ORIGINAL ARTICLES

Serum lactate as predictor of morbidity, mortality and long term survival in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Introduction: Serum lactate elevation has been used as a marker of tissue hypoxia in the setting of perioperative monitoring and critical care. It has also been correlated with perioperative morbidity and mortality. Cytoreductive surgery (CRS) & hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis is a major abdominal operation, requiring meticulous perioperative care. The aim of this study is to assess the clinical use of lactate measurements after CRS & HIPEC and its prognostic value in terms of immediate postoperative morbidity and mortality, as well as long term survival.

Material & Methods: Of 140 patients diagnosed with peritoneal carcinomatosis who underwent cytoreductive surgery and HIPEC were prospectively studied. Serum lactate was measured by air blood gases analyser intraoperatively (just before the administration of HIPEC) and then daily till the fifth postoperative day. Postoperative complications were recorded and divided into two groups according to Clavien Dindo classification.

Results: Intraoperative lactate measurements have not been associated with postoperative morbidity and mortality. On the other hand, lactate measurements on postoperative days 3 and 4 are of clinical significance. Specifically, an increase of 1 mmol/L of the average lactate value of days 3 and 4 raises the risk of a minor complication (Grades I to IIIa) by 1.9, the risk of a major complication (Grades IIIb to V) by 10.9 and the risk of mortality by 32.1%.

Conclusions: The average of day 3 and 4 postoperative day lactate level is an independent predictor of morbidity and mortality in patients undergoing CRS and HIPEC.

Key Words: Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, Lactate, Perioperative management

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1. INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a novel therapeutic modality in the approach of peritoneal carcinomatosis, a previously considered fatal condition. CRS consists of a series of peritonectomy procedures, as described by Sugarbaker,[1] aiming to remove all macroscopically visible disease. After cytoreduction, the peritoneal cavity is perfused with a chemotherapeutic agent at an increased temperature (HIPEC). Therefore, CRS & HIPEC can be viewed as a major abdominal operation, requiring meticulous monitoring over the intraoperative and postoperative period, in order to achieve optimal resuscitation.

Serum lactate has proven to be a useful marker of adequate resuscitation, its elevation being indicative of tissue hypoxia, as well as predictive of morbidity and mortality.[2, 3]

The aim of this study is to assess the clinical use of lactate measurements after CRS & HIPEC and its prognostic value in terms of immediate postoperative morbidity and mortality, as well as long term survival.

2. MATERIAL AND METHODS

Over a period of six years (2008-2013), 140 patients diagnosed with peritoneal carcinomatosis who underwent cytoreductive surgery and HIPEC were prospectively studied. The primary endpoints of the study were perioperative morbidity and mortality in association with serum lactate levels as well as overall survival. Peritoneal carcinomatosis was either primary (mesothelioma) or metastatic (pseudomyxoma, colorectal, ovarian, gastric). The study was approved by our institution's Ethical Committee and all patients agreed to be included in the study, signing an informed consent form.

2.1 Data collection

Serum lactate was measured by air blood gases analyser intraoperatively (just before the administration of HIPEC) and then daily till the fifth postoperative day. Postoperative complications were recorded and divided into two groups according to Clavien Dindo classification.[4] Fatal complications (Grade V) and complications demanding ICU management (Grade IV) or surgical intervention under general aneasthesia (Grade IIIb) were listed as major. All the other complications (Grade I - IIIa) were characterized minor. Peritoneal carcinomatosis was estimated using the Peritoneal Cancer Index (PCI) which ranges from 1 to 39.[5] Cytoreduction result after CRS was assessed using the Completeness of Cytoreduction Score (CCS) which ranges from 0 to 3.[6] Demographic characteristics were also collected (age, gender). Patient follow up was performed every three months for the first year and every six months thereafter.

2.2 Cytoreductive surgery and HIPEC procedure

Anaesthetic management was performed according to hospital protocols, adjusted to the special demands of CRS and HIPEC,[7–9] and patients' individual features. All the patients were operated on by the same surgical team. After midline laparotomy and PCI assessment,[5] extensive cytoreduction was performed, using the Sugarbaker technique (peritonectomies).[1, 10] After the evaluation of cytoreduction, using CC score,[6] HIPEC was delivered for 60 to 90 minutes using either the closed or the open (coliseum) technique.[11] The used chemotherapeutic agents depended on the tumor histological features. The temperature of the infused solution was 41°C-42°C. Postoperatively 20% of the patients were admitted to the ICU for at least one day.

2.3 Statistical analysis

To investigate whether serum lactate levels are related to postoperative complications we used the Mann Whitney test. Moreover, to account for potential confounders we used logistic regression. Specifically, in all cases we adjusted for potential effects of PCI and CCS based on prior knowledge[12] and independent of the estimated p-value; as for the rest of the confounders, we included them in the final model only if they had statistically significant results.

Survival was evaluated using Kaplan - Meier analysis. To quantify the effect of lactate in survival time while adjusting for potential confounders, we used Cox proportional hazards model.

A 2-sided p-value < .05 was considered statistically significant. All analysis was performed in IBM SPSS v.22.

3. RESULTS

One hundred and forty patients underwent CRS and HIPEC were investigated. Details for the patients demographics, the origin of peritoneal carcinomatosis, the procedures performed and the outcomes are given in Table 1.

3.1 Lactate and morbidity

Forty three patients (30.7%) were reported with minor complications. Although the median intraoperative lactate levels between patients with (2.9 mmol/L) and without (1.9 mmol/L) minor complications had a statistically significant difference (p = .006), after adjustment for PCI and CCS, intraoperative lactate levels did not differ significantly (p = .160). On the other hand, average day 3 and 4 lactate levels had a statistically significant difference between patients with and without minor complications (see Figure 1) and for each one unit increase in average day 3 and 4 lactate levels, the probability of having a minor event raises by 1.9 times (95% C.I. = [1.40, 2.57]), after adjusting for PCI and CCS.

Table 1. Descriptive statistics (n = 140)

	n	%
Gender		
Male	100	71.4
Female	40	29.6
Age		
< 36	13	9.3
36-50	51	36.4
51-65	46	32.9
> 65	30	21.4
Origin of peritoneal carcinomatosis		
Colorectal	48	34.3
Ovarian	31	22.1
Gastric	21	15
Pseudomyxoma	19	13.6
Mesothelioma	17	12.1
Sarcoma	4	2.9
Peritoneal Carcinomatosis Index		
PCI < 13	36	25.7
13 ≤ PCI < 26	77	55.0
PCI ≥ 26	27	19.3
Operations Performed		
splenectomy	49	35
cholecystectomy	130	92.9
omentectomy	132	94.3
hysterectomy	27	19.3
gastrectomy	19	13.5
Douglas resection	24	17.1
small bowel resection	127	90.7
partial colectomy	39	27.8
complete colectomy	8	5.7
Completeness of Cytoreduction		
CC-0	98	70
CC-1	33	23.5
CC-2	9	6.5
Complications		
Minor	43	30.7
Major	39	27.8
Survival		
1 year	127	91
2 years	96	69
3 years	85	61

In 39 patients (27.8%) major complications were observed. The median intraoperative lactate levels between patients with and without major complications differ significantly (p = .001). After adjustment for age and PCI intraoperative lactate levels were not statistical significant (p = .143). As regards the average day 3 and 4 lactate levels, a statistically significant difference has been proven between patients with and without major complications (see Figure 2) and for each one unit increase, the probability of having a major event raises by 10.9 times (95% C.I. = [4.37, 26.90]), after adjusting for PCI.

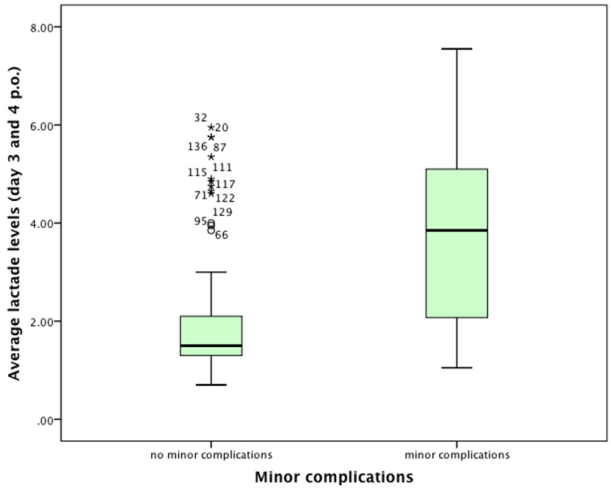

Figure 1. Minor complications

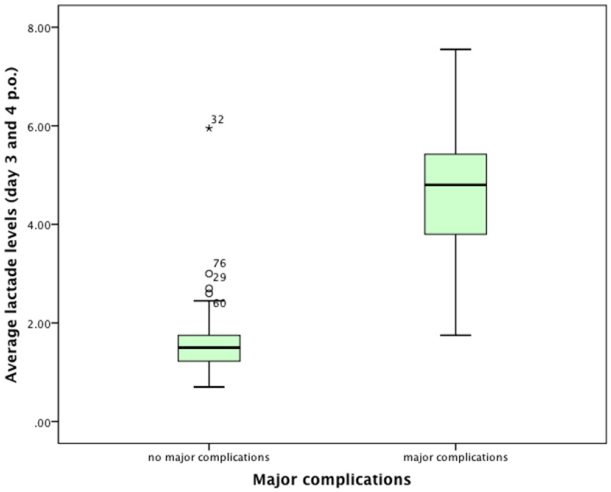

Figure 2. Major complications

3.2 Lactate and survival

Kaplan Meier analysis shows that the survival times for each lactate level category intraoperatively were not equal (p < .05). However, when we used Cox proportional hazards model and adjusted for age, PCI and CCS, the results of intraoperative lactate levels were not statistically significant (p = .233).

3rd and 4th postoperative day average lactate groups had different survival according to Kaplan Meier analysis (p < .05) (see Figure 3). Patients' liver and renal function tests were within normal limits. The cutoff values we used for grouping

the patients were 1.65 mmol/L (0.35 above our analyser's upper limit of normal) and 2.65 mmol/L (since in literature a value of 2.0-2.5 is considered elevated). Cox regression in addition shows that there is a 32.1% increase in the expected hazard of mortality associated with an one unit increase in the average of day 3 and 4 lactate levels, adjusting for age, PCI and CCS (p = .004).

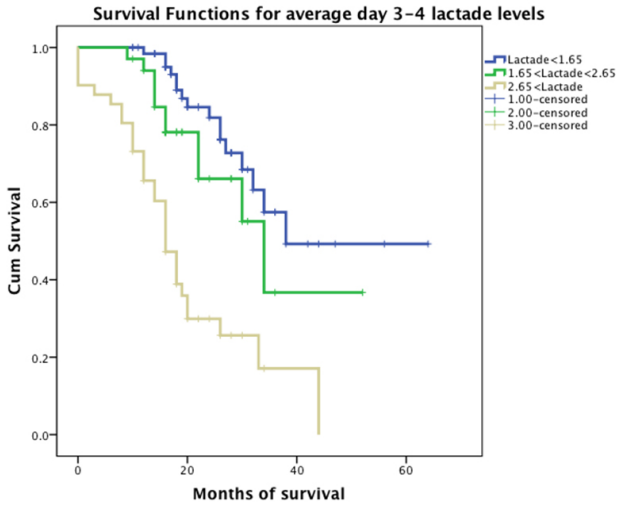

Figure 3. Survival analysis

The above data conclude that the average of day 3 and 4 postoperative day lactate level is an independent predictor of morbidity and mortality in patients undergoing CRS and HIPEC.

4. Discussion

4.1 Lactate physiology and hyperlactaemia

Lactate is produced by most tissues in the human body, its main production occurring in muscle tissue. Under normal conditions, it is rapidly cleared by the liver, and additionally by the kidneys. In aerobic conditions, pyruvate is produced via glycolysis and then enters the Krebs cycle, largely bypassing the production of lactate. Under anaerobic conditions, lactate is an end product of glycolysis and feeds into the Cori cycle as a substrate for gluconeogenesis.[13] It is increased in conditions of tissue hypoperfusion or stress leading to increased glycolysis. Although lactate may be elevated in several conditions, it has been effectively used as a measure of tissue hypoxia.[14–16]

Normal serum lactate values are 0.3-1.3 mmol/L, with several studies using 2.0-2.5 mmol/L as cutoff values for elevated lactate, while in most studies "high" lactate is considered when it measures more than 4.0 mmol/L.

The aetiology of hyperlactaemia is:

- increased lactate production: increased glycolysis, enzyme defects
- decreased hepatic lactate clearance: impaired oxidative metabolism (impaired liver blood flow), impaired glyconeogenesis (oral hypoglycaemic drugs, Hartmann's solution), chronic liver disease
- sepsis
- decreased extra-hepatic metabolism
- reduced renal excretion[17]

4.2 Intraoperative & perioperative management of CRS & HIPEC patients

Patient status should be optimized preoperatively, as peritoneal carcinomatosis patients are often suboptimal surgical candidates, with factors such as older age, comorbidities and cachexia complicating their perioperative course.

Cytoreductive surgery is a major abdominal operation, consisting of peritonectomies and extensive visceral resections, causing significant fluid, blood and protein losses, increased intra-abdominal pressure, systemic hyperthermia and increased metabolic rate therefore significant pathophysiological disturbances.[8]

HIPEC involves the rinsing of the abdominal cavity with a heated chemotherapy solution. Most regimens suggest the administration of the chemoperfusate for 60 to 120 minutes, at 42°C. The chemotherapeutic agent used depends on the site of the initial neoplasia, the most commonly used being mitomycin-c, oxaliplatin, irinotecan and cisplatin.

A retrospective analysis of 78 patients undergoing cytoreductive surgery & HIPEC demonstrated a large intraoperative fluid turnover, increased airway pressure and central venous pressure (due to the increased intraabdominal pressure with the closed technique), while increased body temperature resulted in a mild metabolic acidosis.[9]

According to the findings of another prospective study of 60 patients, haemodynamic disturbances occurred during HIPEC administration, characterized by an increase in heart rate and cardiac output and a decreased systemic vascular resistance on account of increased body temperature and decreased effective circulating volume. Urinary output showed a decreasing tendency over time.[18]

HIPEC with oxaliplatin has been associated with severe hyponatraemia, hyperglycaemia and hyperlactaemia, not observed with cisplatin or mitomycin C.[19,20] This was attributed to the use of dextrose 5% as a carrier for oxaliplatin and to major loss of sodium into the chemoperfusate.[19] Moreover, higher perfusion temperature was related to more pronounced changes in serum glucose, sodium and lactate

levels.[21]

Postoperative ICU admission is often considered protocol after cytoreductive surgery & HIPEC, mainly due to the need for haemodynamic surveillance and stabilization after this major operation. However, it was recently reported that there was no difference in the rate and degree of complications observed in patients who were admitted in the ICU, noting that ICU admission should not be standardized, but based on individual patient characteristics.[22]

Intraoperative parameters may be associated with postoperative outcome, in terms of morbidity and mortality, as demonstrated by a previous study conducted by our team.[23]

4.3 Lactate as a marker of perioperative and long – term outcome

The findings of this study suggest that while intraoperative serum lactate levels do not indicate the postoperative course, it is quite on the contrary with lactate levels on postoperative days 3 and 4. Specifically, an increase of 1 mmol/L of the average lactate value of days 3 and 4 raises the risk of a minor complication (Grades I to IIIa) by 1.9, the risk of a major complication (Grades IIIb to V) by 10.9 and the risk of mortality by 32.1%.

Several studies have evaluated the clinical use of lactate measurement in postoperative patients, not only in abdominal surgery,[2,24,25] but also in cardiac surgery in adults[3] and children.[26] Ours is the first study to assess the efficacy of lactate as a marker of morbidity and mortality in the postoperative course of patients undergoing cytoreductive surgery and HIPEC.

Lactate has been used as a measure of tissue hypoperfusion, with lactate clearance being used to guide resuscitation.[14–16] Therefore, not only increased lactate levels, but also the time to their normalization, have been associated with postoperative mortality.[16]

In a study of 137 surgical intensive care unit patients, elevated lactate values initially and 24 hours later significantly correlated with mortality, indicating lactate as an efficient predictive marker. Moreover, lactate clearance proved to be of great importance, as mortality raised with persistently elevated lactate levels, reaching 67% if lactate failed to normalize.[2]

In a prospective study of 88 patients having undergone major elective abdominal surgery and presented a minor or major complication, it was found that serum lactate levels were significantly increased compared to patients with an uneventful postoperative course. Also the accuracy of lactate to predict morbidity increased with time, and the cut off value was 1.46 mmol/L.[25]

Another useful marker to predict reintervention after abdominal surgery is peritoneal lactate, as well as the peritoneal – serum lactate ratio.[24]

5. CONCLUSION

In conclusion, serum lactate can be effectively used as an indicator of the postoperative course in patients who have undergone cytoreductive surgery & HIPEC. Intraoperative measurements did not correlate significantly with either morbidity or mortality, while an elevated average lactate value of postoperative days 3 and 4 significantly increased the risk of postoperative complications and mortality.

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