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Clinical Study

Serum lactate as a potential biomarker of malignancy in primary adult brain tumours

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ABSTRACT

Lactate, a by-product of glycolysis, is an indicator of poor tissue perfusion and is a useful biomarker with prognostic value in risk-stratifying patients in several diseases. Furthermore, elevated lactate production is observed in tumour glycolysis, also known as the Warburg effect, and is essential in promoting tumour cell invasion, metastasis, and immune system evasion, promoting resistance to cell death. However, there are no studies of elevated serum lactate in brain tumour patients as a potential biomarker, to our knowledge. The aim of this study is to determine possible correlations between the malignancy of tumours and pre- and intraoperative serum lactate elevation in patients undergoing craniotomy for tumour resection. We provide initial evidence that a rise in serum lactate can be used as a non-invasive biomarker that correlates with brain tumour grade. The results from this study and future prospective studies may allow for determination of tumour progression and response to therapy using serum lactate as a biomarker.

1. Introduction

Lactate is an end product of anaerobic metabolism and can be measured in serum to monitor a variety of clinical conditions. Lactate is used as an indicator of poor tissue perfusion and also a measure of the severity of an illness [1]. In acute care settings, hyperlactaemia (serum lactate >4 mmol/L) and metabolic acidosis, along with clinical signs of tissue hypoperfusion (Type A) have been shown to be a predictor of mortality [2,3]. However, hyperlactaemia can occur without tissue hypoxia or hypoperfusion (Type B). This may be due to diseases affecting metabolism and lactic acid elimination (liver disease, renal disease or inborn errors of metabolism) or due to the effects of drugs or toxins [4–6].

We have observed high baseline serum lactate levels (>2 mmol/L) in patients undergoing craniotomy for brain tumour resection. In addition, the metabolic profile of some of these patients indicated a rise in the serum lactate levels during the tumour resection (>3 mmol/L) with a subsequent decline to normal levels during the postoperative period. These lactate elevations were seen in patients who otherwise had stable intraoperative hemodynamics with no perioperative events that could have caused poor tissue perfusion (including heart failure, renal or liver dysfunction, major hemorrhage, massive transfusion or the need for inotropic support).

Lactate has a special role as the end product of aerobic glycolysis in rapidly proliferating tumour cells. Unlike normal cells that undergo glycolysis or fermentation when oxygen is limited, many cancer cells utilise high levels of glucose at a rapid rate with concomitant lactic acid production, even in the presence of adequate oxygen, a phenomenon commonly known as aerobic glycolysis or the Warburg effect [7,8]. Tumour cells exhibit various metabolic anomalies; however preferential metabolism of glucose to lactate regardless of oxygen availability is perhaps the most studied and relevant to tumour proliferation. Excess lactate production is one of the most prominent features of altered tumour metabolism towards fermentation [9]. Surplus intracellular lactate must be secreted from the cell to maintain intracellular alkalinisation. This acidic extracellular environment created by lactate has been shown to promote tumour cell invasion, metastasis and suppress immune surveillance, enhancing cell survival and resistance to apoptosis [9–11]. Increased serum lactate seen in patients undergoing craniotomy for malignant brain tumours may be due to excessive lactate production by the tumour cells. To our knowledge there are no studies of the significance of elevated serum lactate as a biomarker of malignancy in brain tumours. The aim of the

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present study is to determine possible correlations between the aggressiveness of tumours and the pre- and intraoperative serum lactate elevation in patients undergoing craniotomy for tumour resection.

The management of adult brain tumours could immensely benefit from non-invasive diagnostic and prognostic biomarkers. In this study we address whether serum lactate measurements could provide a feasible and efficient biomarker of malignancy for brain tumours and to serve as a marker of tumour progression, response to therapy and recurrence.

2. Materials and methods

2.1. Study population

Following Institutional Ethics Board approval, we retrospectively reviewed the charts of 50 patients who underwent craniotomy for tumour resection from January 2012 to February 2013. Patients who had primary and metastatic brain tumours treated at two institutions (Toronto Western Hospital, Toronto, Canada and Christian Medical College, Vellore, India) were included in the study. Patients with congestive heart failure, renal dysfunction or liver dysfunction during the preoperative period, those who needed perioperative inotropic support to maintain blood pressure and patients who required transfusion of more than four units of red blood cells during the intraoperative period were excluded. The data collected included patient demographics, co-morbidities, tumour pathology, World Health Organization (WHO) grading of the tumour, location and size of the tumour, total amount of fluids given and blood loss during the intraoperative period, use of mannitol, patient position during surgery (supine, lateral, prone) and blood gas results including base deficit, serum lactate and electrolytes (sodium, potassium, chloride). Where applicable WHO tumour grade was recorded as high-grade (WHO grade 3, 4) or low-grade (WHO grade 1, 2). A baseline lactate >2 mmol/L was considered as significant baseline elevation and an intraoperative elevation of lactate >3 mmol/L was considered as significant elevation. Base deficit of >4 mmol/ L was considered as significant change in acid base status during the intraoperative period.

2.2. Statistical analysis

Bivariate (Pearson correlation coefficient) and multivariate regression analyses were performed to determine the correlation between serum lactate and the variables that can potentially increase the serum lactate during the pre- and intraoperative period. After determining a significant correlation between tumour grade and serum lactate, the sensitivity, specificity, positive and negative predictive values were also calculated. Statistical analyses were performed using the Statistical Package for the Social Sciences version 15 (SPSS, Chicago, IL, USA). A p value <0.05 was considered statistically significant.

3. Results

A total of 50 patient charts were retrospectively reviewed. The mean age was 50.98 ± standard deviation (SD) 15.72 years and the mean body mass index (BMI) was 25.54 ± SD 4.70 with male:female ratio of 31:19 (Table 1). Patients were divided based on their baseline serum lactate levels into low or normal lactate group (<2 mmol/L) *versus* high lactate group (>2 mmol/L) and by tumour grade in to high-grade and low-grade (WHO grade 3, 4 *versus* WHO grade 1, 2). Seventeen patients out of 50 (34%) had elevated baseline lactate ($\geqslant$2.0 mmol/L) and 19 patients (38%) had an intraoperative rise in serum lactate ($\geqslant$3 mmol/L) (Fig. 1, 2). Out of the total 50 patients, 27 had high-grade and 23 had low-grade brain tumours (Table 2,3). Sixteen patients (16/27, 59%) in the high-grade tumour group had elevated baseline lactate (>2 mmol/L) compared to one (1/23) in the low-grade tumour group. Of the 19 patients who had an intraoperative rise of serum lactate (>3 mmol/L) during tumour resection, 12 also had baseline lactate elevation and all of these 12 had high-grade brain tumours. Among the remaining seven patients, four had a high-grade brain tumour.

Table 1
Patient demographics

Patients, n	50
Male	31
Female	19
Mean age, years (±SD)	50.98 ± 15.72
Mean BMI (±SD)	25.54 ± 4.70
Tumour grade	
High-grade (WHO 3, 4)	27
Low-grade (WHO 1, 2)	23
Baseline lactate elevation	
High-grade (WHO 3, 4)	16
Low-grade (WHO 1, 2)	1

SD = standard deviation, WHO = World Health Organization.

There was a significant correlation between baseline serum lactate and high-grade brain tumour ($p < 0.0001$) (Table 4, 5). There were no correlations between the baseline serum lactate and age, sex, tumour size or tumour location (Table 6). The baseline serum lactate measurement has sensitivity of 59.25% and specificity of 95.65%. The positive predictive value was 94.11% (95% confidence interval [CI] 69.23–99.69%) and the negative predictive value was 66.67% (95%CI 48.10–81.44%).

Multiregression analysis showed a significant correlation between intraoperative elevation of serum lactate with tumour grade ($p = 0.003$) and base deficit ($p = 0.003$). Although there were correlations between blood loss and duration of surgery ($p < 0.001$) and tumour size ($p = 0.018$), there were no significant correlations between intraoperative lactate elevation with increased BMI, duration of surgery or blood loss (Table 7, 8).

4. Discussion

Serum lactate concentrations represent a balance between production and metabolism and excretion. The production of lactate is primarily from skeletal muscle (25%), skin (25%), brain (20%), intestine (10%), and red blood cells (20%) [5,6,12]. Lactate is metabolised primarily in the liver (60%), kidneys (30%) and heart (10%) [5,6,13]. The normal serum lactate concentration is 0.3–1.3 mmol/L. In critically ill patients, lactate is produced in tissues outside the "usual lactate producers," including the lungs, white blood cells, and splanchnic organs [14,15]. Also, lactate is released in supra-physiologic quantities from sites of infection and inflammation, as a result of the augmented glycolysis by activated leukocytes at these sites.

In the last decade, refocusing research on altered tumour metabolism has established an intimate link between cancer-specific metabolic anomalies and the principal hallmarks of cancer [16–18]. It has been shown that many malignant tumours display a high rate of glycolysis and lactate production, even when ample oxygen is present for mitochondrial respiration. Now it is becoming increasingly apparent that this metabolic reprogramming towards aerobic glycolysis is a critical mechanism by which tumour cells, including high-grade tumours such as glioblastoma multiforme (GBM), proliferate and adapt to their unfavorable microenvironment. In the normal adult human brain, aerobic glycolysis accounts for approximately 10–12% of glucose metabolism