 hours), mental confusion (behavioral change, memory loss or psychomotor agitation) and platelet dysfunction (30% platelets count drop from baseline) up to 24 hours postoperatively. Additionally, infection during the ICU stay, hospital length of stay and intraoperative hyperlactatemia risk factors, such as blood transfusions and vasoactive drugs.

Later, the patients were divided into two groups, survivors and non-survivors. In addition, the complications were assessed and correlated with the arterial lactate collection times.

The intraoperative therapy was conducted as determined by the surgical team, while in the postoperative period, by the intensivist. All patients were followed until their discharge from the hospital.

By the inclusion were evaluated the scores Multiple-Organ Dysfunction Syndrome (MODS),[17] Acute Physiology And Chronic Health Evaluation (APACHE II),[18] and Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM score),[19] using the variables' worst ratings scores. Additionally, before surgery (T0), after anesthesia induction (T1), 3 hours from the surgery start (T2), ICU admission (T4), and 6 hours post- ICU admission (T5) were collected arterial gasometry and lactate samples. It is important to remark that in this institution the patients are transferred to the ICU immediately after the surgery, as both surgical center and ICU are located in the same area. It is thus expected that the ICU admission lactate is similar to the end-of-surgery lactate values.

Statistical analysis

The included patients' demographic, clinical and physiological characteristics were described. For the categorical variables description, the frequencies and percentages were calculated. The quantitative variables were described by central trend and dispersion measures (mean and standard deviations, median and percentiles).

The categorical variables were analyzed with the Chi-square test, and the continuous variables with the t student test and ANOVA for normal distribution variables. Two sided $P < 0.05$ values were considered significant. The calculations were made with the SPSS 13.0 software. The outcomes were compared versus

the lactate samples drawing times.

The predictive ability to discriminate survivors from non-survivors was assessed using Receiver Operating Characteristic (ROC) curves.

RESULTS

Sixty seven patients were included during a 6 months period, being 37 male and 30 female patients, mean age 65.6 ± 12.2 years. Most underwent elective surgeries (Table 1).

Table 1- Patients' baseline characteristics

| Variables	Characteristics
Age (years)	65.6 ± 12.2
Male gender	56.1
APACHE II	16.9 ± 5.6
MODS	3.0 (1.0-4.0)
POSSUM	37.4 ± 7.6
Elective surgery	95.5
Surgical specialty	
Gastrointestinal	78.8
Vascular	7.6
Chest	4.5
Orthopedic	3.0
Neurological	3.0
Gynecological	1.5
Urological	1.5
ASA	
I	6.6
II	68.9
III	24.6
Surgery time (hours)	6.9 ± 2.4
Preoperative lactate (mmol/L)	1.5 ± 0.8
Preoperative base difference (mmol/L)	-0.7 (-3.0- 0.6)
Preoperative blood glucose (mg/dl)	120.0 ± 54.2
ICU length of stay (days)	3.0 (2.0 - 4.0)
Hospital length of stay (days)	20.0 (12.5 – 27.5)

APACHE II - Acute Physiology And Chronic Health Evaluation II; MODS - Multiple-Organ Dysfunction Syndrome; POSSUM - Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity; ASA - American Society of Anesthesiologists; ICU – intensive care unit. Results expressed as percents, mean ± standard deviation or median (25-75% percentiles).

Hospital mortality was 25.8% (17 patients). Survivor and non-survivor patients' lactate dosages 6 hours after the ICU admission were 2.5 ± 1.3 and 4.8 ± 2.8 mmol/L, respectively ($P < 0.0001$). The other times measurements failed to show statistically significant inter-groups differences (baseline, $P = 0.46$; surgery start, $P = 0.57$; 3 hours of surgery, $P = 0.51$, ICU admission, $P = 0.23$) (Figure 1).
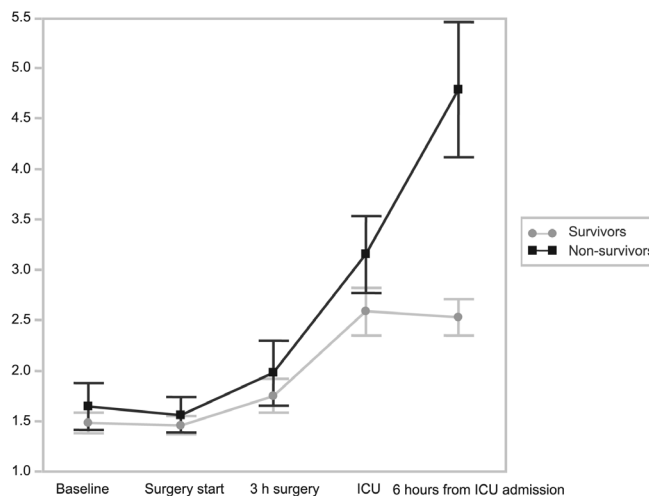
ICU – intensive care unit.

Figure 1 - Perioperative lactate values comparison for survivor and non-survivor patients.

Also in the ROC curve sensitivity and specificity analysis, the intraoperative lactate values had hospital mortality discriminative power. Yet, the ICU admission and 6 hours after the ICU admission values discriminative power, was better (Table 2).

During the surgery, 50% of the patients had blood transfusion, and 32.5% were given vasoactive drugs; 54.5% of the complications were in the postoperative period, with circulatory shock predominance. The lactate values were comparatively higher in the postoperative period (Tables 3 and 4).

Table 2 - ROC for arterial lactate drawing times versus hospital mortality

Lactate (mmol/L)	Area	Cutoff	Sensitivity (%)	Specificity (%)	95% Confidence interval	p value (area=0.5)
Baseline	0.54	>2.0	35.3	87.8	0.41 - 0.66	0.65
Surgery start	0.51	>1.8	29.4	88.0	0.38 - 0.53	0.94
3 h surgery	0.59	> 1.1	88.2	44.0	0.46 - 0.71	0.29
ICU	0.62	>2.7	64.7	68.0	0.49 - 0.73	0.15
6h after ICU admission	0.77	> 1.9	100.0	46.0	0.65 - 0.86	0.0002

ICU – intensive care unit.

Table 3- Patients' characteristics during surgery and postoperatively

Variables	Characteristics
Intraoperative crystalloid (mL)	7000 (4625-8875)
Postoperative crystalloid (mL)	1900 (1000-2500)
Intraoperative colloid (mL)	1000 (500-1000)
Postoperative colloid (ml)	500 (500-875)
Intraoperative PBC units	2.0(2.0-3.0)
Postoperative PBC units	1.5(1.0-2.0)
Intraoperative vasopressors required	32.5
Intraoperative fluid balance (mL)	800 (175-1420)
Surgery start lactate (mmol/L)	1.5±0.7
3 hours surgery lactate (mmol/L)	1.8±1.2
ICU admission lactate (mmol/L)	2.7±1.7
6 hours after ICU admission lactate (mmol/L)	3.1±2.0
Postoperative complications	54.5
Circulatory shock	45.5
Acute renal failure	19.7
Platelet dysfunction	19.7
Infection	16.7
Oxygen exchange worsened	10.6
Confusion state	7.6
Postoperative blood glucose (mg/dL)	175.5 ± 60.0

Crystalloid: saline 0.9% and ringer lactate solutions; colloid: hydroxyethyl starch solution; PBC: packed blood cells. Results expressed as percents, mean ± standard deviation and median (25-75% percentile).

DISCUSSION

One of the major challenges for physicians responsible for severely ill patients is the tissue perfusion control. Its changes lead to several organs dysfunction, and increased mortality. Early tissue hypoxia identification, for a prompt therapy start, is fundamental to improve these patients prognosis.[20]

Currently, few parameters are available in clinical practice for tissue hypoxia assessment, such as urinary output, base difference and blood lactate, however these measures only indicate that hypoperfusion is already ongoing, and may be late tools to guide hemodynamic resuscitation start.[21]

This study has shown that the up to 3 hours intraoperative lactate was not able to discriminate prognosis, while the ICU admission and 6 hours from admission measurements may predict unfavorable outcome.

The serum lactate level has been classically accepted as anaerobic metabolism and tissue hypoxia indicator.[22,23] The blood lactate kinetics-associated pathways are complex, but this does not void this indicator as an excellent surgical patients prognosis pre-

Table 4- Lactate trend versus intraoperative hyperlactatemia and outcomes risk factors

Variables	Baseline	Surgery start	3 hours surgery	ICU	6 hours after ICU admission
Intraoperative transfusion (Yes)	1.6±0.9	1.5±0.8	2.0±1.4	3.1±1.9	3.6±2.4
Intraoperative transfusion (No)	1.4±0.5	1.5±0.5	1.6±0.9	2.3±1.2	2.6±1.3
p value	0.3	0.89	0.15	0.04	0.02
Intraoperative vasopressors (Yes)	1.5±0.8	1.5±0.7	2.0±1.5	3.3±2.1	4.4±2.9
Intraoperative vasopressors (No)	1.4±0.6	1.4±0.5	1.6±1.1	2.2±1.2	2.4±1.1
p value	0.73	0.65	0.29	0.02	0.00
Postoperative complications (Yes)	1.4±0.8	1.4±0.6	1.8±1.3	3.0±1.9	3.7±2.4
Postoperative complications (No)	1.6±0.8	1.6±0.7	1.8±1.1	2.3±1.2	2.4±1.0
p value	0.25	0.33	0.87	0.09	0.01
Shock (Yes)	1.3±0.7	1.4±0.7	1.9±1.3	3.1±1.8	4.0±2.5
Shock (No)	1.7±0.8	1.5±0.7	1.8±1.1	2.4±1.5	2.4±1.1
p value	0.11	0.38	0.72	0.10	0.00
Renal failure (Yes)	1.4±0.7	1.3±0.5	1.5±0.4	3.4±2.0	4.4±3.0
Renal failure (No)	1.5±0.8	1.529±0.7	1.9±1.3	2.6±1.5	2.8±1.6
p value	0.61	0.25	0.30	0.12	0.01
Platelet dysfunction (Yes)	1.4±0.6	1.2±0.4	1.6±0.8	3.4±2.2	4.4±3.4
Platelet dysfunction (No)	1.5±0.8	1.5±0.7	1.8±1.3	2.6±1.5	2.8±1.4
p value	0.53	0.15	0.56	0.11	0.01
Infection (Yes)	1.6±1.0	1.4±0.6	1.7±0.5	3.8±2.3	5.3±3.3
Infection (No)	1.5±0.7	1.5±0.7	1.8±1.3	2.5±1.4	2.7±1.3
p value	0.74	0.81	0.81	0.02	0.00
Oxygen exchange worsened (Yes)	1.7±0.9	1.7±0.8	2.2±1.4	3.1±1.9	3.0±2.4
Oxygen exchange worsened (No)	1.5±0.5	1.5±0.5	1.8±0.9	2.7±1.2	3.1±1.3
p value	0.53	0.45	0.40	0.51	0.94
Confusion state (Yes)	1.2±0.5	1.3±0.2	1.4±0.3	3.2±1.5	3.4±1.9
Confusion state (No)	1.5±0.8	1.5±0.7	1.8±1.2	2.7±1.7	3.1±2.0
p value	0.37	0.50	0.45	0.48	0.71

The values represent mean ± standard deviation; ICU – intensive care unit.

dictor. Normal serum lactate concentration is below 2 mmol/L at rest, and above 4 mmol/L levels indicate systemic inflammatory response syndrome (SIRS) and increased mortality, even in patients with blood pressure considered normal.[24]

Tissue hypoxia increases lactate levels by increased anaerobic glycolysis aimed to keep cell energy production as close as possible to normal, and this is common in the shock settings.[11]

Additionally, in early shock, the increased blood lactate levels were associated with reduced oxygen offer, thus, tissue hypoxia and increased mortality.[13,25] However, it should be remarked that in normal situations the liver is able to increase the lactate metabolism, leading to a delay of some hours before lactate levels increase can be detected in hypoxemic situations and anaerobic metabolism,[26] which may, in part, justify this study findings.

During circulatory shock, lactate levels may also increase during hypoperfusion. The increased production may occur, for instance, when the glucose metabolism exceeds the mitochondrial oxidative capacity due to catecholamines administration, pyruvate desidrogenase disorders, and respiratory alkalosis. Yet, in liver dysfunction, its excretion may be reduced.[27]

Therefore, during the surgical procedure, specially in major surgery, more vasopressors are used, and the liver clearance is reduced by lower oxygen consumption due to anesthesia.[28,29] Thus, immediate postoperative patients have higher serum lactate levels,[29] in addition to that after anesthesia the restored full cell function could provide a washout phenomenon,[30] which is reported following circulatory resuscitation.

Additionally, some already inflamed organs may increase lactate levels. Studies have shown that the lung and muscle are important lactate producers,[31] and important lactate levels increase may be seen in pulmonary injury patients. De Backer et al.[32] have shown increased lactate production in acute pulmonary injury patients, with acute inflammatory process. Thus, the postoperative period is the main organs inflammation time, and this may be correlate with increased lactate during this phase, and its mortality and complications prognostic value, as found in this sample, corroborating its lack of intraoperative prognostic value.

Meregalli et al.[33] have shown that a postoperative 3.1 mmol/L lactate level in hemodynamically stable surgical patients failed to discriminate patients who didn't survive to the first 12 hours from admission,

by the other hand the clearence determined the prognosis. In heart surgery, a postoperative 3 mmol/L value determined increased morbidity and mortality risks.[34] Almeida et al.[29] only found ICU admission values above 3.2 mmol/L to discriminate mortality, and did not evaluate the marker trends.

Attempting to improve the method accuracy, we identified studies evaluating lactate levels development as a prognostic factor, and in one of then this was named "lactime"[35], i.e. the time when lactate was high, and could demonstrate that lactic metabolic acidosis is the best multi-organ dysfunction and death predictor, and that the initial lactate measurement, and in another study, the early lactate clearance,[26] were shown to be correlated with improved prognosis, with worsened survival in patients with delayed lactate normalization following an intervention.[36] A more recent study, conducted in 21 Brazilian ICUs, evidenced that ICU admission lactate is an early risk of death for multi-organs and systems dysfunction determinant in a high risk surgical patients population.[37]

These investigations provide strong evidence to support the role of lactate as a guide for hypoperfusion and surgical patients' prognostic indicator only in the postoperative time.

However, some limiting aspects should be considered for this study. First, it was not evaluated if the reanimation measures for hyperlactatemia had any impact on survival; however as this study was aimed to assess the time when lactate has the best surgical patient prognosis value, this discussions on lactate-guided therapy, in addition to be controversial, would exceed the initial aim.[38]

Second, it should be noted that this study only involved a small population, and larger studies are warranted to better evaluate if these results reliability. Also, additional lactate measurements, in different times of surgery, could bring additional information; however this does not void our findings, as the times selected for lactate samples draws correspond to crucial times during surgery, and the intervals between the draws were short, considering a mean surgery time of 6 hours and the measurements made at the beginning, third hour and end of the procedure.

Finally, the time from the operation room to the ICU admission could influence the results; however, no patient had intercurrences during this time, and the transportation time was short, as the surgical center and the ICU are very close.

CONCLUSION

In surgical patients, intraoperative arterial lactate failed to show prognostic value; however, when evaluated in the ICU and 6 hours after ICU admission, arterial lactate was useful to determine hospital morbidity and mortality.

RESUMO

Objetivos: Classicamente, lactato elevado é considerado como marcador de pior prognóstico, entretanto poucos dados existem a respeito da cinética do lactato no periodo intraoperatório e sua associação com o prognóstico. O objetivo deste estudo foi avaliar em qual momento do período perioperatório o valor do lactato apresenta maior importância prognóstica.

Métodos: Estudo prospectivo observacional de um hospital terciário. Foram incluídos pacientes com solicitação de pós-operatório em unidade de terapia intensiva com idade ≥18 anos, submetidos a cirurgias de grande porte. Pacientes de cirurgias paliativas, com insuficiência cardíaca e/ou hepá-tica grave foram excluídos. Valores de lactato arterial foram mensurados imediatamente antes do início da cirurgia (T0), após indução anestésica (T1), após 3hs de cirurgia (T2), na admissão da unidade de terapia intensiva (T3) e após 6 h da admissão na unidade de terapia intensiva (T4).

Resultados: Foram incluídos 67 pacientes. Os valores médios do lactato dos pacientes no T0, T1, T2, T3 e T4 foram respectivamente 1,5 ± 0,8mmol/L, 1,5 ± 0,7mmol/L, 1,8 ± 1,2mmol/L, 2,7 ± 1,7mmol/L e 3,1 ± 2,0mmol/L. A taxa de mortalidade hospitalar foi 25,8% e as dosagens de lactato dos pacientes sobreviventes e dos não sobreviventes 6 h após admissão na unidade de terapia intensiva foram 2,5 ± 1,3 e 4,8 ± 2,8 mmol/L (p<0,0001), respectivamente. As medidas nos demais períodos não demonstraram diferenças estatisticamente significativas dentre estes grupos.

Conclusões: Em pacientes cirúrgicos o lactato arterial no período intraoperatório não apresentou valor prognóstico, entretanto quando avaliado no pós-operatório, ele foi melhor para determinar mortalidade hospitalar.

Descritores: Período intraoperatório; Cuidados intra-operatórios; Perfusão; Lactatos/administração & dosagem; Prognóstico; Fatores de tempo

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