Original

Early postoperative hyperlactatemia in elective neurosurgical patients: A retrospective study

Hiroaki Yoshikawa[1)]*, Shinichi Nishibe[2)], Daisuke Sakai[3)], Hirokazu Imanishi[4)], Seika Ohno[1)], Katsue Kobayashi[5)], Akira Kitamura[1)]

1) Department of Anesthesiology, Saitama Medical University International Medical Center
2) Department of Anesthesiology, Tokyo Metropolitan Children's Medical Center
3) Department of Anesthesiology, Chiba-Nishi General Hospital
4) Department of Anesthesiology, Tominaga Hospital
5) Division of Disability and Oral Health, Meikai University School of Dentistry

[Purpose] We occasionally encounter early postoperative hyperlactatemia during neurosurgery in the absence of hemodynamic instability or critical illness. We conducted a retrospective study to identify factors causing hyperlactatemia in elective neurosurgical patients and assessed the association between early postoperative hyperlactatemia and postoperative morbidity.
[Methods] The present study enrolled elective neurosurgical patients in whom an arterial blood gas analysis, including the measurement of lactate levels, had been performed at two-time points (i.e., after the induction of anesthesia and immediately before the surgery was completed). Early postoperative hyperlactatemia was defined as a lactate level of ≥2 mmol/L in arterial blood collected immediately before the completion of the surgery. Patients were divided into a high-lactate (HL) group, including those with early postoperative hyperlactatemia, and a normal-lactate (NL) group, including the remaining patients, and were compared. The following variables were retrieved from medical records: patient characteristics; perioperative vital signs; preoperative comorbidities; type of surgery; brain tumor pathology; size of brain tumor; preoperative comorbidities; duration of surgery; blood loss; PaO_2, $PaCO_2$, pH, and lactate; catecholamine use; length of stay in the ICU; mechanical ventilation requirement; and postoperative adverse events. Multiple logistic regression analysis was used to identify factors causing postoperative hyperlactatemia.
[Results] Two hundred and twenty-five patients were involved in this study. Early postoperative hyperlactatemia was observed in 49 of 225 (22 %) patients. Brain tumor surgery, longer duration of surgery, preoperative hyperlactatemia, and larger blood loss volume were found to be more prevalent in the HL group than in the NL group, as per univariate analysis ($P < 0.05$). Risk factors for early postoperative hyperlactatemia were preoperative hyperlactatemia (odds ratio = 27.83; 95 % confidence interval = 8.516 – 90.92, P = 0.000) and brain tumor surgery (odds ratio = 4.806; 95 % confidence interval = 1.006 – 21.67, P = 0.041) in multiple regression analysis. Of the 225 patients, 89 patients underwent a craniotomy for the resection of a brain tumor. The sizes of the brain tumors in the HL group (1016 mm^2 [IQR: 545, 1951 mm^2]) were significantly larger than those in the NL group (780 mm^2 [IQR: 322, 1107 mm^2]) (P = 0.02). Preoperative steroids and diuretics to reduce intracranial hypertension were more often prescribed for patients with high-grade tumors (P = 0.01, P = 0.07, respectively). Of the 49 patients in the HL group, 15 (31 %) stayed in the ICU for ≥2 days after surgery, whereas only 28 of 176 (16 %) patients in the NL group did ($P < 0.05$).
[Conclusion] Preoperative hyperlactatemia and brain tumor surgery are independent risk factors for early postoperative hyperlactatemia. Early postoperative hyperlactatemia is associated with a longer length of stay in the ICU. The role of early postoperative hyperlactatemia as a predictor of adverse postoperative complications in neurosurgical patients needs to be investigated further in future studies.

J Saitama Medical University 2018; 45(1): 1 - 11
(Received April 25, 2017 / Accepted February 15, 2018)

Key words: hyperlactatemia, brain tumor, Warburg effect, neurosurgery

---

* Corresponding author: Department of Anesthesiology, Saitama Medical University International Medical Center
1397-1 Yamane, Hidaka, Saitama 350-1298, Japan
Tel: + 81 42 984 4394, Fax: + 81 42 984 4394, E-mail: tororoaki@yahoo.co.jp
◯ The authors declare that there are no conflicts of interest associated with the present study.

Introduction

Hyperlactatemia is associated with adverse outcomes in cardiac surgery[1], gastrointestinal surgery[2], and critically ill patients[3]. Some reports suggest that hyperlactatemia is associated with ruptured cerebral aneurysms[4] and traumatic brain injury[5]. When blood lactate levels are elevated during surgery, understanding their clinical significance is important for anesthesiologists because lactic acidosis is associated with impaired survival regardless of its source and the mechanism responsible for the increase in lactate levels[6].

However, we occasionally encounter early postoperative hyperlactatemia after an uneventful anesthesia during neurosurgical procedures. The incidence of hyperlactatemia in patients who underwent a craniotomy for brain tumor resection is reportedly high, although most of these patients had an uneventful postoperative course[7]. Therefore, we hypothesized that besides hemodynamic instability and critical illness, other factors may cause high lactate levels in neurosurgical patients.

Our primary objective was to identify the factors causing high lactate levels in elective neurosurgical patients. In addition, our secondary objective was to assess the association between early postoperative hyperlactatemia and postoperative morbidity.

Methods and Subjects

The medical records of patients who underwent general anesthesia for neurosurgical procedures between January 2014 and August 2015 at a single institution were reviewed after the approval of the present study by the Institutional Review Board of Saitama International Medical Center, Saitama Medical University, Saitama, Japan (No. 15 - 152).

In this study, we enrolled elective neurosurgical patients in whom an arterial blood gas analysis, including the measurement of lactate levels, had been performed at two time points, i.e., after the induction of general anesthesia (before the neurosurgical procedure) and immediately before the surgery was completed (after the neurosurgical procedure). Arterial blood gas values were calculated using a commercial blood-gas analyzer (Rapid Lab 1265; Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). Blood lactate concentrations were measured using the lactic acid oxidizing enzyme technique. Patients undergoing emergency surgery or spinal surgery and children under the age of 16 years were excluded.

Data collection

The preoperative test consisted of an arterial blood gas analysis, including the measurement of lactate levels, performed after the induction of general anesthesia. The postoperative test was the same as the preoperative test but was performed immediately before the completion of the surgery. Early postoperative hyperlactatemia was defined as a lactate level of ≥ 2 mmol/L. We selected this criterion based on a review of literature pertaining to neurosurgery and critical care[3, 7-10]. Patients were divided into those with early postoperative hyperlactatemia (high-lactate [HL] group) and the remaining patients (normal-lactate [NL] group). The following preoperative variables were retrieved from the medical records: age; body mass index (BMI); sex; American Society of Anesthesiologists (ASA) physical status classification; blood pressure (BP), heart rate (HR), and peripheral arterial oxygen saturation (SpO_2) upon admission to an operating room; preoperative catecholamine use; and preoperative comorbidities, including osmotic diuresis and steroid use for intracranial hypertension caused by brain tumor, diabetes mellitus (DM), biguanide use for DM, liver failure, and renal failure. For patients with brain tumors, the tumor size was defined as the product of the two largest perpendicular measurements on preoperative MRI scans. Intraoperative variables included the type of surgery (brain tumor surgery [e.g., craniotomy for tumor resection], stroke surgery [e.g., aneurysmal clipping and carotid endarterectomy], and neuroendovascular intervention [e.g., aneurysmal coiling and carotid artery stenting]); the duration of surgery; the operative position; the lowest BP, HR, and SpO_2 values and the highest HR during surgery; preoperative and postoperative tests (partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide [$PaCO_2$], pH, lactate, blood sugar [BS], and hematocrit); intraoperative catecholamine use; and blood loss volume. Brain tumor pathology was classified based on the World Health Organization (WHO) classification for the grading of tumors[11]. Where applicable, the WHO tumor grade was recorded as high-grade (WHO grades 3 and 4) or low-grade (WHO grades 1 and 2) tumors. Metastatic brain tumors were graded as high-grade tumors. Postoperative variables included BP, HR, and SpO_2 upon admission to the intensive care unit (ICU) and postoperative day 1 (POD 1); length of ICU stay; mechanical ventilation requirement; and postoperative complications, including adverse neurological and cardiovascular events.

Statistical analysis

The measurements were presented as the means ± SD or medians (interquartile ranges), as appropriate, or the number of patients. For normally distributed continuous variables, an unpaired t-test was performed to compare the outcomes between the HL and NL groups. For non-normally distributed variables, Mann–Whitney U test was performed to compare the outcomes between the HL and

NL groups. The chi-square test or Fisher's exact test was used for categorical variables where appropriate. A P value of <0.05 was considered statistically significant. A multiple logistic regression analysis was used to calculate the odds ratio (OR) and 95 % confidence intervals (95 % CI) after simultaneously controlling for potential confounders. Preoperative and intraoperative variables with a P value of <0.1 in the univariate analysis were considered for inclusion in the multiple logistic regression analysis.

The univariate analyses were performed using GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA), while the multivariable analysis was performed using SPSS ver. 22.0 for Windows (IBM Japan, Ltd., Tokyo, Japan).

Results

During the study period, 1,292 patients underwent general anesthesia for neurosurgical procedures, and an arterial blood gas analysis, including the measurement of lactate levels, was performed at two time points in 623 patients. The present study included 225 patients after excluding those who had undergone emergency surgery (376 patients) or spinal surgery (4 patients) and those who were younger than 16 years (18 patients).

Early postoperative hyperlactatemia was observed in 49 of the 225 (22 %) patients. Table 1 shows the preoperative characteristics of the patients with and those without early postoperative hyperlactatemia. No significant differences in the preoperative variables were found.

Table 1. Preoperative characteristics

	HL (n = 49)	NL (n = 176)	P value
Age (yr)	58 ± 15	62 ± 15	0.12#1
Body mass index	22.8 ± 4.4	22.7 ± 3.8	0.83#1
Male gender	26 (53%)	95 (54%)	1.00#2
ASA physical status classification			0.33#3
1	15 (31%)	39 (22%)	
2	29 (59%)	124 (70%)	
3	5 (10%)	13 (7%)	
Vital signs			
SBP (mmHg)	146 ± 21	152 ± 28	0.12#1
DBP (mmHg)	73 ± 16	74 ± 15	0.81#1
HR (/min)	73 ± 15	73 ± 15	0.95#1
SpO_2 (%)	99 ± 2	99 ± 1	0.73#1
Preoperative catecholamine use	0	0	
Preoperative comorbidities			
DM	5 (10%)	28 (16%)	0.37#2
DM patients treated with biguanide	2 (2%)	5 (3%)	0.28#2
Liver failure	0	0	
HD patient	0	4 (2%)	0.58#2

ASA indicates American Society of Anesthesiologists; HL, patients with early postoperative hyperlactatemia; NL, patients without early postoperative hyperlactatemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, peripheral arterial oxygen saturation; DM, diabetes mellitus; HD, hemodialysis

Data are presented as mean ± SD or number of patients (%).

#1 an unpaired t-test

#2 Fisher's exact test

#3 Chi-square test

Table 2 shows the intraoperative characteristics. Intraoperative vital signs and catecholamine use were comparable between the groups. A higher proportion of patients in the HL group underwent brain tumor surgery than that in the NL group. Moreover, patients in the HL group had a longer duration of surgery and lost a larger blood volume.

Table 2. Intraoperative characteristics

	HL group (n = 49)	NL group (n = 176)	P value
Type of surgery			< 0.0001#1
Brain tumor	38 (78%)	51 (29%)	
Stroke	4 (8%)	44 (25%)	
Neuroendovascular intervention	7 (14%)	81 (46%)	
Duration of surgery (hr)	6.0 ± 1.9	4.5 ± 2.6	< 0.0001#2
Operative position			0.09#1
Supine	39 (80%)	160 (91%)	
Lateral	3 (6%)	4 (2%)	
Prone	7 (14%)	12 (7%)	
Vital signs			
Lowest SBP (mmHg)	85 ± 10	87 ± 11	0.09#2
Lowest DBP (mmHg)	41 ± 6	41 ± 6	0.96#2
Lowest HR (/min)	64 ± 7	64 ± 8	0.88#2
Highest HR (/min)	74 ± 9	72 ± 10	0.15#2
Lowest SpO_2 (%)	99 ± 1	99 ± 1	0.78#2
Preoperative test			
PaO_2 (mmHg)	217 ± 109	214 ± 87	0.83#2
$PaCO_2$ (mmHg)	35 ± 4	36 ± 6	0.22#2
pH	7.46 ± 0.04	7.45 ± 0.06	0.29#2
Blood sugar (mg/dL)	125 ± 35	111 ± 31	0.007#2
Hematocrit (%)	35 ± 4.5	35 ± 4.8	1.00#2
Postoperative test			
PaO_2 (mmHg)	219 ± 93	210 ± 79	0.52#2
$PaCO_2$ (mmHg)	35 ± 4	38 ± 5	0.0006#2
pH	7.44 ± 0.05	7.43 ± 0.04	0.07#2
Blood sugar (mg/dL)	122 ± 24	111 ± 27	0.009#2
Hematocrit (%)	32 ± 4.6	32 ± 4.8	0.41#2
Intraoperative catecholamine use	10 (20%)	49 (28%)	0.36#3
Blood loss (mL)	299 ± 275	144 ± 262	< 0.0001#2

HL, patients with early postoperative hyperlactatemia; NL, patients without early postoperative hyperlactatemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, peripheral arterial oxygen saturation

Data are presented as mean ± SD or number of patients (%).

#1 Chi-square test

#2 an unpaired t-test

#3 Fisher's exact test

The preoperative lactate levels were higher in the HL group (2.0 mmol/L [IQR: 1.5, 2.3 mmol/L])) than in the NL group (1.0 mmol/L [IQR: 0.8, 1.3 mmol/L]) ($P < 0.0001$) (Figure 1). In addition, the elevation of lactate levels between the two time-points was higher in the HL group (0.8 mmol/L [IQR: 0.2, 1.2 mmol/L]) than in the NL group (0.06 mmol/L [IQR: -0.1, 0.3 mmol/L]) ($P < 0.0001$) (Figure 2).

The results of multiple logistic regression analysis of early postoperative hyperlactatemia are shown in Table 3. Independent risk factors for early postoperative hyperlactatemia were found to be brain tumor surgery, preoperative hyperlactatemia, postoperative $PaCO_2$, and postoperative BS levels.

Table 4 shows the number of patients with preoperative and early postoperative hyperlactatemia among the three types of surgical procedures. More patients undergoing a craniotomy for brain tumors suffered from preoperative and early postoperative hyperlactatemia than those undergoing stroke surgery or a neuroendovascular intervention.

Out of a total of 89 patients undergoing a craniotomy for the resection of a brain tumor, 57 patients had low-grade and 32 patients had high-grade brain tumors. No differences were found between patients with preoperative hyperlactatemia and those with preoperative normo-lactatemia in terms of tumor size, tumor grade, preoperative steroid use, or preoperative diuretics use (Table 5). The sizes of the brain tumors in the HL group were significantly larger than those in the NL group, although an association between hyperlactatemia and tumor grade was not found (Table 6). There was a trend toward an increase in the number of patients with early postoperative hyperlactatemia among patients with preoperative prescriptions for steroids and osmotic diuresis (Table 6). Preoperative steroids and diuretics to reduce intracranial hypertension were more often prescribed for patients with high-grade tumors (Table 7), and correlations between the preoperative use of steroids and diuretics and tumor size were found (Table 8).

Table 9 compares the postoperative outcomes of patients with and those without early postoperative hyperlactatemia. Of the 49 patients in the HL group, 15 (31 %) stayed in the ICU for ≥2 days after the surgery, whereas only 28 of the 176 (16 %) patients in the NL group stayed in the ICU for ≥2 days ($P < 0.05$). No differences in other postoperative outcomes, including adverse neurological and cardiovascular events, were found.

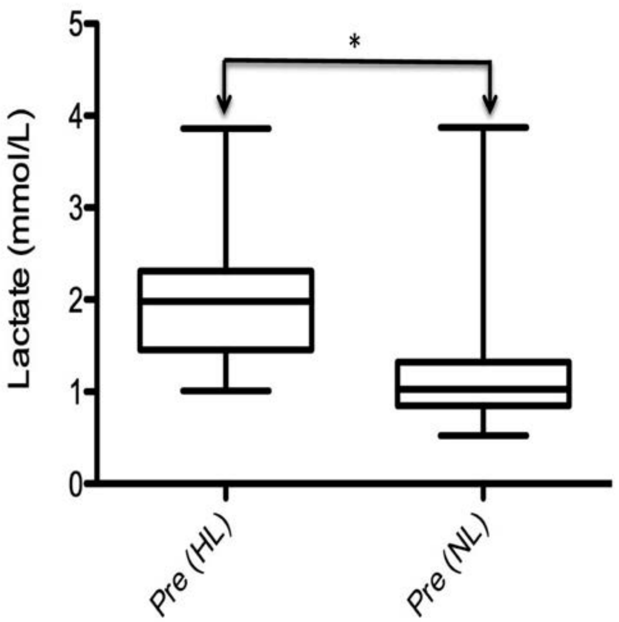

Fig. 1. Preoperative lactate levels Pre, preoperative test; HL, high lactate group; NL, normal lactate group *The preoperative lactate levels were higher in the HL group (2.0 mmol/L [IQR: 1.5, 2.3 mmol/L])) than in the NL group (1.0 mmol/L [IQR: 0.8, 1.3 mmol/L]) ($P < 0.0001$). Mann–Whitney U test was used for comparison between the groups.

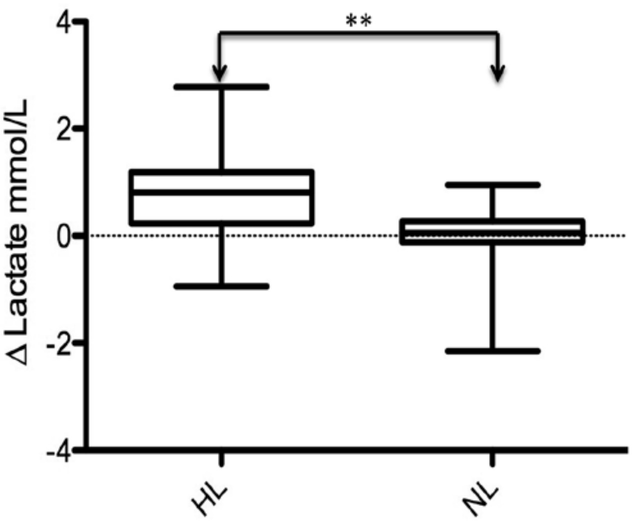

Fig. 2. Change of lactate levels before and after neurosurgical procedure HL, high lactate group; NL, normal lactate group ΔLactate = Early postoperative lactate levels − preoperative lactate levels **The elevation of lactate levels between the two time-points was higher in the HL group (0.8 mmol/L [IQR: 0.2, 1.2 mmol/L]) than in the NL group (0.06 mmol/L [IQR: -0.1, 0.3 mmol/L]) ($P < 0.0001$). Mann–Whitney U test was used for comparison between the groups.

Table 3. Risk factors for early postoperative hyperlactatemia

Variables	Odds Ratio	95% CI	P value
Type of surgery			
Brain tumor	4.806	1.066 – 21.67	0.041
Stroke	1.000	Ref	
Neuroendovascular intervention	2.223	0.401 – 12.32	0.360
Duration of surgery	1.160	0.948 – 1.420	0.149
Operative position			
Supine	1.000	Ref	
Prone	1.939	0.220 – 17.10	0.551
Lateral	0.633	0.146 – 2.745	0.542
Preoperative test			
Lactate	27.83	8.516 – 90.92	0.000
Blood sugar	0.985	0.967 – 1.004	0.120
Postoperative test			
$PaCO_2$	0.877	0.788 – 0.976	0.017
Blood sugar	1.035	1.013 – 1.058	0.002
Intraoperative lowest SBP	0.972	0.926 – 1.021	0.260
Blood loss	1.001	0.999 – 1.003	0.379

CI, confidence interval; Ref, reference; SBP, systolic blood pressure
A multiple logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence intervals (95% CI) after simultaneously controlling for potential confounders.

Table 4. Number of patients with preoperative and early postoperative hyperlactatemia

	BT (n = 89)	Stroke (n = 48)	IVR (n = 88)	P value
Preoperative hyperlactatemia	22 (25%)	3 (6%)	3 (3%)	<0.0001
Early postoperative hyperlactatemia	38 (43%)	4 (8%)	7 (8%)	<0.0001

BT, brain tumor surgery; Stroke, stroke surgery; IVR, neuroendovascular intervention;
Data are presented as number of patients (%).
For comparison among the three groups, Chi-square test was used.

Table 5. Preoperative hyperlactatemia in patients with brain tumor

	Lactate ≥2 mmol/L (n = 22)	Lactate < 2 mmol/L (n = 67)	P value
Tumor size (mm^2)	1162 (462, 2016)	781 (492, 1200)	0.20#1
Tumor grade			0.61#2
High-grade	9(41%)	23(34%)	
Low-grade	13(59%)	44(66%)	
Preoperative steroid			0.06#2
Use	10(45%)	16(24%)	
Non-used	12(55%)	51(76%)	
Preoperative diuretics			0.07#2
Use	11(50%)	19(28%)	
Non-use	11(50%)	48(72%)	

Data are presented as number of patients (%) or median (interquartile ranges).

#1Mann–Whitney U test

#2Fisher's exact test

Table 6. Early postoperative hyperlactatemia in patients with brain tumor

	Lactate ≥2 mmol/L (n= 38)	Lactate < 2 mmol/L (n= 51)	P value
Tumor size (mm^2)	1016 (545, 1951)	780 (322, 1107)	0.02#1
Tumor grade			0.66#2
High-grade	15(39%)	17(33%)	
Low-grade	23(61%)	34(67%)	
Preoperative steroid			0.01#2
Use	17(45%)	9(18%)	
Non-use	21(55%)	42(82%)	
Preoperative diuretics			0.07#2
Use	17(45%)	13(25%)	
Non-use	21(55%)	38(75%)	

Data are presented as number of patients (%) or median (interquartile ranges).

#1Mann–Whitney U test

#2Fisher's exact test

Table 7. Correlation between tumor grade and preoperative medications

	High-grade tumor	Low-grade tumor	P value
Preoperative steroid use (n = 26)	14(54%)	12(46%)	0.03
Preoperative diuretics use (n = 30)	17(57%)	13(43%)	0.005

Data are presented as number of patients(%).

Fisher's exact test was used for comparison.

Table 8. Correlation between tumor size and preoperative medications

	Used	Not used	P value
Preoperative steroid use (mm^2)	1936 (805, 2483)	723 (322, 1033)	< 0.0001
Preoperative diuretics use (mm^2)	1699 (789, 2476)	588 (266, 840)	< 0.0001

Data are presented as median (interquartile ranges).
For comparison, Mann–Whitney U test was used.

Table 9. Postoperative outcomes

	HL group (n = 49)	NL group (n = 176)	P value
Vital signs upon admission to ICU			
SBP (mmHg)	137 ± 27	139 ± 25	0.53#1
DBP (mmHg)	61 ± 13	62 ± 14	0.49#1
HR (/min)	86 ± 19	86 ± 18	0.99#1
SpO_2 (%)	99 ± 2	99 ± 1	0.29#1
Vital signs at POD 1			
SBP (mmHg)	126 ± 15	124 ± 18	0.33#1
DBP (mmHg)	74 ± 12	66 ± 12	0.0002#1
HR (/min)	79 ± 15	77 ± 14	0.48#1
SpO_2 (%)	98 ± 1	98 ± 4	0.97#1
Length of ICU stay ≥2 days	15 (31%)	28 (16%)	0.03#2
MV requirement at POD 1	1 (2%)	6 (3%)	1.00#2
Postoperative adverse event	2 (4%)	9 (5%)	1.00#2
Neurological	1	7	1.00#2
Cardiovascular	0	0	
Other	1	2	0.52#2

HL, patients with early postoperative hyperlactatemia; NL, patients without early postoperative hyperlactatemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, peripheral arterial oxygen saturation; ICU, intensive care unit; POD 1, postoperative day 1; MV, mechanical ventilation
Data are presented as mean ± SD or number of patients (%).
#1an unpaired t-test
#2Fisher's exact test

Discussion

Early postoperative hyperlactatemia, defined as a lactate level of ≥2 mmol/L immediately before the completion of surgery, has been found in 22 % of patients following elective neurosurgical procedures. The independent risk factors for early postoperative hyperlactatemia were preoperative hyperlactatemia and brain tumor surgery.

Preoperative hyperlactatemia is considered to be a strong risk factor for early postoperative hyperlactatemia. However, the preoperative hyperlactatemia observed in the present study was unlikely to reflect preoperative hemodynamic instability or critical illness because no differences were found in the ASA classification, preoperative vital signs, preoperative test results, or preoperative comorbidities, including biguanide use in patients with DM. Recently, two studies described the application of serum lactate as a biomarker for brain tumors[12, 13]. They described that excessive lactate production by the tumor, which is a phenomenon known as the Warburg effect[8, 14], may be responsible for the increased serum lactate level observed in patients undergoing a craniotomy for the resection of a brain tumor. In their studies, they observed a baseline elevation in lactate in patients with high-grade tumors, which agreed with our finding that patients with high-grade tumors tended to have prescriptions for steroids and osmotic diuresis, the use of which is likely to be associated with preoperative hyperlactatemia despite the statistical insignificance. Accordingly, the preoperative hyperlactatemia observed in patients with a brain tumor in the present study might have been caused by lactate production by the brain tumor.

Brain tumor surgery was another risk factor for early postoperative hyperlactatemia. This finding is consistent with a report by Kohli-Seth et al.[7], in which the postoperative lactate levels were higher in a brain tumor group than in an intracranial vascular surgery group. In the present study, 43 % of patients undergoing brain tumor surgery suffered from early postoperative hyperlactatemia. This suggests that more patients undergoing a craniotomy for the resection of a brain tumor suffered from postoperative hyperlactatemia than those undergoing stroke surgery or a neuroendovascular intervention. Moreover, brain tumor size as measured on preoperative MRI scans and the preoperative use of steroids and osmotic diuretics for patients with intracranial hypertension were associated with early postoperative hyperlactatemia, although an association between the occurrence of hyperlactatemia and the tumor grade was not found. In addition, the elevation of lactate levels during the neurosurgical procedure was higher in the HL group than in the NL group. A possible hypothesis for the elevation of the lactate level during intracranial surgery is that brain retraction for adequate exposure of the brain tumor, especially a large tumor complicated with intracranial hypertension, leads to regional ischemia and an increase in interstitial lactate levels[15], followed by increased serum lactate levels. Other findings, such as the fact that preoperative steroid use and osmotic diuresis use to reduce intracranial pressure are correlated with early postoperative hyperlactatemia, also support our hypothesis.

Postoperative BS and low $PaCO_2$ levels were other risk factors for early postoperative hyperlactatemia. However, the postoperative BS levels in the present study were 122 ± 24 mg/dL in the HL group and 111 ± 27 mg/dL in the NL group, which were not sufficiently high to cause clinical problems. Moreover, the postoperative $PaCO_2$ level in the HL group was 35 ± 4 mmHg, which is within the normal range. Therefore, the clinical significance of postoperative BS and $PaCO_2$ appears to be limited.

There are other causes of an intraoperative increase in the serum lactate level that need to be considered. First, we found that patients in the HL group had a longer duration of surgery and lost a larger blood volume. The complexity of the surgeries may affect lactate production despite the absence of any difference between the HL and NL groups in terms of intraoperative and postoperative vital signs, catecholamine use, and postoperative hematocrit value. Second, the reported causes of perioperative hyperlactatemia in neurosurgery include a prone position[16] and a high BMI[17]. These conditions may be attributed to pressure-related muscle hypoperfusion and ischemia. However, an association between these variables and early postoperative hyperlactatemia could not be found in the present study.

In the present study, 22 % of all elective neurosurgical patients and 43 % of patients undergoing brain tumor surgery suffered from early postoperative hyperlactatemia. The incidence of hyperlactatemia in patients who underwent a craniotomy for brain tumor resection was reported to be 67 %[7]. In another study, the incidence of hyperlactatemia in neurosurgical/trauma patients admitted to the ICU was reported to be 45 %[3]. We included only patients undergoing elective surgery because patients undergoing emergency surgery frequently suffer from preoperative hemodynamic instability. This may explain the relatively low incidence of postoperative hyperlactatemia.

We observed that more patients in the HL group than in the NL group stayed in the ICU for ≥ 2 days. Patients who stayed in the ICU for ≥ 2 days had a general tendency to experience adverse events because most of the patients were admitted to the ICU on the day of neurosurgery and those with an uneventful postoperative course were usually discharged from the ICU on POD 1, according to our standard practice. Therefore, early postoperative hyperlactatemia may be associated with postoperative morbidities. This hypothesis is consistent with Brallier's report[9], in which patients who experienced intraoperative hyperlactatemia during a craniotomy had a longer length of ICU stay because of poorer neurological outcomes. Therefore, elevated blood lactate levels, despite normal vital signs, may be a good marker of morbidity among neurosurgical patients, as pointed out by Meregalli et al.[18]

This study had several limitations. First, it was a retrospective study. Second, the number of patients undergoing stroke surgery was smaller than the numbers undergoing either of the other two procedures. This imbalance in sample size might have resulted from the fact that many patients undergoing stroke surgery were excluded because of the emergency nature of their surgeries. Third, we enrolled only those patients in whom an arterial blood gas analysis, including a measurement of lactate levels, was performed at two time points, i.e., after the induction of general anesthesia and immediately before the completion of surgery. This may have resulted in a selection bias. It is possible that only those patients who needed to be assessed with a frequent arterial blood gas analysis were enrolled in this study.

Conclusion

In this study, we observed early postoperative hyperlactatemia in 22 % of patients undergoing elective neurosurgery procedures. Preoperative hyperlactatemia and brain tumor surgery were independent risk factors for early postoperative hyperlactatemia. Early postoperative hyperlactatemia was associated with a longer length of stay in the ICU. The role of early postoperative hyperlactatemia, despite normal vital signs, as a predictor of adverse postoperative complications in neurosurgical patients needs to be further investigated in future studies.

References

1) Maillet JM, Le Besnerais P, Cantoni M, Nataf P, Ruffenach A, et al. Frequency, risk factors, and outcome of hyperlactatemia after cardiac surgery. Chest 2003; 123: 1361-6.
2) Creagh-Brown BC, De Silva AP, Ferrando-Vivas P, Harrison DA. Relationship between peak lactate and patient outcome following high-risk gastrointestinal surgery: influence of the nature of their surgery: elective versus emergency. Crit Care Med 2016; 44: 918-25.
3) Khosravani H, Shahpori R, Stelfox HT, Kirkpatric AW, Laupland KB. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. Crit Care 2009; 13: R90.
4) Aisiku IP, Chen PR, Truong H, Monsivais DR, Edlow J. Admission serum lactate predicts mortality in aneurysmal subarachnoid hemorrhage. Am J Emerg Med 2016; 34: 708-12.
5) Jo YY, Kim JY, Choi JJ, Jung WS, Kim YB, et al. Preoperative serum lactate cannot predict in-hospital mortality after decompressive craniectomy in traumatic brain injury. J Anesth 2016; 30: 637-43.
6) De Backer D. Lactic acidosis. Minerva Anestesiol 2003; 69: 281-4.
7) Kohli-Seth R, Mukkera SR, Leibowitz AB, Nemani N, Oropello JM, et al. Frequency and outcomes of hyperlactatemia after neurosurgery. ICU Director 2011; 2: 211-4.
8) Kraut JA, Madias NE. Lactic acidosis. N Engl J Med 2014; 371: 2309-19.
9) Brallier JW, Dalal PJ, McCormick PJ, Lin HM, Deiner SG. Elevated intraoperative serum lactate during craniotomy is associated with new neurological deficit and longer length of stay. J Neurosurgical Anesthesiology 2017; 29: 388-92.
10) Abraham E. New definitions for sepsis and septic shock. Continuing evolution but with much still to be done. JAMA 2016; 315: 757-9.
11) Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO Classification of Tumours of the Central Nervous System. Lyon, IARC Press, 2007.
12) Mariappan R, Venkatraghavan L, Vertanian A, Agnihotri S, Cynthia S, et al. Serum lactate as a potential biomarker of malignancy in primary adult brain tumors. J Clin Neurosci 2015; 22: 144-8.
13) Bharadwaj S, Venkatraghavan L, Mariappan R, Ebinu J, MengY, et al. Serum lactate as a potential biomarker of non-glial brain tumors. J Clin Neuroscience 2015; 22: 1625-7.
14) Sawayama H, Ishimoto T, Sugihara H, Miyanari N, Miyamoto Y, et al. Clinical impact of the Warburg effect in gastrointestinal cancer (Review). Int J Oncol 2014; 45: 1345-54.
15) Xu W, Mellergård P, Ungerstedt U, Nordström CH. Local changes in cerebral energy metabolism due to brain retraction during routine neurosurgical procedures. Acta Neurochir 2002; 144: 679-83.
16) Ziser A, Friedhoff RJ, Rose SH. Prone position: Visceral hypoperfusion and rhabdomyolysis. Anesth Analg 1996; 82: 412-5.
17) Garavaglia M, Mak T, Cusimano MD, Rigamonti A, Crescini C, et al. Body mass index as a risk factor for increased serum lactate during craniotomy. Minerva Anesthesiol 2013; 79: 1132-9.
18) Meregalli A, Oliveira RP, Friedman G. Occult hypoperfusion is associated with increased mortality in hemodynamically stable, high-risk, surgical patients. Crit Care 2004; 8: R60-5.

予定脳神経外科手術における術後早期高乳酸血症の発症要因

吉川博昭[1]，西部伸一[2]，酒井大輔[3]，今西宏和[4]，大野聖加[1]，小林克江[5]，北村晶[1]

1)埼玉医科大学国際医療センター　麻酔科
2)東京都立小児総合医療センター　麻酔科
3)千葉西総合病院　麻酔科
4)富永病院　麻酔科
5)明海大学　歯学部　障害者歯科学講座

【目的】脳神経外科術後早期に，不安定な循環動態や疾患の重症度とは関連のない高乳酸血症を経験することがある．脳神経外科予定手術患者を対象とし，術後早期の高乳酸血症の発症要因と術後合併症との関連について後方視的に検討した．
【対象と方法】予定脳神経外科手術患者のうち，麻酔導入後および手術終了直前に，動脈血ガス分析で乳酸値を測定した症例を対象とした．手術終了直前の乳酸値が 2 mmol/L 以上を術後早期高乳酸血症と定義し，高乳酸血症群と正常乳酸値群に分類した．患者背景，バイタルサイン，術前合併症と術前投与薬剤，手術術式，脳腫瘍の悪性度と大きさ，手術時間，出血量，動脈血ガス分析結果，周術期カテコラミン投与，集中治療室滞在日数，術後人工呼吸，術後合併症について群間で比較し，多変量ロジスティック回帰分析を行った．
【結果】対象患者 225名のうち 49名に術後早期高乳酸血症を認めた．高乳酸血症群では，脳腫瘍手術患者の割合，手術時間，術前乳酸値，出血量が高値であった（$P < 0.05$）．多変量解析から，術前の高乳酸血症（オッズ比 27.83）と脳腫瘍手術（オッズ比 4.806）が術後早期高乳酸血症の発症要因として考えられた．脳腫瘍手術患者 89名のうち 38名が高乳酸血症群であった．高乳酸血症群では正常乳酸値群に比較して，腫瘍が有意に大きかった（1016 mm^2 [四分位範囲：545,1951 mm^2] vs. 780 mm^2 [四分位範囲：322,1107 mm^2]）（$P = 0.02$）．また，2日以上集中治療室に滞在した患者が，術後早期高乳酸血症群では正常乳酸値群よりも多かった（31 % vs. 16 %, $P < 0.05$）．
【結論】予定脳神経外科手術患者の術後早期高乳酸血症の発症要因は，術前からの高乳酸血症と脳腫瘍手術であった．術後早期高乳酸血症患者は，集中治療室滞在時間が長くなる可能性がある．

