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Hyperlactatemia After Intracranial Tumor Surgery Does Not Affect 6-Month Survival: A Retrospective Case Series

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Background: Patients undergoing neurosurgery frequently exhibit hyperlactatemia. The aim of this study was to identify factors associated with hyperlactatemia and assess how hyperlactatemia impacts survival and hospital length of stay after intracranial tumor surgery.

Materials and Methods: This retrospective cohort study included 496 adult patients that underwent surgery between January 1, 2014 and December 31, 2015. We evaluated patient characteristics, surgery characteristics, pH, lactate, and blood glucose from blood samples collected on admission to the high-dependency unit and the morning after surgery, and 6-month outcome data.

Results: Hyperlactatemia (>2.0 mmol/L) occurred in >50% of patients, but only 7.7% had acidosis. Postoperative hyperlactatemia was not correlated with 6-month survival ($P=0.987$), but was correlated with (median [interquartile range]) longer hospital stays (6 [4 to 8.5] d vs. 5 [4 to 8] d; $P=0.006$), longer surgery duration (4:53 [4:01 to 6:18] h:min vs. 4:28 [3:33 to 5:53] h:min; $P=0.001$), higher dexamethasone dose (16 [16 to 35] mg vs. 16 [16 to 20] mg; $P<0.001$), and higher blood glucose concentration (8.4 [7.5 to 9.6] mmol/L vs. 8.0 [7.1 to 8.9] mmol/L; $P<0.001$). Patients that received total intravenous anesthesia developed hyperlactatemia less frequently than those that received balanced anesthesia with inhalational agents (48.4% vs. 61.5%, $P=0.008$). Hyperlactatemia was not associated with increased postoperative neurological deficits or the need for rehabilitation therapy.

Conclusions: Hyperlactatemia was common after intracranial tumor surgery. It did not influence 6-month outcomes but was associated with longer hospital length of stay. Several potential causative factors for hyperlactatemia were identified.

Key Words: neurosurgery, hyperlactemia, lactic acidosis, dexamethasone, 6-month survival

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Lactic acidosis (hyperlactatemia type A) is a life-threatening clinical state.[1,2] However, little is known about the contributing factors and prognosis of elevated serum lactate without acidosis, also called hyperlactatemia type B.[3] Hyperlactatemia type B is frequently observed in patients undergoing neurosurgery, but it is unclear whether it affects patient outcomes.[4,5] Brallier et al[6] reported that hyperlactatemia was associated with prolonged hospital length of stay and new neurological deficits. Another study found that high-grade brain tumors were associated with elevated serum lactate before treatment, and that elevated serum lactate was correlated with poor progression-free and overall survival.[7] A conclusive view on the causes and implications of hyperlactatemia in neurosurgery remains to be determined.

Several studies have identified factors associated with elevated lactate levels in patients undergoing neurosurgery.[5,8–14] These include the use of volatile anesthetic agents, surgery duration, tumor volume, corticosteroids, diuretics, body mass index (BMI), and mannitol infusion. As expected, the use of dexamethasone, which is common in patients undergoing brain tumor surgery, has been identified as a cause of elevated serum lactate.[15,16] Another substance of special interest in this patient population is mannitol, which is partly metabolized to glycogen in the liver. However, studies have not consistently found a significant increase in serum lactate related to mannitol infusion.[10,11,17,18] In contrast to the aforementioned factors, propofol has been reported to cause hyperlactatemia type A, which might be related to the propofol infusion syndrome (PRIS).[19] An overview of the relevant literature is provided in Supplemental Digital Content 1, http://links.lww.com/JNA/A114.

Most previous studies that focused on patients undergoing neurosurgery have analyzed only small populations, which limited the validity of their conclusions.

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The present study includes the large Rotterdam neurosurgery population, and we mirrored assessments performed in previous studies. The primary outcome of this study was the effect of hyperlactatemia on 6-month survival. Secondary outcomes included the identification of factors potentially associated with a rise in serum lactate, both immediately postoperatively and on the morning after surgery. Finally, we examined differences in clinical outcomes between patients with and without elevated lactate-hospital length of stay, postoperative worsening of neurological status, and need for rehabilitation therapy.

MATERIALS AND METHODS

This study was approved by the Institution's Medical Ethics Committee: reference MEC-2016-125. Because we used anonymous data recorded in the patient data management system, according to Dutch law no formal informed consent was required.

We retrieved data for all patients that underwent neurosurgery at the Erasmus University Medical Center, Rotterdam, between January 1, 2014 and December 31, 2015. We conducted a computerized search to select patients with an intracranial tumor based on surgical coding. We included (stereotactic) biopsies, intracranial tumor surgery, and pituitary adenoma surgery. We initially identified a total of 759 cases, but some procedures were double coded so there were 739 patients for inclusion screening. When patients underwent multiple surgeries within the study period, only the first procedure was included. Despite the digital coding, 52 cases did not undergo intracranial tumor surgery according to the chart records; these patients were excluded from the study population. Cases in which lactate was not measured or data were unavailable were also excluded (n = 143), as were patients that underwent awake craniotomy. Finally, 496 cases were available for inclusion in the study (Fig. 1).

Data Collection

We collected data on patient characteristics; that is, age, weight, height, American Society of Anesthesiologists (ASA) physical status classification, and duration of hospital stay (defined from the day of surgery until discharge). We also collected data on tumor characteristics such as location, pathologic type, and extent of resection. The latter was extracted from the surgery reports and postoperative magnetic resonance imaging scans. Tumor tissues detected macroscopically or radiologically were considered tumor remnants. Nearly complete resection was defined as an unclear margin or recurrence detected in a subsequent scan, and complete resection as the absence of recurrence in multiple magnetic resonance imaging scans.

We also collected perioperative information, including operation duration, blood loss, fluid balance, drugs administered (eg, dexamethasone and mannitol), and anesthesia type. General anesthesia for this type of surgery was not standardized; patients received either total intravenous anesthesia (TIVA) or balanced anesthesia. For all cases involving TIVA, induction was performed with a bolus of propofol. Analgesia during induction was provided mostly with remifentanil infusion but, in some cases, with sufentanil. Anesthesia was maintained with remifentanil and propofol infusions. Balanced anesthesia included induction with sufentanil and propofol, and maintenance with sufentanil and inhalational agents (mainly sevoflurane). Desflurane, nitrous oxide, and dexmedetomidine were not used in any patient. All intravenous fluids were lactate free.

We also collected data on self-reported new postoperative neurological deficits and the need for rehabilitation therapy. This was based on a questionnaire which is described in detail in a previous manuscript that focused on the neuropsychological aspects of brain tumor resections in the same patient cohort.[20]

Finally, we retrieved 6-month survival data from our hospital's patient data management system, which is regularly updated with input from governmental sources.

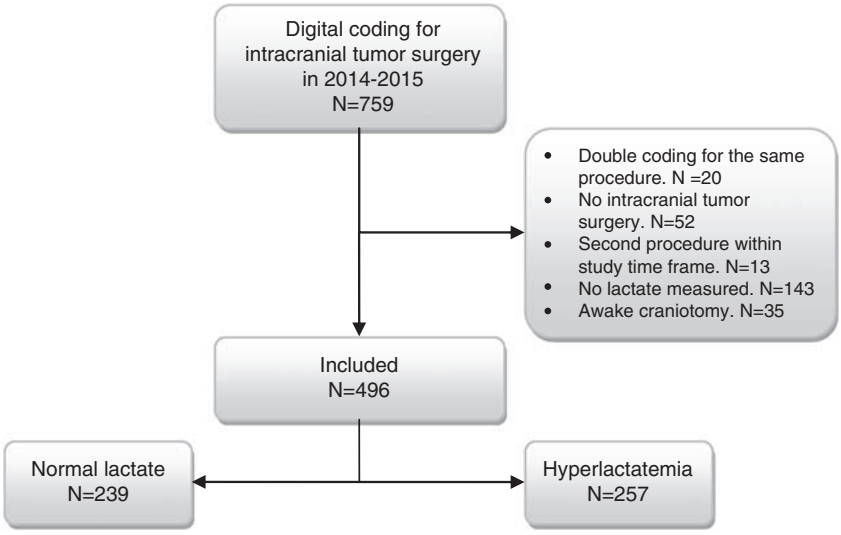

FIGURE 1. Flow chart of patients included in the study.

Blood Sampling for Measurement of Lactate, pH, and Glucose

Laboratory blood tests were collected by an arterial cannula at standardized times as part of our routine patient care for this type of surgery. All patients were transferred to a high-dependency unit (HDU) or intensive care unit (ICU) at the end of surgery. The HDU in our hospital is an environment with intensive care treatment facilities, but admission is limited to those with an expected need of care for <24 hours. For intracranial tumor surgery, only patients with tumors in the posterior cranial fossa, with evident or potential compression of the brainstem, or at high risk of bleeding are admitted to the ICU. The therapeutic protocols in the HDU and ICU are identical so we grouped the patients of both units together and refer to this as the HDU. Arterial blood samples were taken upon admission to the HDU and on the morning after surgery and we retrieved data on pH, lactate, and blood glucose. Serum lactate 2.0 mmol/L or lower was considered normal and pH < 7.35 considered acidosis. There was no routine preoperative blood sampling. For patients registered as deceased, we calculated the time between surgery and death, and this was included in the 6-month survival evaluations.

Statistical Analysis

Numerical variables were tested for normality by visual inspection of histograms and Q-Q plots and with the Shapiro-Wilk test. All continuous variables were not normally distributed and we therefore report medians and interquartile ranges (IQR). Analysis for dichotomous outcome was performed using a Mann-Whitney test. The population was divided into 4 groups, reflecting the course of lactate levels between HDU admission and the morning after surgery: (1) Normal lactate on admission and the morning after surgery; (2) hyperlactatemia on admission, but normal lactate on the morning after surgery; (3) hyperlactatemia on admission, that persisted on the morning after surgery; (4) normal lactate on admission, that had become elevated by the morning after surgery. For this analysis a Kruskal-Wallis test was used. For all categorical data we used a χ^2 test, except for the ASA classification, where a Fisher exact test was performed. A P-value of <0.05 was considered significant.

We performed a regression analysis to quantify the relative contribution of the influencing factors. This was also performed multivariate, to correct for confounding variables. We corrected for all parameters that were suspected of influencing the production of lactate, based on review of the literature. These parameters included: age, BMI, surgery duration, blood loss, fluid balance, total dexamethasone dose, total mannitol dose in g/kg, glucose on HDU admission, pH on HDU admission, tumor type, and anesthesia type.

All data were collected by 2 of the authors, and any inconsistencies were openly discussed. Processing and statistics were performed with IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY).

RESULTS

Of the 496 patients included in the study, 15 (3%) had undergone tumor biopsy and 22 (4.4%) a first intracranial surgery before the study period. Unfortunately, not all data could be extracted from all medical files; where relevant, we indicated the respective number of patients.

The questionnaire response rate was 57% (272 of 476 patients). Our previous study excluded 23 patients from analysis because they were deceased at the time of receiving the questionnaire.[20] The questionnaire response was 180 patients for neurological change and 214 for rehabilitation. Owing to our exclusion criteria we were able to include data on 160 patients for neurological outcome and 191 for rehabilitation needs. Of the patients included in our study, 121 (76%) reported decreased or unchanged neurological deficits and 115 (60%) no need for rehabilitation.

At HDU admission 257 (51.8%) patients had serum lactate levels above the normal upper limit (2.0 mmol/L) and 86 had acidosis (pH < 7.35); 38 (7.7%) patients had both acidosis and hyperlactatemia. Only 2 (0.4%) patients had a pH < 7.25. On the basis of the lactate and pH findings, we concluded that we identified mainly hyperlactatemia type B.

Of the patients with elevated lactate upon admission to the HDU, 72.7% had normalized lactate levels by the following morning. We found no association between hyperlactatemia upon arrival to the HDU and reduced survival at 6 months (Table 1). Patients with hyperlactatemia had a median hospital stay of 6 (IQR: 4 to 8.5) days, compared with 5 (IQR: 4 to 8) days for patients without hyperlactatemia ($P = 0.006$). The 2 groups were similar in their self-reported worsening of neurological status (23.2% vs. 25.6%, $P = 0.716$) and need for rehabilitation (39.2% vs. 40.4%, $P = 0.860$).

Compared with those with normal lactate levels, patients with hyperlactemia on admission to the HDU had significantly longer surgery durations, greater blood loss, less positive fluid balance, higher dose of dexamethasone administration, and higher blood glucose (Table 2). Moreover, patients with elevated serum lactate upon arrival to the HDU had significantly higher lactate levels the morning after surgery compared with those with normal

TABLE 1. Outcomes of Patients Who Underwent Neurosurgery and, Upon Arrival to the HDU, Had Normal (≤2 mmol/L) or Elevated (>2 mmol/L) Serum Lactate

Outcome Parameters	N	Normal Lactate (N = 239)	Elevated Lactate (N = 257)	P
Length of stay (d)	496	5 (4-8)	6 (4-8.5)	0.006*
Increased neurological deficits	160	20 (25.6)	19 (23.2)	0.716
Rehabilitation necessary	191	38 (40.4)	38 (39.2)	0.860
6-mo survival	496	201 (84.1)	216 (84.0)	0.987

Values are the median (IQR) or number of patients (% of group total).
HDU indicates high-dependency unit; IQR, interquartile range.
*$P < 0.05$.

TABLE 2. Characteristics of Patients That Underwent Neurosurgery, Divided Into Groups of Normal (≤2 mmol/L) or Elevated (>2 mmol/L) Serum Lactate at HDU Admission

Variables	N	Normal Lactate (N = 239)	Elevated Lactate (N = 257)	*P*
Age (y)	496	59.3 (48.3-69.3)	58.8 (47.4-67.5)	0.279
BMI (kg/m^2)	496	25.7 (23.0-28.8)	26.0 (23.7-29.4)	0.116
Surgery duration (h:min)	496	4:28 (3:33-5:53)	4:53 (4:01-6:18)	0.001*
Blood loss (mL)	496	200 (100-400)	300 (150-500)	0.001*
Fluid balance (mL)	484	376 (−52 to 734)	185 (−371 to 655)	0.008*
Total dexamethasone administered (mg)	482	16 (16-20)	16 (16-35)	<0.001*
Total mannitol administered (g)	483	30 (0-45)	30 (15-45)	0.890
Total mannitol administered per kilogram (g/kg)	483	0.38 (0-0.63)	0.37 (0.17-0.54)	0.596
Glucose on HDU admission (mmol/L)	494	8.0 (7.1-8.9)	8.4 (7.5-9.6)	<0.001*
Lactate on HDU admission (mmol/L)	496	1.4 (1.0-1.6)	2.9 (2.4-3.6)	<0.001*
pH on HDU admission	492	7.39 (7.36-7.41)	7.39 (7.37-7.42)	0.119
Glucose morning after admission (mmol/L)	482	7.0 (6.3-7.8)	7.1 (6.4-8.1)	0.089
Lactate morning after admission (mmol/L)	459	1.2 (0.9-1.6)	1.7 (1.4-2.1)	<0.001*
pH morning after admission	473	7.43 (7.41-7.45)	7.44 (7.41-7.46)	0.002*
Tumor type	496			0.055
Glioblastoma		55 (23.0%)	82 (31.9%)	
Meningioma (WHO I-III)		72 (30.1%)	56 (21.8%)	
Astrocytoma, oligodendroglioma, medulloblastoma		34 (14.2%)	23 (8.9%)	
Adenoma, craniopharyngioma, cyst		27 (11.3%)	27 (10.5%)	
Ependymoma, schwannoma, hemangioblastoma		11 (4.6%)	15 (5.8%)	
Metastasis		32 (13.4%)	47 (18.3%)	
Lymphoma, other		8 (3.3%)	7 (2.7%)	
ASA class	496			0.404
I		33 (13.8%)	44 (17.1%)	
II		157 (65.7%)	153 (59.5%)	
III		45 (18.8%)	58 (22.6%)	
IV		3 (1.3%)	2 (0.8%)	
V		1 (0.4%)	0 (0.0%)	
Tumor side	496			0.565
Left		99 (41.4%)	98 (38.1%)	
Right		105 (43.9%)	113 (44.0%)	
Both (eg, pituitary)		35 (14.6%)	46 (17.9%)	
Degree of resection	493	N = 237	N = 256	0.177
Complete resection		58 (24.5%)	54 (21.1%)	
Nearly complete resection		35 (14.8%)	27 (10.5%)	
Tumor remnant		144 (60.8%)	175 (68.4%)	
TIVA	484	N = 231	N = 253	0.008*
		176 (76.2%)	165 (65.2%)	

Values are the median (IQR) or number (%), as indicated.

ASA indicates American Society of Anesthesiologists: Performance status; BMI, body mass index; HDU, high-dependency unit; IQR, interquartile range; TIVA, total intravenous anesthesia; WHO, World Health Organization.

*$P < 0.05$.

lactate at HDU admission. Interestingly, despite the elevated lactate levels these patients also had significantly higher pH than those with normal serum lactate on the morning after surgery.

Although there was no significant association between tumor type and serum lactate levels at HDU admission, the following trend was identified: patients with glioblastoma had elevated lactate more often than those with meningioma, astrocytoma, oligodendroglioma, or medulloblastoma. Patients that received TIVA had hyperlactatemia less frequently than those that received balanced anesthesia (48.4% vs. 61.5%, $P = 0.008$). The balanced anesthesia group received sevoflurane (65.7%) or isoflurane (34.3%) as maintenance anesthetic.

After identifying factors that contributed to hyperlactatemia on admission to HDU, we tested these factors for hyperlactatemia on the day after surgery and performed a logistic regression to quantify the size of the effect (Table 3). We also calculated the adjusted odds ratio, corrected for the confounders shown in the table. On the morning after surgery, 79 patients (17%) had hyperlactatemia; this included those with hyperlactatemia that persisted (n = 65) and those with a newly elevated lactate (n = 14). Complete descriptive characteristics of the patients in the 4 groups, based on their serum lactate at HDU admission and the morning after surgery, are shown in Table 4.

The multiple regression analysis revealed that age, surgery duration, amount of dexamethasone administered, and blood glucose upon arrival to the HDU persisted as significant independent factors related to hyperlactatemia at HDU admission. In contrast, blood loss and fluid balance were not independently related to hyperlactatemia at HDU admission. Furthermore, we found that the use of TIVA was associated with reduced risk of hyperlactatemia at HDU admission compared with balanced anesthesia. Patients with a meningioma, astrocytoma, oligodendroglioma, or

TABLE 3. Logistic Regression Analysis of Factors Potentially Associated With Hyperlactatemia on HDU Arrival and the Morning After Surgery

	Odds Ratio (95% CI)			
	Hyperlactatemia on HDU Arrival (N = 257)		Hyperlactatemia Day After Sugery (N = 79)	
Variables	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Age (y)	0.99 (0.98-1.01)	0.98 (0.96-0.99)*	1.00 (0.98-1.02)	0.99 (0.97-1.01)
BMI (kg/m^2)	1.02 (0.99-1.06)	1.01 (0.97-1.06)	1.03 (0.99-1.08)	1.03 (0.98-1.08)
Surgery duration (h)	1.16 (1.06-1.27)*	1.25 (1.11-1.41)*	1.22 (1.09-1.35)*	1.23 (1.10-1.46)*
Blood loss (mL)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Fluid balance (mL)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Total dexamethasone administered (mg)	1.03 (1.01-1.04)*	1.03 (1.01-1.04)*	1.02 (1.00-1.03)*	1.02 (1.00-1.04)*
Total mannitol administered per kilogram (g/kg)	0.87 (0.47-1.60)	0.76 (0.36-1.62)	1.24 (0.53-2.90)	1.59 (0.57-4.44)
Glucose on HDU admission (mmol/L)	1.23 (1.11-1.37)*	1.30 (1.15-1.47)*	1.12 (0.99-1.25)	1.13 (0.98-1.30)
pH on HDU admission	36.85 (0.77-1775)	7.53 (0.09-666)	2.16 (0.01-405)	0.20 (0.00-73)
Tumor type				
Glioblastoma	Reference	Reference	Reference	Reference
Meningioma (WHO I-III)	0.52 (0.32-0.85)*	0.28 (0.15-0.51)*	0.76 (0.39-1.49)	0.42 (0.18-0.94)*
Astrocytoma, oligodendroglioma, medulloblastoma	0.45 (0.24-0.85)*	0.22 (0.10-0.48)*	0.27 (0.08-0.92)*	0.20 (0.05-0.76)*
Adenoma, craniopharyngioma, cyst	0.67 (0.36-1.26)	0.53 (0.25-1.14)	0.88 (0.35-2.23)	0.87 (0.31-2.42)
Ependymoma, schwannoma, hemangioblastoma	0.92 (0.39-2.14)	0.40 (0.15-1.10)	2.08 (0.80-5.37)	1.25 (0.41-3.84)
Metastasis	0.99 (0.56-1.73)	0.81 (0.43-1.50)	1.45 (0.72-2.89)	1.58 (0.75-3.30)
Lymphoma, other	0.59 (0.20-1.71)	0.34 (0.10-1.15)	0.34 (0.04-2.72)	0.28 (0.03-3.36)
TIVA	0.59 (0.39-0.87)*	0.50 (0.31-0.81)*	0.70 (0.42-1.18)	0.55 (0.31-0.99)*

BMI indicates body mass index; HDU, high-dependency unit; TIVA, total intravenous anesthesia; WHO, World Health Organization.
*$P < 0.05$.

medulloblastoma had a reduced risk of developing hyperlactatemia compared with those with a glioblastoma.

Regression analysis showed that patients with hyperlactatemia the morning after surgery had longer surgery durations and higher dexamethasone dose compared with those without hyperlactatemia on the morning after surgery. Also, after correcting for confounders, patients with a meningioma, astrocytoma, oligodendroglioma, or medulloblastoma had hyperlactatemia the morning after surgery less frequently than those with glioblastoma. Finally, patients that received balanced anesthesia had hyperlactatemia the morning after surgery more often than those that received TIVA.

Because the use of TIVA seemed protective for hyperlactatemia in both the univariate and the multivariate analyses, we tested the use of TIVA directly on the outcome parameters. Patients that received TIVA had a shorter hospital length of stay (5 [IQR: 4 to 8] d) than those that received balanced anesthesia (6 [IQR: 5 to 8] d, $P = 0.007$). However, there were no significant differences in 6-month survival, neurological deficits, or rehabilitation needs.

We performed a subgroup analysis on patients with acidosis on arrival to the HDU; the same variables were used in analysis. These patients had significantly higher BMI (26.8 [IQR: 24.0 to 32.0]) compared with those without acidosis (25.6 [IQR: 23.2 to 28.8], $P = 0.006$). The morning after surgery, these patients also had a higher glucose (7.4 [IQR: 6.8 to 8.2] mmol/L vs. 6.9 [IQR: 6.3 to 7.9] mmol/L, $P = 0.015$) and lower pH (7.41 [IQR: 7.39 to 7.44] vs. 7.44 [IQR: 7.41 to 7.46], $P < 0.001$) compared with those without acidosis. We found no significant difference for age, duration of surgery, blood loss, fluid balance, dexamethasone, or mannitol administration, glucose on HDU arrival, lactate the morning after surgery, tumor type, ASA class, tumor side, degree of resection or anesthetic used. Patients with acidosis on HDU admission showed no difference in length of hospital stay, 6-month survival, neurological deficits or rehabilitation needed, when compared with nonacidotic patients.

DISCUSSION

In this study 51.8% of 496 patients had serum lactate levels above the upper normal limit of 2.0 mmol/L on admission to the HDU following intracranial tumor surgery. Combined with normal pH values, these findings suggest that hyperlactatemia type B was the predominant abnormality. The morning after surgery, lactate levels had normalized in the majority of patients. Hyperlactatemia was not associated with reduced survival at 6 months, a finding consistent with other studies.[4–6] Although subgroup analysis of the patients that had acidosis revealed statistically significant differences, it is unlikely that these are clinically relevant.

Our study included the second largest population of patients undergoing brain tumor resection in which factors associated with postoperative hyperlactatemia were assessed. Moreover, our database included most factors that were highlighted in previous studies and provides supporting evidence for some potentially causative factors for the development of hyperlactatemia type B after intracranial

TABLE 4. Characteristics of Patients, Divided Into 4 Groups According to Their Lactate on HDU Admission and the Morning After Surgery

Variables	No Hyperlactatemia at all (N = 207)	Hyperlactatemia That Resoluted (N = 173)	Hyperlactatemia That Persisted (N = 65)	Normal Lactate That Became Elevated (N = 14)	*P*
Age (y)	58.6 (46.9-69.3)	58.8 (47.4-67.4)	56.7 (44.3-69.0)	64.7 (58.9-73.4)	0.128
BMI (kg/m^2)	25.7 (23.2-28.7)	25.5 (23.2-29.2)	26.8 (24.4-30.5)	26.8 (24.5-30.8)	0.225
Surgery duration (h:min)	4:32 (3:38-5:42)	4:52 (3:57-5:58)	5:29 (3:50-7:24)	4:46 (3:25-6:47)	0.017*
Blood loss (mL)	200 (100-400)	300 (150-500)	350 (200-650)	150 (88-363)	0.006*
Fluid balance (mL)	357 (−54 to 740)	170 (−422 to 702)	304 (−358 to 655)	574 (−408 to 887)	0.086
Total dexamethasone administered (mg)	16 (16-20)	16 (16-56)	16 (16-55)	16 (16-48)	<0.000*
Total mannitol administered (g)	30 (0-45)	30 (15-45)	30 (15-45)	45 (23-45)	0.520
Total mannitol administered per kilogram (g/kg)	0.41 (0.00-0.64)	0.38 (0.19-0.53)	0.39 (0.16-0.57)	0.41 (0.25-0.68)	0.886
Glucose on HDU admission (mmol/L)	7.9 (7.0-8.8)	8.4 (7.4-9.7)	8.6 (7.6-9.5)	8.7 (7.7-10.5)	<0.000*
Lactate on HDU admission (mmol/L)	1.4 (1.0-1.7)	2.8 (2.3-3.5)	3.2 (2.8-3.8)	1.4 (1.3-1.7)	<0.000*
pH on HDU admission	7.39 (7.36-7.41)	7.39 (7.37-7.42)	7.40 (7.37-7.42)	7.41 (7.35-7.44)	0.365
Glucose morning after admission (mmol/L)	6.9 (6.2-7.7)	6.9 (6.2-7.7)	7.9 (6.9-8.8)	7.8 (6.8-9.2)	<0.000*
Lactate morning after admission (mmol/L)	1.1 (0.9-1.5)	1.5 (1.2-1.8)	2.5 (2.2-2.9)	2.3 (1.2-2.6)	<0.000*
pH morning after admission	7.43 (7.41-7.45)	7.44 (7.41-7.46)	7.43 (7.42-7.46)	7.43 (7.42-7.45)	0.024*
Tumor type					0.015*
Glioblastoma	47 (22.7%)	59 (34.1%)	19 (29.2%)	5 (35.7%)	
Meningioma (WHO I-III)	66 (31.9%)	38 (22.0%)	15 (23.1%)	3 (21.4%)	
Astrocytoma, oligodendroglioma, medulloblastoma	30 (14.5%)	20 (11.6%)	3 (4.6%)	0 (0%)	
Adenoma, craniopharyngioma, cyst	23 (11.1%)	12 (6.9%)	7 (10.8%)	0 (0%)	
Ependymoma, schwannoma, hemangioblastoma	8 (3.9%)	9 (5.2%)	5 (7.7%)	3 (21.4%)	
Metastasis	27 (13.0%)	28 (16.2%)	16 (24.6%)	2 (14.3%)	
Lymphoma, other	6 (2.9%)	7 (4.0%)	0 (0%)	1 (7.1%)	
ASA class					0.351
I	27 (13.0%)	30 (17.3%)	14 (21.5%)	2 (14.3%)	
II	141 (68.1%)	100 (57.8%)	37 (56.9%)	6 (42.9%)	
III	35 (16.9%)	41 (23.7%)	14 (21.5%)	6 (42.9%)	
IV	3 (1.4%)	2 (1.2%)	0 (0%)	0 (0%)	
V	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	
Tumor side					0.160
Left	90 (43.5%)	67 (38.7%)	27 (41.5%)	3 (21.4%)	
Right	85 (41.1%)	81 (46.8%)	26 (40.0%)	11 (78.6%)	
Both (eg, pituitary)	32 (15.5%)	25 (14.5%)	12 (18.5%)	0 (0%)	
Degree of resection					0.169
Complete resection	53 (25.9%)	39 (22.5%)	12 (18.8%)	1 (7.1%)	
Nearly complete resection	30 (14.6%)	19 (11.0%)	4 (6.3%)	1 (7.1%)	
Tumor remnant	122 (59.5%)	115 (66.5%)	48 (75.0%)	12 (85.7%)	
TIVA	153 (76.1%)	117 (68.4%)	41 (64.1%)	9 (69.2%)	0.200

Values are the median (IQR) or number (%), as indicated.

ASA indicates American Society of Anesthesiologists: Performance status; HDU, High-dependency unit; IQR, Interquartile range; TIVA, total intravenous anesthesia; WHO, World Health Organization.

*$P < 0.05$.

tumor surgery. Our finding that hyperlactatemia did not have a negative effect on outcomes might justify less aggressive management of hyperlactatemia type B in this patient population.

After brain tumor resection, many patients are managed in the immediate postoperative period in an HDU or ICU where hyperlactatemia is typically assumed to result from circulatory deterioration. Such hyperlactemia (type A) requires rapid assessment and fluid resuscitation, as recommended, for example, by the Surviving Sepsis Campaign guidelines.[21] Lactate-guided fluid resuscitation is recommended in the initial phase, regardless of the source of hyperlactatemia. However, research has shown that fluid overload can cause adverse effects and negative outcomes after general surgery.[22] Brallier et al[6] also found that patients with elevated lactate were given approximately extra

1 L of crystalloids. A more restrictive fluid management of hyperlactatemia, particularly in patients undergoing neurosurgery, could increase patient safety and potentially reduce complications and costs. Finally, in some patients, controlling hyperglycemia can reduce serum lactate levels. However, aggressive management of hyperglycemia also increases the risk of hypoglycemia-related incidents and complications.[23] Therefore, accepting hyperglycemia at the cost of apparently harmless hyperlactatemia seems appropriate.

Lactic acid dehydrogenase (LDH) is a tetrameric enzyme, composed of H and M subunits. Five isoforms exist; LDH_1 and LDH_2 are specifically expressed in the heart and LDH_5 in liver and muscle.[24] A previous Japanese study found that corticosteroid administration elevated heart-specific LDH_1 and LDH_2 levels.[25] In contrast, propofol has been shown to inhibit the release of LDH and reduce lactate accumulation in cell cultures treated with lipopolysaccharide.[26,27] Furthermore, in vitro data revealed that hyperlactatemia occurred in rodent brain and liver samples more often with volatile than with propofol anesthesia.[28,29] That finding was confirmed in humans during prolonged spinal surgery[30] and carotid endarterectomy.[31] Taken together, these findings suggest that the use of propofol might be protective against hyperlactatemia. However, this notion must be considered in the context of concerns about PRIS, which is a potentially hazardous complication of propofol administration.[32] PRIS is characterized by early metabolic acidosis, which can lead to cardiac failure. There is no published evidence that opioids might contribute to hyperlactatemia in vitro or in vivo.

Another potential contributing factor to elevated serum lactate is a high BMI. Garavaglia et al[10] hypothesized that muscle ischemia and tissue breakdown caused hyperlactatemia, which was potentially aggravated by a high BMI. However, we did not find that BMI was an independent risk factor for the development of postoperative hyperlactatemia. However, increases in BMI can lead to insulin resistance,[33] and this may contribute to the increased serum lactate levels observed in obese patients.

In contrast to the aforementioned study by Garavaglia et al,[10] a longer surgery duration was associated with elevated serum lactate in our study. This might be explained by immobility during anesthesia, since prolonged immobility can cause regional hypoperfusion and tissue breakdown. In addition, the positioning of the patient, supine or prone, can increase tissue stress, and thus, stimulate anaerobic metabolism.

Recent studies have suggested that lactate can have a neuroprotective role because it serves as a substrate for oxidation under certain conditions. For example, hypertonic sodium lactate can modulate cerebral metabolism[34,35] and potentially attenuate brain damage after traumatic injury.[36] Although this finding is controversial[37] and requires more research, it is interesting to consider that an innate protective mechanism might be activated during iatrogenic brain injury (ie, a craniotomy).

Increased blood loss and less positive fluid balance are indications of a change in intravascular volume. Although both blood loss and fluid balance remained within normal clinical limits in our study, taken together, these factors could implicate a relative hypovolemia and, potentially, impaired oxygen delivery to tissues in patients with elevated serum lactate. However, in the multiple regression analysis these factors lost significance as independent predictors. Moreover, impaired oxygen delivery should induce metabolic acidosis, which was infrequently observed. Our subanalysis of patients with acidosis showed that blood loss and fluid balance were not significantly associated with acidosis.

We performed additional analyses for patients with hyperlactatemia the day after surgery and the associated factors were similar to those for elevated lactate on admission to HDU. We also provided a detailed description of the characteristics of the patients divided into 4 groups: those with hyperlactatemia on HDU admission that resolved or persisted, and those with normal lactate on admission that remained normal or became elevated by the following morning. Because the number of patients is small for these 4 groups, we lost power for statistical analysis.

Brallier et al[6] found that intraoperative hyperlactatemia was associated with longer hospital stay and more neurological deficits. Although our study confirmed the association with hospital stay, we found no difference in neurological deficits or rehabilitation needs of patients with hyperlactemia. Whether it is the hyperlactatemia itself, or the treatment of the high lactate levels, that is responsible for the increased length of hospital stay remains unclear. Nonetheless, this outcome is clinically relevant because longer hospital stay leads to higher health care costs and additional patient exposure to the high-risk hospital environment.

Brallier et al[6] hypothesized that regional hypoperfusion during surgery is a cause of hyperlactatemia. This should be accompanied by (cerebrospinal fluid) acidosis but, unfortunately, no data on pH were reported to confirm that hypothesis. An important difference between the present study and that by Brallier and colleagues is the timing of blood sampling. Brallier and colleagues sampled blood intraoperatively whereas we sampled blood postoperatively on admission to the HDU.

A few studies have attempted to correlate tumor volume and elevated serum lactate, but the results are conflicting.[5,14,38] Some authors have suggested that lactate can be used as a biomarker for tumor progression and therapy response in glioblastoma patients,[38] whereas others have been unable to confirm this finding.[5] Our data demonstrate an association between tumor type (glioblastoma) and hyperlactatemia at HDU admission, but we did not measure tumor volume.

An important limitation of our study was its retrospective design. Consequently, we could not investigate some potentially important factors such as preoperative serum lactate or patient positioning. Moreover, we could not avoid evident biases. Another limitation was that the anesthesia technique was not standardized and this could

have led to differences in the anesthesia provided in terms of type and dosing of drugs and fluid management. Finally, an anesthesia record was not available in some patients' files and, thus, some data were missing.

CONCLUSIONS

Hyperlactatemia type B occurred in over 50% of almost 500 patients that underwent intracranial tumor resection. Age, surgery duration, amount of dexamethasone administered, blood glucose, and glioblastoma tumor type were associated with elevated serum lactate on admission to the HDU. Patients that received TIVA had hyperlactatemia less frequently than those that received inhalational agents. The development of hyperlactatemia did not affect 6-month survival, but was associated with longer hospital lengths of stay. On the basis of our data, we were unable to determine whether the prolonged hospital stay was due to the hyperlactatemia itself or to its treatment. There was no association between elevated serum lactate and worsening of neurological status or need for rehabilitation therapy. Prospective trials are necessary to confirm the potential associations with hyperlactemia identified in this study.

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