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Comparison of Blood Lactate Concentrations in Patients with Closed Traumatic Brain Injuries after Surgical and Conservative Interventions

Topan Sugara Kiaydemak[1,2]*, Willy Adhimarta[3], Nasrullah Nasrullah[3], Andi Ihwan[3], Mulawardi Mulawardi[1], Andi Alfian Zainuddin[4], Prihantono Prihantono[1], Djoko Widodo[3], Andi Asadul Islam[3], Muhammad Faruk[1]*

[1]Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [2]Department of Surgery, Dr. Chasan Boesoirie General Hospital, Ternate, Indonesia; [3]Department of Neurosurgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [4]Department of Public Health and Community Medicine Science, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

Abstract

BACKGROUND: A major public health problem, brain injury can cause disability and death. Managing traumatic brain injury (TBI) can involve surgical interventions (e.g., evacuation and decompressive craniotomy) and/or conservative interventions without surgery (e.g., oxygenation, resuscitation, antibiotics, osmotherapy, and analgesics). Lactate, a biomarker that exerts physiological effects, is sensitive to the lack of oxygen and ischemia in organs such as the brain in both types of interventions.

AIM: The aim of our study was thus to compare lactate concentrations in patients with closed brain injuries after conservative and surgical interventions.

METHODS: In a cohort study, lactate concentration between patients with TBI in the conservative versus surgical intervention groups was analyzed using the Chi-square test, the independent t-test, and Spearman's correlation test.

RESULTS: Lactate concentrations in patients with closed brain injuries at the baseline, 24-h, and 72-h blood sampling time points did not significantly differ between conservative and surgical interventions (p > 0.05). However, reductions in lactate concentrations after 24 h and 72 h did significantly differ between the intervention groups, despite being more reduced in surgical interventions ($\rho = 0.001$) than in conservative ones ($\rho = 0.002$). Lactate concentrations were also significantly lower after 24 h and 72 h in the surgical intervention group for patients with epidural hematoma (epidural hematoma [EDH], p = 0.001) than ones without EDH ($\rho < 0.001$).

CONCLUSION: Lactate concentration is a reliable prognostic predictor for assessing the severity of brain injury other than the Glasgow coma scale, another common clinical predictor.

Introduction

Traumatic brain injury (TBI) is a public health problem that can lead to disability and death as well as long-term adverse societal and economic impacts [1]. Closed brain injury is a type of head trauma that pushes brain tissue against the fragments of the skull that are still intact after the traumatic incident [2].

Managing TBI can involve surgical interventions (e.g., evacuation and decompressive craniotomy) and/or conservative interventions without surgery (e.g., oxygenation, resuscitation, antibiotics, osmotherapy, and analgesics) [3], [4]. Decompressive craniotomy is an intervention in which a part of the skull is removed and the dura mater is expanded to allow the brain to swell without crushing it or causing herniation [3].

In some borderline cases of brain injury, it is possible to conduct conservative interventions to postpone surgical interventions. Managing brain injury is focused mainly on preventing secondary brain injury, elevated intracranial pressure, and reduced intracranial pressure. One of the conservative intervention modalities is head elevation at 15–30° to decrease intracranial pressure without reducing cerebral perfusion pressure [5].

As such, lactate is a sensitive biomarker of intracerebral metabolic changes. The incidence of ischemia after brain injury is responsible for increased lactate concentration. Brain injury with more severe level leads to higher concentrations of lactate [6], [7].

Research on TBI calls for an extensive, circumspect understanding of outcome variability, the relationship between the severity of initial traumatic incidence and outcomes, and the consideration that brain injury is a dynamic process. For those reasons, we aimed to compare lactate concentrations in closed brain injuries among patients with TBI involving brain

hemorrhaging after surgical or conservative intervention. Our findings are expected to inform the management of closed brain injuries with hemorrhaging that refers to lactate concentration as a clinical biological predictor aside from the Glasgow coma scale (GCS), another commonly used clinical parameter of the severity of brain injury.

Methods

Our study was an observational cohort study conducted at Dr. Wahidin Sudirohusodo Hospital in Makassar, Indonesia, from October 2019 to February 2020. Our Institutional Review Board approved all protocols in this study (number 229/UN4.6.4.5.31/PP36/2021).

Population and sample

Screening potential participants for the study referred to various inclusion, exclusion, and dropout criteria. Six inclusion criteria were adopted: (1) suffering from closed brain injuries with brain hemorrhaging from previous traumatic incidents as indicated by head computed tomography (CT) scans, (2) adhering to therapeutic procedures, (3) being 18–65-years-old, (4) suffering from brain injury for <24 h, (5) having no previous surgical intervention for TBI, and (6) signing the informed consent form. By contrast, three exclusion criteria were adopted: (1) suffering from severe complications that can lead to impairments in other organs (e.g., thoracic trauma, abdominal trauma, multiple fracture, or surgical intervention in other organs), (2) having no hemodynamic impairments, and (3) suffering from primary systemic diseases (e.g., diabetes mellitus, kidney disease, and chronic obstructive pulmonary disease).

Blood sampling

After a physical examination, head CT scan, and laboratory tests, blood samples were taken from the capillaries and veins of patients at three time points: (1) upon admission at the accident and emergency unit after diagnosis following examinations of the head CT scan (baseline), (2) 24 h after conservative or surgical intervention, and (3) 72 h after conservative or surgical intervention. Lactate concentrations are presented in this paper as M ± SD (mmol/L).

Data analysis

Lactate concentration between patients with TBI in the conservative versus surgical intervention groups at the three blood sampling time points (i.e., at baseline, at 24 h, and at 72 h) was analyzed using the independent t test, the Chi-square test, and an analysis of variance. Results of the statistical tests were considered to be significant at $\rho < 0.05$. All data were processed using Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Seventy patients with TBI met the study's criteria: 35 in the surgical intervention group and 35 in the conservative intervention group. Table 1 presents the results of the univariate analysis of the patients' characteristics by sex and by type of intervention.

Table 1: Proportions of patients with TBI by sex in the two intervention groups

Sex	Intervention group	
	Conservative n (%)	Surgical n (%)
Male	22 (62.9)	27 (77.1)
Female	13 (37.1)	8 (22.9)
Total	35 (100)	35 (100)

TBI: Traumatic brain injury.

As shown in Table 2, the mean age of patients in the conservative intervention group, 37.2 ± 17.8 years, differed significantly from the mean age in the surgical intervention group, 27.5 ± 14.5 years ($\rho = 0.018$).

Table 2: Mean age and GCS scores of patients with TBI by intervention group according to the independent t-test

Variable	Intervention group	n	M	SD	ρ
Age	Conservative	35	37.2	17.8	0.018
	Surgical	35	27.5	14.5	
GCS	Conservative	35	10.5	2.9	0.592
	Surgical	35	10.8	2.4	

TBI: Traumatic brain injury, GCS: Glasgow coma scale.

Table 3 and Figure 1 present a comparison of lactate concentrations at the three blood sampling time points (i.e., baseline, after 24 h and after 72 h) after conservative and surgical interventions using the independent t-test.

Table 3: Comparison of lactate concentrations among patients with TBI at three blood sampling time points between the intervention groups according to the independent t-test

Blood sampling time point	Intervention group	n	M	SD	ρ
Baseline	Conservative	35	2.3	1.3	0.320
	Surgical	35	2.6	0.8	
After 24 h	Conservative	35	2.2	1.11	0.575
	Surgical	35	2.3	0.8	
After 72 h	Conservative	35	1.5	0.7	0.083
	Surgical	35	1.7	0.6	

TBI: Traumatic brain injury.

Table 4 and Figure 2 show that the conservative and surgical intervention groups, lactate concentrations became significantly reduced across the three blood sampling points, whereas the overall mean lactate concentration between the intervention groups did not significantly differ ($\rho = 0.002$ and $\rho = 0.001$, respectively).

Table 4: Comparison of lactate concentrations among patients with TBI by intervention group at three blood sampling time points according to an ANOVA

Intervention group	Blood sampling time point	n	M	SD	ρ
Conservative	Baseline	35	2.3	1.3	0.002
	After 24 h	35	2.21	1.11	
	After 72 h	35	1.47	0.69	
Surgical	Baseline	35	2.6	0.84	<0.001
	After 24 h	35	2.34	0.83	
	After 72 h	35	1.74	0.62	

TBI: Traumatic brain injury, ANOVA: Analysis of variance.

Lactate concentrations in patients with epidural hematoma (EDH)

A subsequent analysis was conducted to assess the number and proportions of patients with and without EDH - that is, a blood clot between the skull and brain. As shown in Table 5, results placed 23 patients in the EDH group (32.9%) and 47 in the non-EDH group (67.1%).
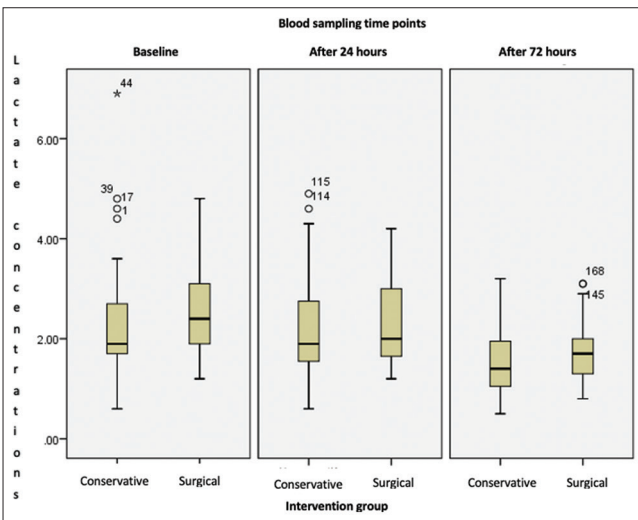

Figure 1: Lactate concentrations of patients with traumatic brain injury at baseline, after 24 h, and after 72 h between the intervention groups

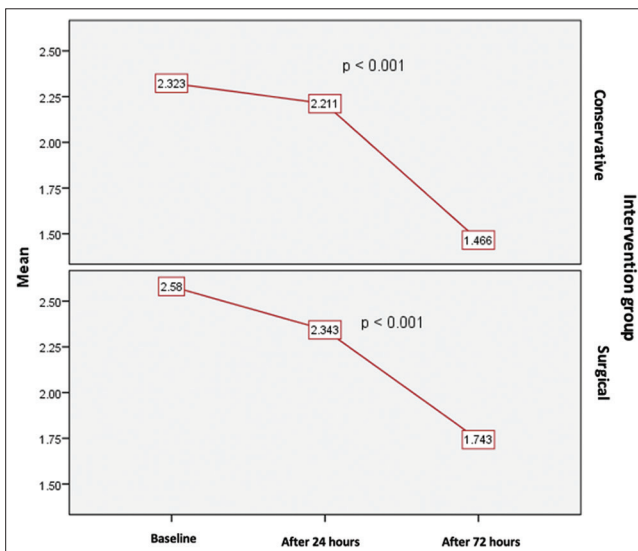Table 6 showed that mean lactate concentrations among patients with EDH did not

Figure 2: Lactate concentrations in patients with traumatic brain injury by intervention group at three blood sampling time points

Table 5: Number and proportion of patients in the EDH and the non-EDH groups

Diagnostic outcome	n	%
EDH	23	32.9
Non-EDH	47	67.1
Total	70	100.0

EDH: Epidural hematoma.

significantly differ between the intervention groups at baseline (ρ = 0.162), after 24 h (ρ = 0.158), and after 72 h (ρ = 0.382).

Table 6: Comparison of lactate concentrations of patients with EDH by blood sampling time points between the conservative and surgical intervention groups according to the independent t-test

Blood sampling time point	Intervention group	n	M	SD	ρ
Baseline	Conservative	7	1.7	0.83	0.162
	Surgical	16	2.0	0.44	
After 24 h	Conservative	7	1.5	0.69	0.158
	Surgical	16	1.7	0.33	
After 72 h	Conservative	7	1.1	0.56	0.382
	Surgical	16	1.5	0.48	

EDH: Epidural hematoma.

Table 7 and Figure 3 showed mean lactate concentrations among patients with EDH in the conservative intervention group differed significantly across the three blood sampling time points (ρ = 0.032), with a particularly significant reduction of lactate concentration after 72 h.

Table 7: Comparison of lactate concentrations among patients with EDH by intervention group at three blood sampling time points according to an ANOVA

Intervention group	Blood sampling time point	n	M	SD	ρ
Conservative	Baseline	13	2.1	1.17	0.032
	After 24 h	13	2.4	1.01	
	After 72 h	13	1.4	0.58	
Surgical	Baseline	16	3.0	0.84	0.001
	After 24 h	16	2.8	0.79	
	After 72 h	16	2.6	0.57	

EDH: Epidural hematoma, ANOVA: Analysis of variance.

Lactate concentrations in patients without EDH

Table 8 showed that mean lactate concentrations among patients without EDH did not
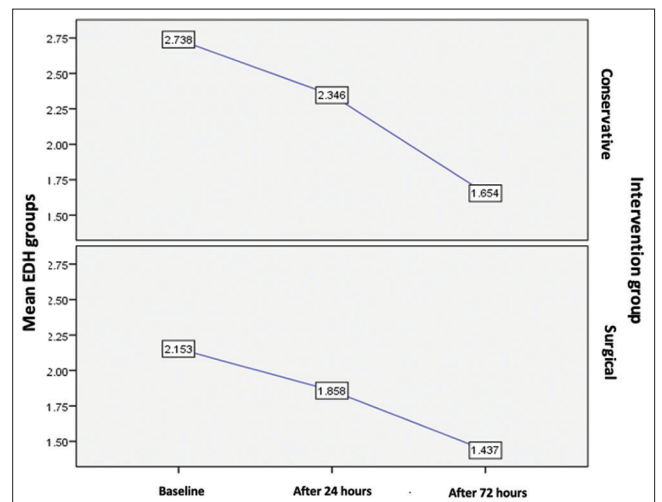

Figure 3: Lactate concentrations of patients with EDH in the conservative and surgical intervention groups at three blood sampling time points

Table 8: Comparison of lactate concentrations among patients without EDH at three blood sampling time points between the conservative and surgical intervention group according to the independent t-test

Blood sampling time point	Intervention group	n	M	SD	p
Baseline	Conservative	28	2.5	1.34	0.001
	Surgical	19	3.1	0.79	
After 24 h	Conservative	28	2.4	1.14	0.010
	Surgical	19	2.9	0.76	
After 72 h	Conservative	28	1.5	0.69	0.001
	Surgical	19	2.1	0.56	

EDH: Epidural hematoma.

significantly differ between the intervention groups at baseline (ρ = 0.001), after 24 h (ρ = 0.010), and after 72 h (0.001).

Table 9: Lactate concentrations among patients with TBI in the non-EDH group according to an ANOVA

Intervention group	Blood sampling time point	n	M	SD	ρ
Conservative	Baseline	22	2.4	1.33	0.018
	After 24 h	22	2.1	1.13	
	After 72 h	22	1.5	0.76	
Surgical	Baseline	16	2.1	0.84	0.001
	After 24 h	16	1.8	0.79	
	After 72 h	16	1.3	0.57	

TBI: Traumatic brain injury, EDH: Epidural hematoma, ANOVA: Analysis of variance.

Table 9 and Figure 4 showed patients in the conservative intervention group, ones with EDH showed concentrations that differed significantly across the time points (ρ = 0.018), whereas ones without EDH showed a significant reduction after 72 h relative to the baseline. Meanwhile, among patients in the surgical intervention group, ones with EDH also showed significantly different lactate concentrations at the three time points (ρ = 0.001), whereas ones without EDH showed a significant reduction in concentrations at the 72-h and 24-h time points relative to the baseline.
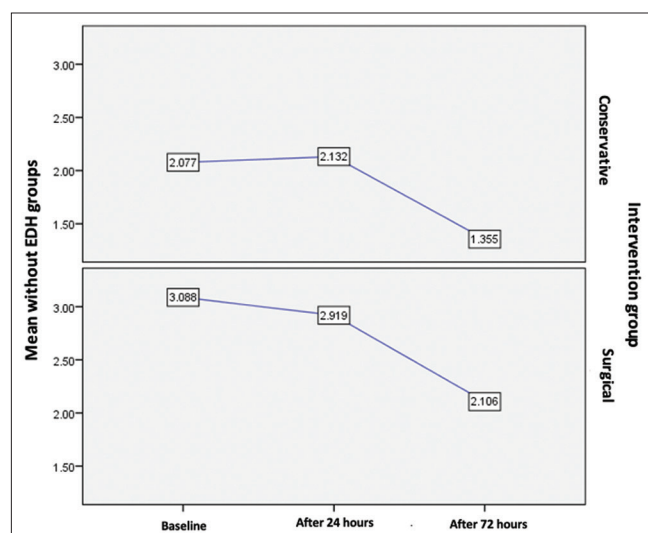

Figure 4: Serial alterations of lactate concentrations among patients without EDH by intervention group at three blood sampling time points

Discussion

According to results in Table 1, the proportion of male patients with TBI (70%) exceeded that of female

patients with TBI (30%), although the distribution of such patients between the conservative and surgical intervention groups did not differ significantly (ρ > 0.05). In the adult population, the greater tendency to perform outdoor activities among men than women raises men's risk of experiencing traffic accidents, which is the leading cause of brain injury in developing countries (42.4%) [8], [9]. In developed countries, where the top cause of brain injury is falls, men also have a greater risk of brain injury than women [4], [10].

In our study, the mean GCS score among patients in the surgical and conservative intervention groups was 10–11 points. On the GCS, which we administered after confirming consciousness following oxygenation and resuscitation, the accuracy of measurement pivots on the diagnosis and type of initial treatment.

As shown in Table 3, lactate concentration at the three time points between the groups decreased consistently but not to a statistically significant degree. Those findings are in line with the result of Glenn *et al.* also found that patients with TBI with acute brain injury had altered lactate concentrations at the cutoff level of 2.0–4.0 mmol/L, which indicated increased anaerobic glycolysis and brain hypoxia (i.e., inadequate blood oxygen levels) [7].

Initial brain injury after trauma can directly damage tissue, cerebral blood flow, and metabolism, which, in turn, can result in ischemic manifestations along with the accumulation of lactate due to the increase of anaerobic glycolysis and the elevated capillary permeability with local edema. Because anaerobic metabolism cannot sufficiently maintain cellular energy, it prompts a cascade of ATP and failures in the ion pumps of the membranes, a pump system that needs energy [7], [11]. Another factor of increased lactate concentration is primary brain injury, due to brain tissue damage caused directly by trauma, or secondary brain injury, due to a series of changes in more complex conditions (e.g., increased intracranial pressure, perfusion disturbance, metabolism disruption, inflammation, release of neurotransmitters of excitation, and ionic imbalance) that worsen metabolism processes in the brain, as demonstrated by the production of lactate in the brain that enter the circulation system and, in turn, cause hyperlactatemia [11].

Our study revealed no significant difference in lactate concentrations between the three blood sampling time points among patients with EDH in the conservative versus surgical intervention groups, as shown in Table 6. That finding is consistent with the findings Cureton *et al*. [12] that blood lactate concentrations rose by 23.7% from the baseline shortly after traumatic acute subdural hematoma but returned to normal levels within 24–36 h as the subdural hematoma properly recovered.

As shown in Figure 1, our study also revealed significantly reduced lactate concentrations among

patients with TBI at the 24 h and 72-h blood sampling time points compared to the baseline in the conservative intervention group, from 1.7 mmol/L (i.e., baseline) to 1.5 mmol/L ($\rho > 0.05$). By contrast, patients in the surgical intervention group, who underwent either evacuation craniotomy or decompressive craniotomy, had more severe brain injury than their peers in the conservative intervention group. Furthermore, the relationship between blood lactate concentration and severity of injury was significant; higher concentrations of lactate signified a greater level of brain injury, whereas a higher level of parenchymal damage indicated higher a lactate concentration [6], [7].

Figure 2 presents a comparison of lactate concentrations between the conservative and surgical intervention groups, including a significant reduction at the 24-h and 72-h blood sampling time points relative to the baseline in the conservative intervention group from 2.3 mmol/L to 1.5 mmol/L ($\rho > 0.05$). That outcome means that lactate concentration can be reduced by conservative intervention. In particular, management involving the adequate treatment of oxygenation and resuscitation, antibiotics, mannitol, and analgesics can prevent the incidence of secondary brain injury and its adverse effects.

Multiple studies have shown that inflammatory responses in the brain due to physical trauma play a significant role in secondary injury due to the inhibition of inflammatory reactions that prompted the prevention of secondary injury and improved outcomes of patients with TBI [13]. That inflammatory process occurs shortly after trauma, as demonstrated by the activation of mediating substances that dilate blood vessels, reduce blood flow, and elevate the permeability of capillaries. In turn, those effects lead to the accumulation of fluids (i.e., edema) and leukocytes at the site of trauma. Mannitol has proven to be effective in treating cerebral edema in patients with elevated intracerebral pressure (ICP). In a prospective study of such patients, the administration of bolus doses of mannitol at 0.25–0.5 mg/kg of body weight reduced ICP in up to 50% of patients with TBI [14].

The comparison of lactate concentration measured at the three blood sampling time points revealed a non-significant reduction 24 h following surgical intervention, from 2.5 to 2.3 mmol/L, but a significant reduction ($\rho > 0.05$) to 1.7 mmol/L after 72 h. Lactate concentration at the three time points in the surgical intervention group showed consistent reductions. As a result, lactate concentration seems to be a reliable predictor for assessing the outcomes of interventions for closed brain injury. Its non-significant reduction 24 h after surgical intervention may have been due to the damage of brain cells, depending upon the severity of brain injury.

Our study showed that surgical intervention reduced lactate concentration in patients with brain hemorrhaging. Evacuation craniotomy and decompressive craniotomy play important roles in reducing high intracranial pressure due to brain edema and the congestion of vena cerebri and, beyond that, in improving the perfusion and metabolism of the brain to normal levels. The elevation or reduction of lactate concentration may occur after either surgical or conservative intervention due to multiple, potentially overlapping factors, including the severity of brain injury, hypermetabolism, persistent hyperglycemia, inflammatory reactions, excitement of amino acids, free radicals, and hormonal reactions [15], [16].

Last, our results also indicate a significant relationship between lactate concentration and type of hemorrhaging in the brain among patients with TBI, particularly ones without EDH, in both the surgical and conservative intervention groups at baseline ($\rho = 0.001$), after 24 h ($\rho = 0.010$), and after 72 h ($\rho < 0.001$).

Conclusion

Lactate concentration is a reliable prognostic predictor for assessing the severity of brain injury other than the GCS, another common clinical predictor.

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