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Serial measurements of blood lactate and early outcome of neonatal hypoxic ischemic encephalopathy after therapeutic hypothermia

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Abstract

Objective: To assess predictive value of blood lactate measurements in infants during therapeutic hypothermia due to moderate to severe asphyxia in relation to early outcome.

Patients and methods: We retrospectively evaluated records of 47 full-term newborns that underwent therapeutic hypothermia after moderate to severe perinatal asphyxia from January 2011 to December 2015. Criteria for whole body cooling were established according to Bristol Cooling Protocol UK, including clinical signs of HIE using Sarnat&Sarnat scale and aEEG. Blood samples were taken from venous catheter in recommended intervals (3, 6, 12, 24, 48, 72 hours). Early outcome is evaluated on the base of survival rate, neurologic status at discharge and presence of post hypoxic lesions confirmed with brain MRI. All investigated infants were categorized into 3 groups 1) Infants with normal brain MRI finding and normal neurologic examination at the discharge; 2) Infants with abnormal brain MRI finding at the discharge (with 2 subgroups depending of neurological status at the discharge); 3) Newborns with lethal outcome.

Results: Mean value of blood lactate at admission for all subjects was 11.87 ± 5.41 (3.2- 24.0), without statistical difference between groups. Three hours after beginning of cooling mean value was 8.36 ± 3.70 (2.2-17.0) with statistical difference between all groups of survived infants compared to infants who died. After 6 and 12 hours mean values were 6.311 ± 3.69 and 6.269 ± 3.37 respectively with statistical difference between neurologically asymptomatic infants (including those with MRI finding interpreted as a mild lesion) compared to infants with abnormal neurological examination at the discharge and infants who died. Values of blood lactate after 24h, 48h and 72 h were 4.46 ± 2.00 (1.0–11.7), 3.60 ± 1.36 (1.6–6.9), 3.36 ± 1.93 (1.2- 9.3) respectively. After 24 h we did not find statistical difference between groups.

Conclusion: Serial measurements of blood lactate during therapeutic hypothermia in asphyxiated infants are important. Initial value of lactate is not proved to be predictive, but prompt decreasing of lactate values within 24 hours of cooling is associated with better early outcome.

Background

Hypoxic-ischemic encephalopathy (HIE) is one of the leading causes of mortality or neurodevelopmental disability among newborn infants around the world. HIE is estimated to contribute significantly in 23% of the 4 million neonatal deaths that occur annually [1]. In term neonates HIE can result in a range of motor and neurodevelopmental disabilities [2-5].

Currently, the only established therapy for neonatal encephalopathy in full-term infants is induced therapeutic hypothermia. There is clinical evidence that moderate hypothermia significantly improves survival and disability, including cerebral palsy and neurocognitive outcomes in infants with moderate to severe hypoxic–ischemic encephalopathy at 18 months of age, which persists into middle childhood [2-7], although it offers only a reduction in risk and requires a high level of neonatal intensive care support, which is not available in many lower resource settings [8].

The relationship between intrapartum asphyxia and neurological abnormalities is not clear enough. When full-term neonates suffer asphyxia during labor or delivery, some may develop HIE with outcomes ranging from complete recovery to death. Searching for predictors of outcome can facilitate parental counseling, helping to provide appropriate levels of care.

Clinical examination at discharge improves predictive value of the stage of HIE at <6 hours, for death and disability (6). Clinical examination is non-invasive tool, good to track changes state as injury involves, but requires clinical experience and may be affected by intubation, medications and hypothermia. Studies have shown that in full term infants, the best prediction of outcome is achieved by the examination at discharge [9,10].

Magnetic resonance imaging (MRI) provides excellent detail of the typical brain lesions in hypoxic-ischemic injury: lesions in the basal ganglia, thalamus and posterior limb of the internal capsule (PLIC) that are characteristic and predictive for cerebral palsy. Less commonly, infants with HIE sustain mainly white matter lesions, which are associated with later cognitive impairments [11,12].

Biomarkers have been essential topics in HIE research (13). As an early predictor within blood biochemistry, blood lactate concentration

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was used to predict severity and outcome of neonatal hypoxic ischemic encephalopathy even before the era of therapeutic hypothermia [14,15].

Lactate is produced during hypoxia and poor tissue perfusion. In absence of oxygen, aerobic metabolism through Krebs's cycle cannot be sustained, so it switches to anaerobic metabolism; oxidative phosphorylation falls and high energy metabolites as ATP fall below the critical threshold with accumulation of lactic acid [14-17]. After a latent period of at least six hours, the secondary phase includes reperfusion, cytotoxic edema, mitochondrial failure, accumulation of excitotoxins, cell death, nitric oxide synthesis, free radical damage and cytotoxic actions of activated microglia. The delayed phase is associated with encephalopathy and increased seizure activity [16,17].

We focused our attention to the prognostic value of blood lactate in newborns with HIE during therapeutic hypothermia and undertook this study to determine the role of serial lactate measurements related to the short-term prognosis.

Patients and methods

This is the retrospective study conducted in Neonatal Intensive Care Unit, Pediatric Clinic, University Clinical Center Sarajevo, which is level III NICU, referral for sick indoor patients (annual rate is approx. 6000 deliveries) and patients transferred from other smaller hospitals throughout Bosnia and Herzegovina. Study was conducted from January 2011 to December 2015. During this period 66 patients with moderate to severe asphyxia underwent therapeutic hypothermia, 47 of them fulfilled criteria for inclusion in the study. Data were collected from mother's medical history and child's medical records. Therapeutic hypothermia is provided according to Bristol Cooling Protocol Marianne Thorensen, Bristol, UK, whose principles follow original studies [2,3]. Inclusion criteria were GA > 36 weeks, Apgar score ≤ 5, 10 minutes after birth or need for resuscitation 10 minutes after birth, or pH < 7,00 or BE ≥ 16mmol/L within 60 minutes after birth, signs of moderate or severe encephalopathy using modified Sarnat&Sarnat scale. Abnormal EEG activity or seizures registered on aEEG during at least 30 minutes is used to confirm metabolic and neurologic criteria. Eighteen infants were excluded from the study: 15 infants due to incomplete medical records, 1 due to secondary hypoxia as result of severe heart defect and 2 because of GA<36 weeks. Therapeutic hypothermia started within 12 hours after birth using whole body cooling by servo control equipment (Arctic Sun) with target temperature 33,5 C during 72 hours, and gradually warming within minimally 6-8 hours. During whole body cooling infants were mechanically ventilated (target pCO2 in limits 6-7,5kPa using coefficient of correction 0,83), with analgosedation (morphine, midazolam), magnesium to maintain level 1,0 mmol/L, anticonvulsive drugs if needed, inotropic agents (dopamine, dobutamine) if needed and large spectrum antibiotics preventively. During whole body cooling newborns were not fed, intake was limited to 60 ml/kg/day. Urine output and all vital parameters were continuously monitored and recorded. aEEG is used as a tool for establishing criteria, and for monitoring of seizures activity during procedure. Blood samples, including lactate levels are taken from venous catheter in recommended intervals (3, 6, 12, 24, 48, 72 hours). Outcome is evaluated on the base of survival rate, neurologic status at discharge and presence of post hypoxic lesions confirmed with MRI of the brain, performed 1-2 weeks after cooling period.

Al investigated infants were categorized into groups:

Group 1. Infants with normal brain MRI finding and normal neurological examination at the discharge.

Group 2. Infants with abnormal brain MRI finding at the discharge; this group is divided into 2 subgroups.

2A- Neurologically asymptomatic infants at the discharge with detected MRI lesions (generally interpreted as a mild);

2B- Infants with abnormal neurological examination before discharge, including previous prolonged mechanical ventilation, poor reflex of sucking, disturbances in position, muscle tone, and movements, with detected MRI lesions (mostly interpreted as comprehensive - leucomalacia; affection of basal ganglia).

Group 3. Newborn with lethal outcome.

Statistical analysis is done by SPSS program- Statistical Package for Social Sciences (Version 20). Quantitative variables between groups are compared by Student t-test; for multiple comparators between more groups analysis variance (ANOVA-Bonferroni) is used. Data are shown as average value ± SD (min; max) P-value <0.05 considered as a significant.

Results

Overall 47 neonates were included in this study. 23/47 were indoor patients, 24/47 were transferred from other regional hospitals. Average age at admission was 2 hours 47 minutes (167.18 ± 164.70). 27 out of 47 patients (57.4%) were male, 20 (42.6%) were female. Average gestational was 39 weeks (36-42GW). Average BW was 3465.21 ± 627.62g. In 29 (61.7%) cases pregnancy was terminated by vaginal delivery, in 18 (38.3%) by cesarean section. Average Apgar score in 1. minute was 2 (2-4), in 5. minute 4 (1-7). Apgar score in 10. minute was registered in 15 patients, with average 5 (3-8). Average time of initiation body cooling was 3 h 55 min (235.47 ± 157.99). Average pH at admission for all patients was 7.08 ± 0.22. Average base excess was -15.26 ± 8.45 (Table 1).

Majority of infants with moderate asphyxia 17/29 (58 %) had normal brain MRI finding and normal neurological examination at the discharge; 11 (37%) infants with detected MRI lesions (qualified as a mild) were neurologically asymptomatic at the discharge, 3 (10%) infants had abnormal neurological status, one infant died. Outcome of severely asphyxiated infants was worse: only 3 out of 18 (16%) infants had normal MRI with normal neurological examination at the discharge; 2 out of 8 infants with MRI brain lesions were neurologically asymptomatic; 6 had obviously abnormal neurological examination before discharge; 7/18 (38%) severely asphyxiated infants died (Table 2).

Mean value of blood lactate at admission for all subjects was 11.87 ± 5.41 (3.2- 24.0), without statistical difference between groups and subgroups. 3 hours after beginning of cooling mean value was 8.36 ± 3.70 (2.2-17.0) with statistical difference between group 3 vs. groups 1, 2 and 2A. After 6 hours of cooling 6.31 ± 3.69 there was statistical difference between groups 1 and 2A compared to groups 2B and 3. After 12 hours of cooling there was difference between groups 1 and 2A compared to groups 2A and 2B. 24 hours after beginning of cooling blood lactate value was 4.46 ± 2.00 (1.0 – 11.7) without statistical difference between groups and subgroups. Mean value after 48 hours of cooling was 3.60 ± 1.36 (1.6 – 6.9); mean value at the end of body cooling (72 hours) was 3.36 ± 1.93 (1.2- 9.3). Multiple comparisons between groups and subgroups were not realized because of small sample in group of infants who died.

Seizures occurred in 10 out of 47 (21.3%) infants before initiation of therapeutic hypothermia; during and after hypothermia seizures were noted in 15 out of 47 (31.9%) and 5 out of 47 (10.6%), respectively.

Table 1. Classification and early outcome at discharge depending on severity of asphyxia. **Group 1.** Normal brain MRI finding at the discharge + normal neurological examination; **Group 2.** Abnormal MRI finding; **Subgroup 2A.** Abnormal MRI finding + neurologically asymptomatic infants; Subgroup 2B. Abnormal MRI finding + neurologically symptomatic infants; **Group 3.** Infants who died.

	Group 1 N=20		**Group 2** N=19		**Subgroup 2A** N=10		**Subgroup 2B** N=9		**Group 3** N=8		**Total**	
	N	%	N	%	N	%	N	%	N	%	N	%
Sarnat II	17	58.62	11	37.93	8	27.59	3	10.34	1	3.45	29	100
Sarnat III	3	16.67	8	44.44	2	11.11	6	33.33	7	38.89	18	100

Table 2. Blood Lactate values during therapeutic hypothermia. **Group 1.** Normal brain MRI finding at the discharge + normal neurological examination normal; **Group 2.** Abnormal MRI finding; **Subgroup 2A.** Abnormal MRI finding + neurologically asymptomatic infants; **Subgroup 2B.** Abnormal MRI finding + neurologically symptomatic infants; **Group 3.** Died infants. *$p < 0.05$.

Lactate (mmol/l) + SD												
Groups	**0h**	**P value**		**3 h**	**P value**		**6h**	**P value**		**12h**	**P value**	
Group 1	11.1 6 4.71	2	1.00	7.58 + 2.12	2	1.00	4.60 2.47	2	1.00	4.63 1.61	2	0.04*
		2A	1.00		2A	0.61		2A	1.00		2A	1.00
		2B	1.00		2B	1.00		2B	0.02*		2B	0.00*
		3	0.27		3	0.02*		3	0.04*		3	0.28
Group 2	11.2 9 4.93	1	1.00	7.00* + 3.12	1	1.00	6.23 4.10	1	1.00	8.17 3.63	1	0.04*
		3	0.31		3	0.01*		3	0.40		3	1.00
Subgroup 2A	9.12 3.60	1	1.00	4.73 + 2.33	1	0.61	3.62 1.10	1	1.00	3.15 0.77	1	1.00
		2B	0.36		2B	0.19		2B	0.01*		2B	0.02*
		3	0.12		3	0.00*		3	0.02*		3	0.34
Subgroup 2B	13.7 1 5.25	1	1.00	9.26 + 1.78	1	1.00	10.53 3.43	1	0.02*	9.85 1.50	1	0.00*
		2A	0.36		2A	0.19		2A	0.01*		2A	0.02*
		3	1.00		3	0.13		3	1.00		3	0.86
Group 3	15.0 2 7.48	1	0.27	14.80 + 3.11	1	0.02*	9.50 3.15	1	0.04*	7.48 5.0	1	0.28
		2	0.31		2	0.01*		2	0.40		2	1.00
		2A	0.12		2A	0.00*		2A	0.02*		2A	0.34
		2B	1.00		2B	0.13		2B	1.00		2B	0.86

Average duration of hospitalization was 21 day; separately for each group: 1, 2, 2A, 2B and 3 was 20, 28, 19, 38 and 8 days, respectively.

Average time to establish bottle feeding in groups 1, 2, 2A, 2B and 3 was 14, 18, 13, 26 days, respectively. 3 out of 9 infants from group 2B at discharge practiced feeding through orogastric tube.

Discussion

Results of several large studies confirmed benefit of therapeutic hypothermia in infants with moderate to severe HIE, with reduction of death outcome and also better neurological outcome in survived infants, with typical RR 0.76 (95% CI 0.65, 0.89) [18,19].

Our study included 47 newborn infants assessed to have moderate (n=29) or severe HIE (n=18) who underwent therapeutic hypothermia. 30 patients (64%) had normal neurological examination at the discharge with MRI finding interpreted as a normal or as a presence of mild changes; 9 (19%) had abnormal neurological status at discharge with post-hypoxic MRI lesions generally interpreted as a comprehensive, 8 (17%) infants died.

In one of basic studies (5) with evaluation at the age 18-22months, 24% infants in the hypothermia group died, compared to 37% in the control group. Death or moderate or severe disability occurred in 44% in the hypothermia group and 62% in the control group.

Hypothermia is a time sensitive intervention, with a very narrow therapeutic window and must be performed within 6 h or earlier [20] following delivery to be effective. Prompt identification of infants who will benefit from this neuroprotective therapy will help guide appropriate application of resources and permit prognostication. Average time of initiation body cooling in our patients was 3 h 55 min (235.47 ± 157.99) (7 min. to max 720 min. - 12 hours).

Current researches are directed to identification of biomarkers which could be the predictors of outcome in infants with HIE (20). Concentrations of plasma lactate were used to assess neonatal encephalopathy before hypothermia was introduced [14,15], and also later, in infants who underwent induced hypothermia [17,22,23].

In this study we investigated blood lactate levels taken in series, at admission and in regular intervals (3, 6, 12, 24, 36h) during hypothermia, related to short-term outcome, using clinical examination at the discharge and MRI finding performed between 1-2 weeks after birth, bearing in mind that both are in relation with long-term outcome [9-12].

Early outcome is defined as death or survival with/without clinically manifested deviation in neurological status at discharge and presence/absence of lesions detected on brain MRI.

The mean value of lactate taken at the admission was 11.87 mmol/l, and it was significantly higher compared to the normal value, but without statistical difference between investigated groups. This suggests that first lactate value taken at admission in NICU has no the predictive value in terms of outcome, which is not in accordance with study [14] suggesting that initial value >7.5 ± mmol/l can be a good predictor for moderate-or-severe HIE.

After 3 hours of cooling statistical analysis in our study showed significant difference in lactate values between all groups of survived infants and died infants. After 6 and 12 hours there was statistical difference between neurologically asymptomatic infants (including those whose MRI finding was interpreted as mild post-hypoxic lesions) compared to infants with abnormal neurological examination at the discharge and infants who died. Infants with detected MRI lesions showed to be inhomogeneous in relation to normalization of lactate levels; in those with normal neurological examination at discharge,

time to normalize lactate values was similar with those with normal MRI finding, and significantly shorter than in those with abnormal neurological examination at the discharge and infants who died. 24 hours after beginning of cooling there was no statistical difference between groups and subgroups in lactate levels. Multiple comparisons between groups and subgroups after 48 and 72 hours were not realized because of small group of infants who died.

Our study indicates that time needed to normalize lactate levels can be a good predictor for short and indirectly long-time outcome. Similar studies [22,23] demonstrate significant difference in lactate levels even to 72 h after birth (6, 12, 18, 24, 48 and 72 h) between infants who died and those with normal neurological follow up.

On the same track is study [24] showing that lactate levels in the first 30 minutes of life do not predict severity of the ensuing encephalopathy, but sustained lactic acidosis is associated with severe encephalopathy on EEG and correlates with seizure burden [17] also showing that higher blood lactate following hypothermia and abnormal results of brain MRI are associated with poor neurodevelopmental outcome.

Our study confirmed that blood lactate may increase rapidly to high levels following HIE, but usually falls soon and returns to normal. A maintaining of high lactate levels suggests worse prognosis, and should trigger further investigations [25].

Conclusion

Serial measurements of lactate during therapeutic hypothermia in asphyxiated infants are important. Initial value of lactate has not proved as predictive, but prompt decreasing of lactate values within 24 hours of cooling is associated with better early outcome.

References

1. Lawn JE, Cousens S, Zupan J; Lancet Neonatal Survival Steering Team (2005) 4 million neonatal deaths: when? Where? Why? *Lancet* 365: 891-900. [Crossref]
2. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, et al. (2005) Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. *Lancet* 365: 663-670.
3. Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, Thoresen M, et al. The TOBY Study. Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: A randomised controlled trial. *BMC Pediatr* 8: 17.
4. De Vries LS, Jongmans MJ (2010) Long-term outcome after neonatal hypoxic-ischemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed* 95: F220–F224.
5. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, et al. (2005) Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 353: 1574-1584. [Crossref]
6. Shankaran S, Laptook AR, Tyson JE (2012) Evolution of encephalopathy during whole body hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Pediatr* 160: 567-572.e3.
7. Edwards AD, Brocklehurst P, Gunn AJ. Et al. (2010) Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. *BMJ* 340:c363.
8. Bharadwaj SK, Bhat BV (2012) Therapeutic hypothermia using gel packs for term neonates with hypoxic ischaemic encephalopathy in resource-limited settings: A randomized controlled trial. *J Trop Pediatr* 58: 382-388.
9. Caroline E Ahearne, Geraldine B Boylan, Deirdre M Murray (2016) Short and long term prognosis in perinatal asphyxia: An update. *World J Clin Pediatr* 5: 67-74.
10. Murray DM, Bala P, O'Connor CM (2009) The predictive value of early neurological examination in neonatal hypoxic–ischaemic encephalopathy and neurodevelopmental outcome at 24 months. *Dev Ned Child* 2: e55–e59.
11. Rutherford MA, Ramenghi LA, Edwards AD (2010) Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic–ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurol* 9: 39-45.
12. Twomey E, Twomey A, Ryan S, Murphy J, Donoghue VB (2010) MR imaging of term infants with hypoxic-ischaemic encephalopathy as a predictor of neurodevelopmental outcome and late MRI appearances. *Pediatr Radiol* 40: 1526-1535.
13. Beken S, Aydın B, Dilli D, Erol S, ZenciroÄŸlu A, et al. (2014) Can biochemical markers predict the severity of hypoxic-ischemic encephalopathy? *Turk J Pediatr* 56: 62-68. [Crossref]
14. Shah S, Tracy M, Smyth J (2004) Higher serum level of lactate following TH and abnormal results of brain MRI are associated with poor ND outcome. Postnatal Lactate as an Early Predictor of Short-Term Outcome after Intrapartum Asphyxia. *J Perinatol* 24: 16-20.
15. Kimberly A. Allen, Debra H Brandon (2011) Hypoxic Ischemic Encephalopathy: Pathophysiology and Experimental Treatments. *Newborn Infant Nurs Rev* 11: 125-133.
16. Douglas-Escobar M, Weiss MD (2015) Hypoxic-ischemic encephalopathy: a review for the clinician. *JAMA Pediatr* 169: 397-403. [Crossref]
17. Chiang MC, Lien R, Chu SM (2016) Serum Lactate, Brain Magnetic Resonance Imaging and Outcome of Neonatal Hypoxic Ischemic Encephalopathy after Therapeutic Hypothermia. *Pediatr Neonatol* 57: 35-40.
18. Jacobs SE, Hunt R, Tarnow-Mordi WO, Inder T, Davis PG (2010) Evidence-Based Child Health: A Cochrane Review Journal 5: 474–531.
19. Shankaran S, Laptook AR, Pappas A (2017) Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy A Randomized Clinical Trial. *JAMA* 318: 57-67.
20. Thoresen M, Tooley J, Liu X, Jary S, Fleming P, et al. (2013) Time is brain: Starting therapeutic hypothermia within three hours after birth improves motor outcome in asphyxiated newborns. *Neonatology* 104: 228-233.
21. Massaro AN, Wu ZW, Bammler TK, Comstock B (2018) Plasma Biomarkers of Brain Injury in Neonatal Hypoxic-Ischemic Encephalopathy. *The Journal of Pediatrics* 194: 67-75.e1
22. Hardisty H, Musson R, Clark S (2014) Lactate Clearance and Neurological Outcome in Neonates cooled for Hypoxic Ischaemic Encephalopathy. British Academy of Childhood Disability: British Paediatric Neurology Association Arch Dis Child 99: 1-10.
23. Musson RE, Clark SJ, Kachroo R (2013) Lactate Clearance and Outcome in Neonates Cooled For Hypoxic Ischaemic Encephalopathy. ADC Fetal and Neonatal Editions. *BMJ* 98: 1.
24. Murray DM, Boylan GB, Fitzgerald AP, Ryan CA, Murphy BP, et al. (2006) Persistent lactic acidosis in neonatal hypoxic-ischaemic encephalopathy correlates with EEG grade and electrographic seizure burden. *Arch Dis Child Fetal Neonatal Ed* 93: F183-F186.
25. Martinello K, Hart AR, Yap S (2017) Management and investigation of neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed* F1–F13.