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Lactic Acidosis during Anesthesia for Glioblastoma Multiforme Resection: The Warburg Effect

Farhan Mazhar, MD[1*] and David M. Rothenberg, MD, FCCM[2]

[1]*Anesthesiologist, Infinity Healthcare, Milwaukee,WI, USA*

[2]*Professor of Anesthesiology, Vice-Chair, Academic Affairs, Department of Anesthesiology, Associate Dean, Academic Affairs/Rush University Medical Center, USA*

[*]**Corresponding author**: Farhan Mazhar MD, Anesthesiologist, Infinity Healthcare, Milwaukee, WI USA, Tel: 847-340-7755; E-mail: Fmazhar@infinityhealthcare.com

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Abstract

Background

The purpose of this case report is to present a case of significant lactic acidosis without clinical evidence of hypoperfusion, and show that it is likely due to lactic acid production by the brain tumor glioblastoma multiforme (GBM), the so-called Warburg Effect.

Methods

Observational Methods (vitals and lab tests conducted) were conducted for a 57 year old female.

Results

Final pathologic report of the tumor was recurrent GBM and therapy related changes. Hyperlactatemia and chronic lactic acidosis were attributed to her brain tumor as a diagnosis of exclusion.

Conclusion

Lactic acidosis due to the Warburg Effect was a diagnosis of exclusion, and coupled with the patients' hyperchloremic metabolic acidosis, caused a significant metabolic acidosis. Although perioperative lactic acidosis, however mild, is usually a marker for tissue hypoperfusion and/or cellular hypoxia, the anesthesiologist must be aware of the wider differential diagnosis including drugs, thiamine deficiency, and tumor based lactate production.

Keywords: Lactic acidosis; Warburg effect;Glioblastoma multiforme.

Case History

A 57 year old female presented as a same day admission for an awake craniotomy for resection of a recurrent, 4x3.5 cm, high grade GBM involving the speech center of the left parietal lobe. Her past medical history was significant for anxiety and depression treated with alprazolam, diazepam, zolpidem, risperidone and lamotrigine. She had recently completed a six week course of temozolomide (120 mg daily) and radiation therapy for her GBM. Her past surgical history was significant for gastroplasty and duodenal switch for morbid obesity, eight years prior to admission. She had no history of alcohol, tobacco or drug abuse. Her only other medication was dexamethasone 4 mg daily for 3 days prior to admission.

Vital Signs:

BMI 22 kg/m^2, BP 120/80 mmHg, HR 73 bmp, RR 20 bmp, T 98.1°F, Oxygen saturation 100 %. Lung and heart examinations were normal. Neurologic examination was positive for mild gait impairment. Other motor, sensory and cranial nerve function were normal.

Laboratory Data (Eight Days Prior to Surgery)

Sodium 140 meq/L, chloride 110 meq/L, total CO_2 20 meq/L, potassium 3.6 meq/L, creatinine 0.7 mg/dl, BUN 32 mg/dl, albumin 3.7 g/dl, hemoglobin 9.8 gm/dl, hct 30.6%, wbc 5.8 x 103/uL, MCV 107 fL. Platelet count, liver function and coagulation profiles were normal.

Due to the location of the tumor, an awake craniotomy was planned. Routine monitors and a right radial artery catheter were placed preoperatively. Oxygen was delivered at 4 liters per nasal cannula. PlasmaLyte® was administered intravenously and midazolam 2mg was administered IV prior to admission to the operating room. Infusions of dexmedetomidine and propofol were initiated at 0.4 mcg/kg/hr and 50 mcg/kg/min respectively prior to scalp infiltration (with 1% lidocaine/epinephrine 1:200,000 mixed with an equal volume of 0.5% bupivacaine). Prior to surgical incision an arterial blood gas analysis was performed (see Table 1). Vital signs remained stable, and the patient was not noted to be tachypneic. Hyperchloremic acidosis and coexisting lactic acidosis were both noted (Hyperchloremia defined as sodium:chloride ratio ≤1.36:1), and as such IV fluids were changed to 0.45% saline with 100 meq of sodium bicarbonate added to the liter in order to decrease the amount of infused chloride and in an attempt to buffer the lactic acid.

Level	Prior to incision	Approximately 2 hours after incision	Normal Levels[1]
pH	7.33	7.41	7.35-7.45
$PaCO_2$	26 mmHg	28 mmHg	
PaO_2	173 mmHg	186 mmHg	
lactate	4.1 meq/L	4.1 meq/L	<2.0 meq/L
sodium	139 meq/L	140 meq/L	
chloride	118 meq/L	115 meq/L	
potassium	3.1 meq/L	3.2 meq/L	
glucose	151 mg/dl	91 mg/dl	
ionized calcium	1.16 mmol/l	1.12 mmol/l	
hemoglobin	8.1 gm/dl	7.1 gm/dl	

Table 1 – Arterial Blood Gas Analysis

The etiology of the hyperchloremia was assessed to be chronic and secondary to her prior gastric/duodenal surgery. The etiology of the hyperlactatemia was unclear however, as the patient showed no signs or symptoms of hypoperfusion, hypoxemia or hepatic dysfunction. She had only received a total of 128 mg of propofol over 30 minutes, which was nonetheless discontinued in order to maintain a more alert state during tumor resection. Approximately, two hours after incision, an arterial blood gas analysis was repeated (see Table 1).

The surgical procedure was completed without complication and the patient was transferred to the Neurosciences ICU. In light of the persistent hyperlactatemia and the history of macrocytic anemia, thiamine level was assessed and noted to be normal. The patient was discharged home on post-operative day two with a persistent hyperchloremia (116meq/L) and a serum lactate of 3.1 meq/L. Final pathologic report of the tumor was recurrent GBM and therapy related changes. Hyperlactatemia and chronic lactic acidosis were attributed to her brain tumor as a diagnosis of exclusion.

Discussion

Lactic acid is typically generated from the redox-coupled conversion of pyruvate to lactate by LDH during anaerobic glycolysis in cellular cytosol, which is mostly produced in highly glycolytic tissues such as skeletal muscle [1]. In the early 1920's Warburg noticed that in normal tissues, glycolysis generates about 10% of total cellular ATP. However, in cancer cells more the 50% of cellular ATP is generated from glycolysis even in the presence of oxygen and functional mitochondria. This is now referred to as the Warburg Effect [2]. It has been hypothesized that malignant brain tumors, such as GBM (which are often refractory to chemotherapy and radiotherapy with a mean patient survive of approximately six months), have high glycolytic activity and efflux lactic acid to the tumor microenvironment through transmembrane transporters called monocarboxylate transporters (MCTs) [3]. This metabolic remodeling in GBM tumors favors cancer cell proliferation, angiogenesis, and metastasis leading to poorer clinical outcomes for this disease process [3].

Intraoperative lactic acidosis is often attributed to decreased oxygen delivery to tissues, shock, sepsis, severe hypoxemia, severe anemia, liver disease and certain drugs and toxins. In this case none of these obvious causes of lactic acidosis were apparent. Thiamine deficiency, which can impair pyruvate dehydrogenase, was also ruled out.

Lactic acidosis due to the Warburg Effect was a diagnosis of exclusion, and coupled with the patients' hyperchloremic metabolic acidosis, caused a significant metabolic acidosis. Although minimizing the chloride concentration of isotonic intravenous solutions is important to treat hyperchloremic metabolic acidosis, and in so doing perhaps minimize perioperative acute kidney injury[4]. The use of sodium bicarbonate as an additive to 0.45% saline could have increased lactic acid production in an otherwise acidic microenvironment and promoted tumorigenesis, angiogenesis and metastasis.

Therefore, from a purely oncologic perspective, the addition of sodium bicarbonate, 100 meq/L of 0.45% saline may have been ill-advised. The use of this solution was nonetheless appropriate in the management of preexisting hyperchloremic metabolic acidosis. In this way, we were able to avoid using a high chloride solution which would have predictably worsened the systemic acidosis.

Although perioperative lactic acidosis, however mild, is usually a marker for tissue hypoperfusion and/or cellular hypoxia, the anesthesiologist must be aware of the wider differential diagnosis including drugs, thiamine deficiency, and tumor based lactate production.

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