



Original Article

# Factors affecting serum lactate in patients with intracranial tumors – A report of our series and review of the literature

Eleonora Ioannoni<sup>1</sup>, Giuseppe Grande<sup>1</sup>, Alessandro Olivi<sup>2</sup>, Massimo Antonelli<sup>1</sup>, Anselmo Caricato<sup>1</sup>, Nicola Montano<sup>2</sup>

Departments of <sup>1</sup>Anesthesiology and Intensive Care Medicine, <sup>2</sup>Neurosurgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Rome.

E-mail: Eleonora Ioannoni - e.ioannoni@libero.it; Giuseppe Grande - grandegiu@gmail.com; Alessandro Olivi - alessandro.olivi@policlinicogemelli.it; Massimo Antonelli - massimo.antonelli@policlinicogemelli.it; Anselmo Caricato - anselmo.caricato@policlinicogemelli.it;

\*Nicola Montano - nicolamontanomd@yahoo.it



\*Corresponding author:

Nicola Montano, MD, Ph.D.,  
Department of Neurosurgery,  
Fondazione Policlinico  
Universitario Agostino Gemelli  
IRCCS, Catholic University,  
Largo Agostino Gemelli,  
Rome - 800168, Italy.

nicolamontanomd@yahoo.it

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## ABSTRACT

**Background:** A hyperlactemia may occur in the presence of tissue hypoperfusion, in diseases affecting metabolism and in cases of malignant neoplasm. However, the factors affecting the serum lactate levels in patients submitted to craniotomy for the resection of an intracranial tumor have been investigated only marginally. Here, we assessed the factors possibly affecting the levels of serum lactate in intracranial tumors and carried out a thorough literature review on this topic.

**Methods:** All patients submitted to elective craniotomy from January 2017 to August 2018 for the resection of a glioblastoma (GBM; 101 cases) and a benign meningioma (WHO I; 105 cases) were included in this study. The sex, age, histological diagnosis, body mass index (BMI), and diabetes were assessed as possible factors affecting the level of the preoperative and postoperative serum lactate in these patients.

**Results:** We found that preoperative hyperlactemia (> 2 mmol/l) was more frequent in patients with GBM than in patients with meningioma ( $P = 0.0003$ ). Moreover, a strong correlation between a preoperative lactemia and postoperative lactemia ( $P < 0.0001$ ) was observed. On univariate analysis, we found increased preoperative serum lactate levels in GBM patients ( $P = 0.0022$ ) and in patients with a BMI  $\geq 30$  ( $P = 0.0068$ ). Postoperative serum lactate levels were significantly higher in GBM patients ( $P = 0.0003$ ). On multivariate logistic regression analysis, a diagnosis of GBM was an independent factor for higher level of preoperative ( $P = 0.0005$ ) and postoperative ( $P < 0.0001$ ) serum lactate.

**Conclusion:** The malignant phenotype of GBM is the strongest factor associated with a pre- and postoperative hyperlactemia in patients submitted to craniotomy for the resection of an intracranial tumor.

**Keywords:** Brain tumor metabolism, Craniotomy, Glioblastoma, Meningioma, Serum lactate

## INTRODUCTION

Serum lactate, an end product of anaerobic metabolism, is used as an indicator of poor tissue perfusion and a measure of illness severity. Two types of hyperlactemia have been described. Type A is seen in acute care settings, with a serum lactate >4 mmol/L and metabolic acidosis, along with clinical signs of tissue hypoperfusion. This kind of hyperlactemia has been associated with higher

mortality in that clinical context.<sup>[6]</sup> In type B, hyperlactemia occurs without tissue hypoxia or hypoperfusion. 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.<sup>[10,13]</sup> A hyperlactemia can also be seen in the presence of a malignant neoplasm because these tumors often switch to aerobic glycolysis for their energy needs, producing lactate even in the presence of oxygen. While the significance of hyperlactemia in solid tumors has been previously studied,<sup>[7,8,16]</sup> the factors affecting the serum lactate levels in patients submitted to craniotomy for the resection of intracranial tumors have been only marginally investigated.

The aim of this study was to assess the factors possibly affecting the levels of serum lactate in intracranial tumors. Moreover, we also reviewed the pertinent literature.

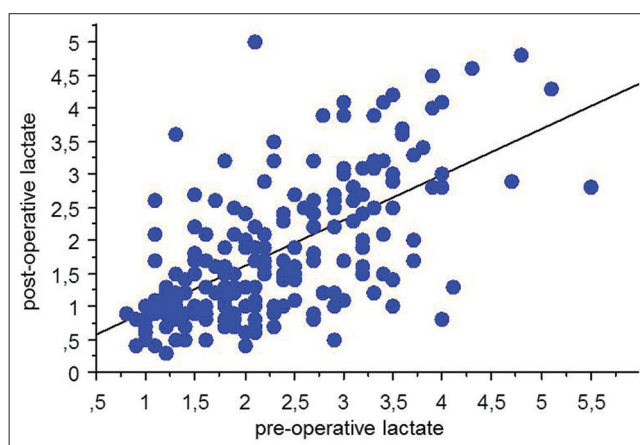
## MATERIALS AND METHODS

In this retrospective observational study, we included all patients submitted to elective craniotomy for the resection of a glioblastoma (GBM) and a benign meningioma (WHO I) consecutively admitted to our neurointensive care unit from January 2017 to August 2018. Exclusion criteria were considered age <18 and >80, and all known factors involved in hyperlactemia, such as sepsis, shock, hepatic and renal failure, catecholamine infusion, and antiretroviral drugs. Serum lactate levels were evaluated immediately before anesthesia induction and on admission in neurointensive care unit after surgery by enzymatic method (normal ranges 0.7–2.0 mmol/L; Nova Biomedical, Stat Profile CCX, Waltham, MA, USA). A formal ethical approval was not required by local Ethical Committee due to retrospective and observational nature of the study. Sex, age (<70 vs. ≥70 years), histological diagnosis, body mass index (BMI) (<30 vs. ≥30), and diabetes were assessed as possible factors affecting the level of the preoperative and postoperative serum lactate. Statistical comparison of continuous variables was performed by the Student's t-test. Statistical comparison of categorical variables was performed by Chi-square statistic. A multivariate logistic regression model was used to estimate the odds ratio to have a high serum lactate levels (> 2 mmol/l) in the preoperative and postoperative, while adjusting for baseline variables that included sex, age (<70 vs. ≥70 years), histological diagnosis, BMI (<30 vs. ≥30), and the presence of a history of diabetes. Differences were considered significant at  $P < 0.05$ . Statistical analyses were conducted using StatView version 5 software (SAS Institute Inc.).

## RESULTS

We observed 101 patients with primary GBM (63 males and 37 females) and 105 patients with benign meningioma (39

males and 66 females). The mean age was  $63.2 \pm 16.9$  years in GBM group and  $61.0 \pm 14.4$  in meningioma group, respectively. Preoperative hyperlactemia (> 2 mmol/l) was more frequent in patients with GBM than in patients with meningioma (65.34% in patients with GBM and 40.00% in patients with meningioma;  $P = 0.0003$ , Fisher's exact test). A strong correlation between preoperative lactemia and postoperative lactemia was found ( $P < 0.0001$ , Spearman rank correlation; Figure 1). Preoperative and postoperative serum lactate values stratified for sex, age (<70 vs. ≥70 years), histological diagnosis, BMI (<30 vs. ≥30), and the presence of a history of diabetes are reported in Table 1. We found a statistically significant increased preoperative serum lactate level in GBM patients if compared with meningioma ( $P$



**Figure 1:** Scatter plot. A strong correlation between preoperative lactemia and postoperative lactemia was found ( $P < 0.0001$ , Spearman rank correlation).

**Table 1:** Univariate analysis of possible prognostic factors of hyperlactemia in brain tumor surgery.

	Preoperative serum lactate	P	Postoperative serum lactate	P
Sex				
Male	2.31±0.93	0.4478	1.86±1.05	0.3371
Female	2.21±0.95		1.72±1.00	
Age (years)				
≥70	2.18±0.96	0.3705	1.69±0.95	0.3333
<70	2.30±0.93		1.84±1.06	
Diagnosis				
Glioblastoma	2.46±0.90	0.0022	2.05±1.05	0.0003
Meningioma	2.07±0.94		1.54±0.94	
Body mass index				
≥30	2.60±0.93	0.0068	1.83±0.95	0.7632
<30	2.17±0.92		1.78±1.05	
Diabetes		0.2259		
Yes	2.45±1.08		1.86±1.25	0.6791
No	2.23±0.91		1.78±0.98	

= 0.0022) and in patients with a BMI  $\geq 30$  in comparison with BMI  $< 30$  ( $P = 0.0068$ ). Postoperative serum lactate levels were significantly higher in patients with GBM than in patients with meningioma ( $P = 0.0003$ ). The multivariate logistic regression analysis evidenced that GBM ( $P = 0.0005$ ) was an independent factor associated with a higher level of preoperative serum lactate [Table 2]. Moreover, GBM ( $P < 0.0001$ ) was confirmed as the only factor independently associated with higher level of lactate in the postoperative period [Table 3].

## DISCUSSION

The main results of this study were the following: (1) hyperlactemia is more frequent in GBM, the most malignant brain tumor than in benign meningioma; (2) preoperative lactemia and postoperative lactemia are strictly related; and (3) the histological diagnosis of GBM is the only independent factor significantly associated with pre- and post-operative hyperlactemia.

GBM is the most frequent and most malignant central nervous system (CNS) tumor with an incidence of 3.9 cases/100,000/year. It represents 65–70% of astrocytic tumors and 12–15% of CNS neoplasms with a classical incidence peak between 55 and 74 years.<sup>[4]</sup> Despite surgery and adjuvant radiochemotherapy, the prognosis of GBM patients is very poor with a median survival from the diagnosis of 14.6 months.<sup>[15]</sup> Meningiomas originate from meningotheelial cells and account for approximately 30% of all new diagnoses of CNS neoplasms. Benign Grade I meningiomas can be usually cured by surgery.<sup>[11,12]</sup> In this

study, we assessed the possible role of different clinical factors in determining the preoperative and postoperative serum lactate levels in patients submitted to craniotomy for intracranial tumor and found that a diagnosis of GBM was the strongest factor associated with an increased level of pre- and post-operative serum lactate. Moreover, we searched the PubMed database with a combination of the following terms: “serum lactate,” “brain tumors,” “GBM,” and “meningioma.” The research was conducted up to April 2019 and yielded 215 studies. The articles<sup>[1-3,5,9,14]</sup> in which the correlation between the level of serum lactate and intracranial tumors was studied are reported in Table 4. In an initial series of 18 patients submitted to craniotomy for intracranial tumor, the authors found an increase of serum lactate during surgery regardless to the diagnosis. They suggested that hyperlactemia could be related to the regional cerebral hypoperfusion as a result of a brain retraction occurring during the surgery.<sup>[5]</sup> Nonetheless, other authors found a significant higher baseline serum lactate in high-grade gliomas compared with low-grade gliomas.<sup>[1,9,14]</sup> Moreover, patients with intracranial metastases showed higher preoperative serum lactate compared with meningioma and pituitary tumors in another series.<sup>[1]</sup> Our results confirm the findings of the literature that GBM malignant phenotype contributes to higher serum lactate levels regardless the possible influence of other factors. Moreover, in our series, a strong correlation between preoperative and postoperative serum lactate was found, and this seems to exclude the hypothesis that hyperlactemia could be related to systemic hypoperfusion or to the surgical manipulation of the brain. These data are of particular interest in the intensive care setting and should kept in

**Table 2:** Multivariate (logistic regression analysis) of factors possibly influencing the preoperative serum lactate level in intracranial tumor surgery.

	Coef.	Std. error	Coef./SE	Chi-square	P-value	Exp. (Coef.)	95% lower	95% upper
t: constant	-0.153	0.887	-0.173	0.030	0.8628	0.858	0.151	4.879
Histological diagnosis of glioblastoma	1.052	0.303	3.475	12.074	0.0005	2.865	1.582	5.187
Diabetes mellitus	-0.161	0.419	-0.386	0.149	0.6999	0.851	0.375	1.933
Sex	0.114	0.309	0.370	0.137	0.7114	1.121	0.612	2.054
Age	0.390	0.315	1.240	1.538	0.2149	1.477	0.797	2.738
Body mass index	-0.024	0.033	-0.745	0.555	0.4561	0.976	0.916	1.040

**Table 3:** Multivariate (logistic regression analysis) of factors possibly influencing the postoperative serum lactate level in intracranial tumor surgery.

	Coef.	Std. error	Coef./SE	Chi-square	P-value	Exp. (Coef.)	95% lower	95% upper
t: constant	-1.133	0.931	-1.217	1.482	0.2235	0.322	0.052	1.997
Histological diagnosis of GBM	1.376	0.333	4.135	17.094	<0.0001	3.960	2.062	7.604
Diabetes mellitus	-0.242	0.445	-0.545	0.296	0.5861	0.785	0.328	1.878
Sex	0.306	0.330	0.929	0.863	0.3530	1.358	0.712	2.592
Age	0.024	0.337	0.071	0.005	0.9430	1.024	0.529	1.982
Body mass index	0.039	0.034	1.151	1.326	0.2496	1.040	0.973	1.111

**Table 4:** Literature review of studies investigating the serum lactate role in intracranial tumors.

Author/year	Number of patients	Studied tumor
Garavaglia <i>et al.</i> , 2013 <sup>[5]</sup>	18	5–meningioma 2–atypical meningioma 1–GBM 1–anaplastic hemangiopericytoma 9–other benign tumor
Mariappan <i>et al.</i> , 2015 <sup>[9]</sup>	50	27–HGG 23–LGG
Bharadwaj <i>et al.</i> , 2015 <sup>[1]</sup>	121	28–meningioma 37–pituitary 17–metastasis 39–other (non-glial cell tumors)
Shih <i>et al.</i> , 2017 <sup>[14]</sup>	74	20–HGG 54–LGG
Cata <i>et al.</i> , 2017 <sup>[2]</sup>	275	275–GBM
de Smalen <i>et al.</i> , 2019 <sup>[3]</sup>	496	137–GBM 128–meningioma (WHO I-III) 57–astrocytoma, oligodendroglioma, medulloblastoma 52–adenoma, craniopharyngioma, cyst 26–ependymoma, schwannoma, hemangioblastoma 79–metastasis 15–lymphoma, other
Present study	206	101–GBM 105–meningioma (WHO Grade I)

GBM: Glioblastoma, LGG: Low-grade glioma, HGG: High-grade glioma

mind in the perioperative management of these patients to avoid unnecessary treatment of hypoperfusion. It has been demonstrated that cancer cells show a high rate of aerobic glycolysis which produces lactate that participates in tumor progression,<sup>[8]</sup> promoting angiogenesis,<sup>[7]</sup> and invasion and metastasis.<sup>[16]</sup> This phenomenon is called the Warburg effect<sup>[17]</sup> and may explain the finding of higher serum lactate levels in patients with GBM. Interestingly, this finding seems to be confirmed by our data on serum lactate in elective craniotomies in nontumor patients. In the same period (January 2017–August 2018), we identified 42 patients (14 males and 28 females; mean age was  $62.72 \pm 12.20$  years) submitted to craniotomy for unruptured cerebral aneurysm clipping (as for tumor patients, we excluded patients with age <18 and >80 and all known factors involved in hyperlactemia; Materials and Methods section). In these patients, we found that preoperative serum lactate level was  $1.11 \pm 0.27$  with a

postoperative serum lactate level of  $1.02 \pm 0.40$ , significantly lower than GBM patients.

The main strength of our study is that through a rigorous statistical analysis, we demonstrated that the main factor involved in the hyperlactemia in patients submitted to craniotomy is the malignant phenotype of the tumor and this can help the anesthesiologist and the neurointensivist in correctly managing these patients. Moreover, we carried out an extensive review of the literature on this topic. On the other hand, our study has some limitations such as the lack of a correlation with the survival of these patients. This is an important topic to address in future although the previous studies failed to demonstrate a correlation between increased serum lactate and patient's prognosis.<sup>[2,3,14]</sup>

## CONCLUSION

Our data and the literature review showed that the malignant phenotype of GBM is the strongest factor determining the pre- and post-operative hyperlactemia in patients submitted to craniotomy for the resection of an intracranial tumor. This should always be kept in mind in the intraoperative and postoperative management of these patients.

## Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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## Conflicts of interest

There are no conflicts of interest.

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