CLINICAL STUDY

Normalization of blood lactate as early end-point of polytrauma treatment

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Abstract: *Background:* The main aim of the early treatment of polytrauma is recovery of patient's physiological functions. The early achievement of therapeutic goals, mainly adequate tissue perfusion and repayment of oxygen debt, are postulated.

The aim of the study was to confirm whether blood lactate level as a quantifier of oxygen deficit, as well as normalization of blood lactate level within the first 24 hours, have an impact on the mortality and morbidity of seriously injured patients.

Methods: Sixty-nine mechanically ventilated patients with a severe trauma and organ dysfunction defined according to SOFA score and ISS >17, age >15 years, were enrolled into this retrospective study. 8 patients died within first 24 hours, 8 patients did not reach serum lactate level above 2 mmol/l on admission to hospital. The hypothesis that normalization of serum lactate level within 24 hours is related to lower mortality and morbidity, was assessed. Reduced mortality and morbidity were represented by lower severity of multi-organ dysfunction, the highest SOFA score during hospitalization, lower incidence of sepsis, number of days in ICU and artificial ventilation.

Results: The association between severity of multi-organ failure (p=0.0006), mortality (p=0.0022) and repayment of oxygen debt was confirmed. Hypothesis of sepsis incidence was not confirmed (p=0.34). The association between number of days on artificial ventilation and number of days in ICU to repayment of oxygen debt was not confirmed either. Multivariate significant factors were age, GCS, ISS and SOFA score on patient's admission.

Conclusion: The patients, who repaid oxygen debt within first 24 hours, have lower morbidity and mortality *(Tab. 6, Ref. 19)*. Full Text in PDF *www.elis.sk.*

Key words: polytrauma, lactate, MOF, SOFA score.

Abbreviations: APACHE – Acute Physiology and Chronic Health Evaluation; BE adm – Base Excess et admission; FIO_2 – Fractional Inspired Oxygen; GCS – Glasgow Coma Scale; ICU – Intensive Care Unit; ICU days – days of ICU stay; ISS – Injury Severity Score; LACT clear – Lactate Clearance; LACT adm – serum lactate at admission; LACT 24H – serum lactate over first 24 hours; MAP – Mean Arterial Pressure; MOD – Multiple Organ Dysfunction; MOF – Multiple Organ Failure; PaO_2 – arterial oxygen tension; RTS – Revised Trauma Score; SOFA – Sequential Organ Failure Assessment; TRISS – Trauma Injury Severity Score; AV days – days of artificial ventilation.

Polytrauma patients have common systemic pathophysiological consequences. Hypoperfusion leads to shock with dysfunction of macro and microcirculation. The presence of oxygen debt results in an inflammatory cascade that can lead to multiorgan dysfunction. From this point of view, rapid identification and restoration of oxygen debt are key end-points of severe trauma treatment, which can lead to better outcome of polytrauma.

Historically, we used clinical signs to identify shock: heart rate, blood pressure, urine output, which is not adequate to asses imbalance between oxygen delivery and metabolic demands of tissue, likewise cardiac output. Occult hypoperfusion can be present also in the case of normal vital signs. In the case of tissue hypoxia, lactate levels increase. Lactate as an adaptive mechanism of intermediate metabolism allows human organism to survive oxygen debt. Hyperlactatemia but better lactate clearance correlate with mortality and MOF in different types of shock (1, 2, 3).

The aim of our study was to asses whether lactate and its normalization in blood within first 24 hours have impact on morbidity and mortality of severe trauma patients.

The management of trauma patients requires timely intervention and damage control in an attempt to achieve adequate hemodynamic parameters and systemic perfusion.

Methods

We retrospectively studied polytrauma patients at the Department of anesthesiology and intensive medicine, Faculty Hospital Nitra, who were admitted between January 1st 2008 and December 31st 2009. During this period there were 124 polytrauma patients

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Tab. 1. The SOFA scoring system (PaO$_2$ arterial oxygen tension. FIO$_2$ fractional inspired oxygen. MAP - mean arterial pressure).

SOFA score	0	1	2	3	4
Respiration				≤200	
PaO$_2$/FiO$_2$ (mmHg)	>400	≤400	≤300	With respiratory support	≤100
Coagulation					
Platelets x10³/mm³	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin (mg/dl)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12
(umol/l)	<20	20–32	33–101	102–204	>204
Cardiovascular				dopamine >5	dopamine >15
hypotension	No hypotension	MAP<70mmHg	dopamine ≤5 or dobuta-min (any dose)	or epinephrine ≤0.1 or norepinephrine ≤0.1	or epinephrine >0.1 or norepinephrine >0.1
Central nervous system					
Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal					
creatinin(mg/dl)	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
(umol/l)	<110	110–170	171–299	300–440	>440
or urine output				or < 500ml/day	or<200ml/day

Tab. 2. Patients characteristics.

Variable			Descriptive Statistics (trauma1)				
	Valid N	Mean	Confidence -95.000 %	Confidence 95.000	Minimum	Maximum	Std.Dev
age	69	39.04348	34.42715	43.65981	16.0000	87.0000	19.21659
GCS	68	9.26471	8.08881	10.44060	3.0000	15.0000	4.85804
ISS	69	37.23188	33.03487	41.42890	17.0000	75.0000	17.47111
LACT adm	68	3.81765	3.38145	4.25384	1.20000	7.80000	1.80207
LACT24h	61	2.13410	1.85893	2.40927	0.90000	7.40000	1.07443
BEadm	68	-5.37353	-6.50203	-4.24503	-15.5000	8.30000	4.66222
APACHE	68	15.20588	13.43626	16.97550	0.00000	36.0000	7.31092
SOFA adm	69	6.27536	5.65480	6.89592	1.00000	12.0000	2.58323
SOFAmax	61	6.49180	5.69329	7.29031	1.00000	16.0000	3.11781
ICUdays	69	15.31884	11.76251	18.87518	0.00000	60.0000	14.80411
AVdays	69	10.33333	7.56669	13.09998	0.00000	45.0000	11.51682

Tab. 3. Mann-Whitney's U Test by variable lactate clearance.

variable	Mann-Whitney U Test (trauma1) By variable lactate clear Marked tests are significant at p <.05000									
	Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level	Z adjusted	p-level	Valid N Group 1	Valid N Group 2	2*1 sided exact p
SOFAmax	591.000	840.000	156.000	**-3.43076**	**0.000602**	**-3.45325**	**0.000554**	29	24	**0.000430**
ICU days	759.500	671.500	324.500	-0.41991	0.6745551	-0.42038	0.674210	29	24	0.677060
AV days	703.000	728.000	268.000	-1.42948	0.152866	-1.43432	0.151482	29	24	0.156650

admitted, and 69 of them fulfilled the inclusion criteria. Patients were eligible for inclusion when ventilated, with ISS >17, SOFA score >2. The exclusion criterion was: age below 17. Eight patients died within first 24 hours, 8 patients did not reach serum lactate level above 2 mmol/l on admission to hospital. A decline of serum lactate level was assessed. Lactate measurements were performed using arterial blood samples by standard colorimetric laboratory method. Serum lactate level below 2 mmol/l was considered as a repayment of oxygen debt. The hypothesis, thatnormalization of serum lactate level within 24 hours is related to lower mortality and morbidity, was assessed. Reduced mortality and morbidity were represented by lower severity of multiorgan dysfunction, the highest SOFA score during hospitalization, lower incidence of sepsis, number of days in ICU and mechanical ventilation.

We collected demographic data, blood lactate levels at admission and after 24 hours, ICU days and days of artificial ventilation (AV days). Each patient was calculated for Glasgow Coma Scale (GCS), Injury Severity Score (ISS) and Acute Physiology and Chronic Evaluation (APACHE) score at admission. Severity Organ Failure Assessment (SOFA) scores were calculated at admission and then every day and a maximum during staying SOFA score was recorded (Tab. 1) and characteristics of the patients are shown on Table 2.

Used statistic methods: Mann–Whitney's U test to compare SOFA score, ICU stay, AV days in two groups categorized according to normalization of blood lactate up to 24 hours. Statistical significance was accepted to respond to p. Fisher's exact test was used on categorical data to asses the correlation of sepsis and

Tab. 4. Fisher's exact test of dependency of mortality and lactate normalization.

	2x2 tab (lact.clear-exitus)		
	Column 1	Column 2	Row Totals
Frequencies. row 1	17	7	24
Percentage of	**32.075%**	**13.208**	**45.283%**
Frequencie. row 2	29	0	29
Percentage of	**54.717%**	**0.000%**	**54.717%**
Column totals	46	7	53
Percentage of	**86.792%**	**13.208%**	
Chi-square (df =1)	9.75	p= .0018	
V-square (df =1)	9.56	p= .0020	
Yates corrected Chi-square	7.37	p=.0066	
Phi-square	18388		
Fisher exact p.one -tailed	7.37	p=.0022	
Two-tailed		p=.0022	
McNemarChi-square(A/D)	15.06	p=.0001	
Chi/square (B/C)	12.25	P=.0005	

Tab. 5. Fisher's exact test of incidence of sepsis related to lactate normalization.

	2x2 tab (lact.clear-sepsa)		
	Column 1	Column 2	Row Totals
Frequencies. row 1	11	13	24
Percentage of	**20.755%**	**24.528%**	**45.283%**
Frequencie. row 2	16	13	29
Percentage of	**30.189%**	**24.528%**	**54.717%**
Column totals	27	26	53
Percentage of	**50.943%**	**49.057%**	
Chi-square (df =1)	46	p= .4984	
V-square (df =1)	45	p= .5025	
Yates corrected Chi-square	16	p=.6884	
Phi-square	00865		
Fisher exact p.one -tailed		p=.3444	
Two-tailed		p=.5857	
McNemarChi-square(A/D)	04	p=.8383	
Chi/square (B/C)	14	p=.7103	

surviving with early normalization of lactate within first 24 hours. Multivariate analysis of covariants was done.

Results

The association between severity of multi-organ failure and normalization of lactate level <2 mmol/l in the first 24 hours of polytrauma patients was confirmed by the Mann–Whitney's rank-sum test. The level of statistical significance was p<0.05 (Tab. 3).

Significant correlation between days of ICU stays and days on artificial ventilation was not confirmed. Dependency of mortality and lactate normalization was confirmed with Fisher's exact test (p=0.0022) (Tab. 4).

Hypothesis of the incidence of sepsis related to lactate normalization was not confirmed by Fisher's exact test (p=0.34) (Tab. 5).

Multivariate significant factors were age, ISS and SOFA score on patient's admission. On the contrary, serum lactate at admission, base excess and number of transfusions over the first 24 hours were not multivariable significant (Tab. 6).

Discussion

Though management of severe trauma during last period has changed, morbidity and mortality is still high. The mechanisms underlying morbidity and mortality in trauma patients are divided into (1) direct trauma associated alterations (e.g., organ injury, hemorrhage, and/or severe traumatic brain injury) and (2) secondary or delayed alterations, such as overwhelming inflammatory reactions, deterioration of microcirculation, and multiple organ failure (MOF). Currently, MOF is thought to be responsible for up to 80 % of all deaths in the intensive care unit (4). Multiple organ dysfunction is known to be the leading cause of mortality in the patients survived the initial hours after trauma (5).

The early achievement of therapeutic goals, mainly early restoration of perfusion and repayment of oxygen debt are crucial to prevent MOF, which is the main cause of morbidity and mortality not only in polytrauma, but also in other critically ill patients.

Tab. 6. Multivariate tests.

Effect		Value	F	Hypothesis df	Error df	Sig
Intercept	Pillai´s Trace	.018	.261[a]	3.000	42.000	.853
	Wilk´s Lambda	.982	.261[a]	3.000	42.000	.853
	Hotelling´s Trace	.019	.261[a]	3.000	42.000	.853
	Roy´s Largest Root	.019	.261[a]	3.000	42.000	.853
Age	Pillai´s Trace	.318	6.524[a]	3.000	42.000	.001
	Wilk´s Lambda	.682	6.524[a]	3.000	42.000	.001
	Hotelling´s Trace	.466	6.524[a]	3.000	42.000	.001
	Roy´s Largest Root	.466	6.524[a]	3.000	42.000	.001
GCS	Pillai´s Trace	.243	4.499[a]	3.000	42.000	.008
	Wilk´s Lambda	.757	4.499[a]	3.000	42.000	.008
	Hotelling´s Trace	.321	4.499[a]	3.000	42.000	.008
	Roy´s Largest Root	.321	4.499[a]	3.000	42.000	.008
ISS	Pillai´s Trace	.185	3.172[a]	3.000	42.000	.034
	Wilk´s Lambda	.815	3.172[a]	3.000	42.000	.034
	Hotelling´s Trace	.227	3.172[a]	3.000	42.000	.034
	Roy´s Largest Root	.227	3.172[a]	3.000	42.000	.034
Transf	Pillai´s Trace	.138	2.240[a]	3.000	42.000	.098
	Wilk´s Lambda	.862	2.240[a]	3.000	42.000	.098
	Hotelling´s Trace	.160	2.240[a]	3.000	42.000	.098
	Roy´s Largest Root	.160	2.240[a]	3.000	42.000	.098
Lakta-p	Pillai´s Trace	.033	.471[a]	3.000	42.000	.704
	Wilk´s Lambda	.967	.471[a]	3.000	42.000	.704
	Hotelling´s Trace	.034	.471[a]	3.000	42.000	.704
	Roy´s Largest Root	.034	.471[a]	3.000	42.000	.704
BE_prij	Pillai´s Trace	.143	2.330[a]	3.000	42.000	.088
	Wilk´s Lambda	.857	2.330[a]	3.000	42.000	.088
	Hotelling´s Trace	.166	2.330[a]	3.000	42.000	.088
	Roy´s Largest Root	.166	2.330[a]	3.000	42.000	.088
SOFA_p	Pillai´s Trace	.382	8.664[a]	3.000	42.000	.000
	Wilk´s Lambda	.618	8.664[a]	3.000	42.000	.000
	Hotelling´s Trace	.619	8.664[a]	3.000	42.000	.000
	Roy´s Largest Root	.619	8.664[a]	3.000	42.000	.000
Lact_clear	Pillai´s Trace	.228	4.130[a]	3.000	42.000	.012
	Wilk´s Lambda	.772	4.130[a]	3.000	42.000	.012
	Hotelling´s Trace	.295	4.130[a]	3.000	42.000	.012
	Roy´s Largest Root	.295	4.130[a]	3.000	42.000	.012

[a] Exact statistic [b]Design: intercept +age + GCS+ISS + transf + lacta_prij + BE_prij + SOFA_p +Lact_clear

Resuscitation end-points allow the physician to rapidly identify a perturbation between oxygen delivery and consumption. End-points allow uniformity to assess the adequacy of resuscita-

tion: preventing under- and over resuscitation and act as a basis to compare outcome measures in resuscitation trials.

As in other studies, we used blood lactate level as metabolic correlate of oxygen debt and stress metabolism together with effective lactate clearance as therapeutic end-point. Blood lactate levels are closely related to outcome in critically ill patient (1, 2, 3, 6, 7, 8, 9). We also showed that early normalization of lactate level is significantly connected with lower morbidity and mortality in polytrauma.

Consistently with previous literature (10, 11), we defined organ dysfunction according to the SOFA score definitions. There are three classes of scoring systems available in the evaluation of trauma patients in the intensive care unit (ICU): those based on physiological parameters (APACHE score), Simplified Acute Physiology Score, and Revised Trauma Score (RTS)], those based on definition of the entity and localization of trauma (ISS) , and those considering either anatomical lesions or deranged physiological parameters – Trauma Injury Severity Score (TRISS).

The main limitations of these scoring systems in evaluating critically ill patients are: some authors have emphasized that the prognostic value of the available scoring systems is strictly dependent on treatment. Two patients with a similar severity of illness might have greatly differing scores based on appropriate or inadequate resuscitation. The prognosis assessment based on scores is only applicable to a study population, not to an individual patient. The components of some scores are not easily obtained. An ideal prognostic index should be based on variables available by standard routine examinations, applicable to heterogeneous patient groups, readily and widely measurable, and not related to personal judgments or affected by the treatment. Majority of current severity scoring is based on an estimation of mortality. A treatment that does not affect mortality may still be effective: if morbidity rather than mortality is considered as the major outcome measure, the impact of intensive care on quality of life, length of stay in the ICU, costs, etc. can be evaluated. SOFA score is composed of scores from six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological) graded from 0 to 4 according to the degree of dysfunction/failure. The SOFA score can reliably describe organ dysfunction in trauma patients. Regular and repeated scoring may be helpful in identifying categories of patients at major risk of prolonged ICU stay or death.

SOFA score better correlates with physiological changes and the therapeutic response than anatomical scores. SOFA score is common for septic patients but lots of authors use it for scoring of MOF in trauma patients over time (10, 11). SOFA score quantifies and describes the evolution of organ dysfunction over time (12, 13), and has been validated in trauma patients. The incidence of MOF after injury in recent studies differs between 5–25 % (10). In Ulvik study (14) half of patients had MOF. Differences in ICU admission policies and case-mix may complicate direct comparison with other studies. In addition, the application of different scoring systems for assessment of MOF makes direct comparison difficult. In our hospital, trauma patients without severe organ failure are usually treated outside the ICU.

To assess the degree severity of MOF we use the highest number during hospitalization in ICU. In our study significant association between normalization of lactate within first 24 hours and severity of MOF was confirmed by the Mann-Whitney's rank-sum test. Multivariate significant factors were GCS, ISS and also SOFA score at admission. Also Antonelli showed that surviving patients had lower SOFA score at admission as patients who died (15). The dependency of mortality onthe early normalization of blood lactate was confirmed by Fisher's exact test.

There is a therapeutic window when hypoxic cells are able to revert to normal state without damage. This hypothesis was confirmed also by Shoemaker (16) with supra-normal hemodynamic support, because his interventions were tight with surgical insult. Also Rivers (17) with septic patients ScvO2 changes and lactate in interval a few hours was effective in time.

We have to understand lactate as an adaptation to an anaerobic condition, but also other processes may induces high serum lactate, like stimulation of aerobic glycolysis by catecholamines in stress metabolism, which helps organism to survive (18). But our intervention must be in the window of time while metabolic failure is not present. The time to intervention becomes relevant: early and effective treatment may allow the cell to revert to a normal state, as long as the oxygen machinery is intact. Once the mitochondria are deranged, energy failure occurs even in the presence of normoxia. The lactate increase in critically ill patients may therefore be viewed as an early marker of a potentially reversible state (19).

Conclusion

Early normalization of blood lactate level is related to low grade of MOF and lower mortality of seriously injured patients. Targeted resuscitation strategy after severe trauma should comprise of early identification of oxygen debt and use of resuscitation end point – blood lactate level to achieve better outcomes of patients.

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