Cord blood and serial lactate levels in predicting short-term outcome in term new-born babies with perinatal asphyxia

Anusha S, Mahesh B Maralihalli, Mahantesh R Matti

SDM college of medical sciences and hospital, Dharwad Affiliated to Shri Dharmasthala Manjunatheswara University Dharwad, Karnataka, India.

Abstract

Introduction: Birth asphyxia is a leading cause of neonatal deaths across the globe. Clinical examination, Apgar score, pH, EEG/aEEG, Lactate are being used as markers for prediction of outcome. Serum Lactate is a better reflector of metabolic mechanism. We intend to study cord blood lactate and serial lactate levels in term birth asphyxia babies.

Aim: To determine correlation between cord blood lactate, serial lactate levels and short term outcome in term new-born babies with perinatal asphyxia.

Materials and Methods: It was a prospective, observational study. Thirty term babies with birth asphyxia were selected. Their Cord blood lactate, serum lactate at 6, 12, 24 hours of life were correlated to short term outcomes (NICU stay, shock, Acute kidney injury, mortality).

Results: Eighteen babies with moderate asphyxia and 12 with severe asphyxia had mean cord blood lactate of 10.4mmol/L and 13.47mmol/L respectively. There was difference in mean lactate levels at 6, 12, 24 hours of life between the babies who survived and expired; also survivors had significant reduction in mean lactate levels at various time points. Babies with moderate asphyxia had no shock and AKI. Babies with severe asphyxia and shock had mean lactate levels of 12mmol/L in survivors and 13.8mmol/L in who expired. Babies with severe asphyxia and AKI had mean lactate of 14mmol/L in survivors and 14.6mmol/L in who expired. Babies with moderate asphyxia had no mortality. In babies with severe asphyxia, survivors had mean lactate of 12.74mmol/L and 14mmol/L in babies who expired. There was no correlation between the lactate levels and the length of the NICU stay.

Conclusion: Serial lactate levels can be used to predictor the short term prognosis in term babies with perinatal asphyxia. There was significant difference in mean lactate levels between the babies who survived and expired. Serial lactate levels showed significant reduction in babies who survived.

Key words: NICU, Cord blood ABG, Cord blood lactate, Serial serum lactate, perinatal asphyxia, Short term outcome.

Introduction

Birth asphyxia accounts for approximately 23% of the 3.6 million neonatal deaths per year and may occur in the antenatal, intrapartum, or postpartum period[1]. The majority of all neonatal deaths (75%) occur during the first week of life, and about 1 million new-borns die within the first 24 hours. Preterm birth, intrapartum related complications (birth asphyxia or lack of breathing at birth), infections and birth defects cause most neonatal deaths in 2017[2].

Several biologic factors aid in preserving critical organ viability during and after asphyxia. The cerebral metabolic rate is lower in the foetus versus the term infant or adult, creating a more favourable ratio of energy supply and demand and the neonatal brain has the capacity to use alternate energy sources when needed. In situations of relative oxygen and glucose depletion, energy substrates such as lactate and ketones become critical for cerebral metabolism. When fetal oxygen demand exceeds placental

Address for Correspondence:

Dr. Mahesh B Maralihalli

SDM College of medical sciences and hospital,
Dharwad, Karnataka, India
Email: drmaheshmaralihalli@gmail.com

oxygen delivery, cells resort to anaerobic respiration to combat energy needs, via the anaerobic pathway, lactic acid accumulates, and pH decreases. The non-carbonic acid slowly diffuses across the placenta into the maternal circulation. The primary non-carbonic acid, lactic acid, accumulates as a result of oxygen deprivation and anaerobic glycolysis and does so more slowly. During anaerobic metabolism, lactate production is predominant and is a major component of metabolic acidosis [3].

Hence, this study was designed to investigate the role of serial lactate measurements (cord blood lactate, serum lactate at 6, 12, 24 hours of life) as a predictor of short term outcome in term perinatal asphyxia -babies. Different clinical parameters have been used to both diagnose and predict the prognosis for asphyxia, including non-reassuring foetal heart rate patterns, prolonged labour, meconium-stained fluid, low 1-minute Apgar score, and mild to moderate acidemia defined as arterial blood pH less than 7 or base excess greater than 12 mmol/L [4].

Lactate is invariably produced in the event of hypoxia and poor tissue perfusion. The blood lactate concentrations in critically ill and injured can be used to detect tissue hypoxia at an early stage, assess illness severity, and predict outcome. Lactate concentration in umbilical cord blood at delivery might be a more precise tool in the assessment of fetal metabolic acidosis during labour and serial lactate levels can predict the outcome.

Material and Methods

The study was a prospective observational study, conducted in the Department of Paediatrics of a Tertiary Care Hospital for a period of 1 year. The study was approved by the Institutional Ethical Committee. Informed consent was taken from the guardians of all the subjects. Convenience sampling technique was used to collect the cases. The study included 30 inborn new-born babies who had perinatal asphyxia; fulfilling the National Neonatal-Perinatal Database (NNPD) criteria. NNPD criteria for moderate perinatal asphyxia: slow/gasping breathing or an APGAR score of 4 to 6 at 1 minute of life and for severe perinatal asphyxia: no breathing or an APGAR score of 0-3 at 1 minute of life [5]. Babies with major congenital anomalies, suspected inborn errors of metabolisms and babies who developed sepsis were excluded from the study population.

After the delivery, for the babies with perinatal asphyxia 2ml of umbilical venous blood sample was collected for lactate level assay; umbilical cord blood gas analysis was obtained with 1ml of heparinized blood sample. 2ml of blood samples from peripheral veins or umbilical vein were collected at 6, 12 and 24 hours of life to monitor serial lactate levels. The samples were analysed for lactate levels using Cobas 6000 analyser. A detailed clinical history and serial general examination and systemic examinations including encephalopathy (HIE) staging were carried out for all babies. Babies underwent laboratory evaluation for complete blood count, renal function test, liver function tests, coagulation parameters, arterial blood gas analysis, chest roentgenogram, neuro-sonogram, 2D-ECHO and blood culture wherever clinically indicated.

Development of complications like acute kidney injury (AKI), coagulopathy, hypoxic ischemic encephalopathy (HIE), liver dysfunction etc., were noted and appropriate therapies initiated. The short term outcomes such as organ injuries, shock, mortality and length of NICU stay were analysed. HIE staging was defined based on Sarnat and Sarnat classification [6].

AKI was defined as, serum Creatinine >1.5mg/dl, oliguria/anuria, FENA >2. Hepatic dysfunction was defined as AST >100, ALT >100 & PT > twice the normal. Intravenous fluids, Colloids, ionotropic support, intubation and mechanical ventilation were carried out when required.

Outcome measures: Cord blood and serial lactate measurements in moderate and severe perinatal asphyxia, correlation of these lactate levels with pH, HIE staging, shock, acute kidney injury and duration of NICU stay. Comparisons of cord lactate, serial lactate in the babies who survived and those who expired.

Statistical analysis: Data was analysed using SPSS version 22 software. Demographic data were analysed using descriptive statistics. The results were expressed in frequencies, percentage, means, t-value, r- value and standard deviations. Chi square test, one way ANOVA was used for categorical variables. Results with p value < 0.05 were considered as significant.

Results

There were 30 cases included in the study population. Among them 20 (66.67%) were male babies and 10 (33.33%) female babies. The mean weight was 2.83kgs. Out of 30 babies, 50% babies had detectable antenatal risk factors like premature rupture of membranes (23.3%), non-severe pre-eclampsia (13.3%), oligohydramnios (6.3%) etc. The intranatal risk factors were fetal distress (40%), MSAF (20%), non-reassuring NST(16.6%), eclampsia(6.6%), cord around neck(3.3%) and deep transverse arrest(3.3%). 13% had no detectable intranatal risk factors.

In our study 18 babies suffered moderate and 12 suffered severe perinatal asphyxia. Their mean cord blood lactate levels were 10.4mmol/L and 13.47mmol/L respectively. There were 8 babies delivered by full-term vaginal delivery, among them 7 had moderate and 1 had severe birth asphyxia, cord blood lactates were 10.3mmol/l and 15mmol/L respectively. There were no deaths in this group. There were 18 babies delivered by LSCS, among them 9 had moderate and 9 had severe birth asphyxia, their cord blood lactates were 10.1mmol/l and 13.4mmol/L respectively. There were 6 deaths in severe birth asphyxia group and none in moderate asphyxia. There were 4 babies delivered by instrumental delivery, among them 2 had moderate and 2 had severe birth asphyxia, their cord blood lactates were 12.3mmol/l and 15mmol/L respectively. There were 1 death in severe birth asphyxia group and none in moderate asphyxia. There was no significant correlation between the mode of delivery and the mean cord blood lactate levels.

Among the 30 babies, 11 babies requiring mechanical ventilation support had mean cord blood lactate of 13.36mmol/L. Remaining 19 babies who required ambu bag/mask resuscitation and oxygen supplementation had a mean cord blood lactate of 10mmol/L.

Six babies with moderate asphyxia (mean cord lactate- 10.8 mmol/L)and 9 babies with severe asphyxia (mean cord lactate- 13.96 mmol/L) had pH of ≤7.1.Twelve babies with moderate asphyxia (mean cord lactate- 10.3 mmol/L)and 3 babies severe asphyxia (mean cord lactate- 12 mmol/L) had pH of >7.1. There was no correlation between the pH and mean cord blood lactate levels.

It was noted that the mean cord blood lactate levels were significantly higher in severe asphyxia babies in all 3 stages of HIE when compared to moderate asphyxia babies (Table 1).

Table 1: Comparison of HIE stage with mean cord blood lactate in moderate and severe asphyxia

HIE	Moderate asphyxia			Severe asphyxia			Z-value	p-value
	n	Mean CBL	SD CBL	n	Mean CBL	SD CBL		
1 HIE	14	10.56	1.29	2	12.50	3.54	-0.7144	0.4749
2 HIE	4	10.00	0.82	7	13.53	1.87	2.2677	0.0233
3 HIE	0	0.00	0.00	3	14.00	1.73	-	-
Total	18	10.43	1.21	12	13.48	1.96	-3.4290	0.0006

Chi-square analysis, Data expressed as mean and SD, significant p<0.05

In this study, 16 babies had HIE stage 1, 11 babies had HIE stage 2, 3 babies had HIE stage 3. Their mean cord blood pHs were 7.09, 7.06 and 6.93 respectively. There was no correlation between cord blood pH and HIE stages. Mean cord blood lactate levels were 10.8mmol/L in HIE 1, 12.25mmol/L in HIE stage 2, 14mmol/L in HIE 3. There was significant correlation between cord blood lactates and HIE stages (Table 2).

Table 2: Comparison of HIE scores with pH and mean cord lactate levels

HIE stage (Sarnat staging)	Number (N=30)	cord pH (mean±SD)	cord lactate (mean±SD)
1	16	7.09±0.16	10.80±1.65
2	11	7.06±0.16	12.25±2.34
3	3	6.93±0.12	14.0±1.73
F-value		1.2324	4.2604
p-value		0.3075	0.0247

One way ANOVA.Data expressed as mean and SD

The serial serum lactate levels among the babies who survived/discharged were analysed at 6, 12, 24 hours of life. Their mean serum lactate levels were 8.17mmol/L, 5.43mmol/L, and 2.53mmol/L respectively. With the treatment, the reduction in the mean serial serum lactate levels between 6hrs to 12hrs was 2.74mmol/L. Between 6hrs to 24hrs, the reduction in the mean serum lactate levels was 5.63mmol/L. The mean serum lactate levels among the babies who died were 9.90mmol/L, 8.37mmol/L, and 7.73mmol/L at 6, 12 and 24hours of life respectively. With the treatment, reduction in the mean serum lactate levels between 6hrs to 12hrs was 1.53mmol/L. Between 6hrs to 24hrs, the reduction in the mean serum lactate levels was 2.17mmol/L. There was significant difference in mean lactate levels at various time points between the babies who survived and expired (Figure 1).

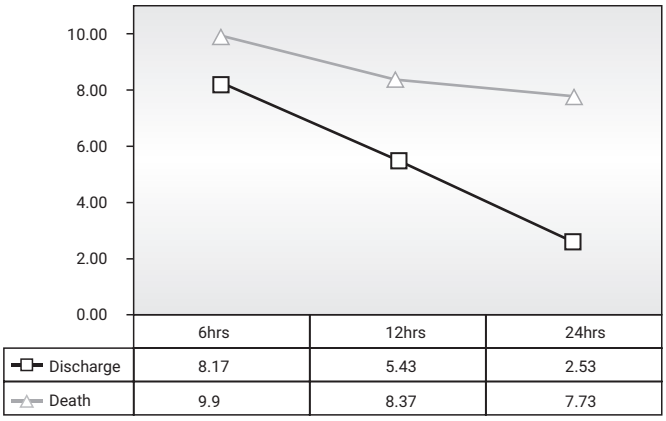

Figure 1: Comparison of outcome with respect to serum lactate levels at different treatment time points - independent t test

The reduction in mean lactate levels between various time points among the babies who improved and expired was significant (Table 3).

Table 3: Comparison of outcome with respect to serum lactate levels at different treatment time points

Treatment times	Discharge		Death		t-value	p-value
	Mean	SD	Mean	SD		
6hrs	8.17	1.55	9.90	2.60	-2.1991	0.0363*
12hrs	5.43	1.43	8.37	2.56	-3.9273	0.0005*
24hrs	2.53	1.08	7.73	0.99	-11.335	0.0001*
Changes from 6hrs to 12hrs	2.74	1.41	1.53	1.44	1.9758	0.0500*
Changes from 6hrs to 24hrs	5.63	1.55	2.17	2.06	4.7917	0.0001*

Independent t test, data expressed as mean and SD, significant p<0.05

Percentage of reduction in serum lactate from 6 hours to 12 hours were 33.55% and 15.44% in babies who survived and expired respectively; similarly percentage of reduction in serum lactate from 6 hours to 24 hours were 68.96% and 21.93% among babies who survived and expired respectively (Table 4).

Table 4: Comparison of different treatment time points with respect to serum Lactate levels in outcome

Samples	Treatment times	Mean	SD	Mean Diff	SD Diff.	% of change	t-value	p-value
Survived	6hrs	8.17	1.55	2.74	1.41	33.55	9.2957	0.0001
	12hrs	5.43	1.43					
	6hrs	8.17	1.55	5.63	1.55	68.96	17.408	0.0001
	24hrs	2.53	1.08					
Expired	6hrs	9.90	2.60	1.53	1.44	15.44	2.8048	0.0310
	12hrs	8.37	2.56					
	6hrs	9.90	2.60	2.17	2.06	21.93	2.7937	0.0314
	24hrs	7.73	0.99					

Dependent t test, data expressed as mean and SD, significant p<0.05

We noted more drop in serum lactate levels in babies survived compared to those who expired.

We observed that babies who suffered moderate asphyxia had no shock and AKI. Among babies with severe asphyxia and shock, mean lactate levels was 12mmol/L in survivors and 13.8mmol/L in babies who expired. Among babies with severe asphyxia and AKI, mean lactate levels were 14mmol/L in survivors and 14.6mmol/L in babies who expired (Table 5).

Table 5: Mean cord blood lactate and shock, AKI

Asphyxia	Shock		AKI	
	Survivors	Death	Survivors	Death
Moderate	0	0	0	0
Severe	2 (Mean cord blood lactate- 12mmol/L)	6 (mean cord blood lactate- 13.8mmol/l)	2 (mean cord blood lactate level of 14mmol/L)	5 (mean cord blood lactate level of 14.6mmol/L)

Data expressed as mean

The babies who suffered moderate asphyxia had no mortality and their mean cord blood lactate was 10.43mmol/L. Among babies with severe asphyxia, mean lactate levels were 12.74mmol/L in survivors and 14mmol/L in babies who expired (Table 6).

Table 6: Outcomes and mean cord blood lactate

Asphyxia	Outcome	n	%	Mean cord blood lactate
Moderate	Survivors	18	60.00	10.43
	Death	-	-	-
	Total	18	60.00	10.43
Severe	Survivors	5	16.67	12.74
	Death	7	23.33	14.00
	Total	12	40.00	13.48
Total		30	100.0	11.65

Data expressed as mean, percentage and number

In this study, the mean hospital stay was 11.13 days, ranging from 5- 25 days. Among them, the mean hospital stay of the babies who were discharged was 10.09 days. Mean hospital stay of babies who died was 14.57 days. There was no correlation between the lactate levels and the length of the NICU stay (Figure 2)

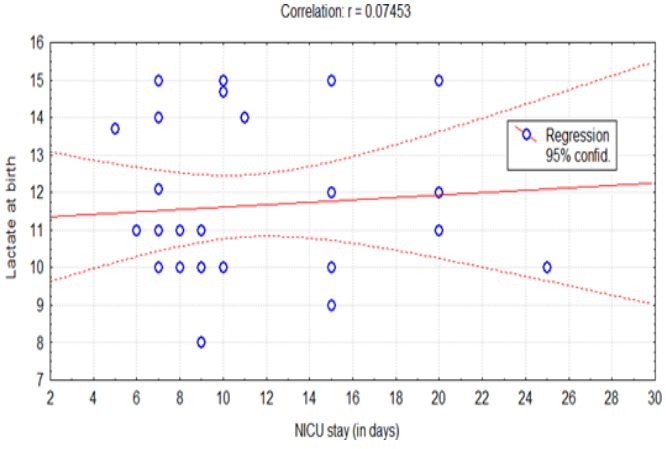

Figure 2: Scatter diagram of correlation between lactate at birth and NICU stay in days

Discussion

Perinatal asphyxia is an important contributor to the neonatal mortality rate especially in developing countries. Most of these deaths occur in the first week of life[7]. Birth asphyxia can cause HIE, cerebral palsy, seizures etc contributing to significant morbidity.

Anaerobic metabolism which occurs during asphyxia generates lactate, the level assessment of which can help in predicting severity of asphyxia and prognosis. Both umbilical cord lactate and pH proved to be accurate predictors of neonatal morbidity caused by intrapartum hypoxia. Lactate proved to be superior to pH in predicting adverse neonatal outcome[8].

In our study, 50% of the mothers had no detectable antenatal risk factors contributing to perinatal asphyxia. Among those 50% mothers, 40% of them had fetal distress in the intranatal period. Among 30 babies, 10 (33%) babies had MSAF, among them, 2 babies had severe asphyxia with mean cord blood lactate of 13.5mmol/L. A prospective study conducted by Joseph et al with 35% babies had MSAF history with a mean cord blood lactate level of 11mmol/L[9].

In our study, the cord blood lactate levels were found to be higher in severe asphyxia. A study conducted by Silva et al had similar observations[10]. Another study conducted by Frey et al, found that neonates who died in first week of life had severe brain damage with higher plasma lactate levels than in mild or no impairment[11].

Few studies observed that cord blood levels were higher in instrumental and vaginal deliveries [12] and a significant relationship between the type of delivery with neonatal asphyxia[13]. In our study there was no correlation between mode of delivery and mean cord lactate among babies with moderate and severe asphyxia.

Six babies with moderate asphyxia and 9 babies severe asphyxia had pH of ≤7.1.Twelve babies with moderate asphyxia and 3 babies severe asphyxia had pH of >7.1. There was no correlation established between Cord pH and staging of encephalopathy, this in contrast to findings of Singh N et al[14]. Mean cord blood lactate levels were correlating with staging of encephalopathy similar to a study by Wiberg et al where they found lactate in cord arterial blood at birth is at least as good as base deficit to reflect an impaired condition at birth, and best when gestational age-adjusted values are used[15], similar observations

are made by Simalti AK et al[16].

Heljic S et al concluded serial measurements of lactate during therapeutic hypothermia in asphyxiated infants are important and decreasing of lactate values within 24 hours of cooling is associated with better early outcome[17]. In our study we tried to correlate neonatal outcome with respect to serial lactate levels at different treatment time points. We observed that there was significant difference in mean lactate levels at various time points between babies who survived and expired, survived babies had greater fall in serial lactate levels.

There studies available demonstrating usefulness of serial lactate levels in managing and predicting prognosis in pediatric and adult intensive care settings[18,19]. But there is limited data on role of serial lactate levels in prediction of outcomes in asphyxiated neonates. Thus our study adds on to the literature about the role of serial lactate levels.

No mortality observed in babies with moderate asphyxia. Among babies with severe asphyxia survivors had mean cord lactate of 12.74mmol/L and 14mmol/L in babies who expired. We observed no correlation between lactate levels and length of NICU stay.

Conclusion: Serial lactate levels can serve as a predictive marker for the short term prognosis in term babies with perinatal asphyxia. There was significant difference in mean lactate levels; also the reduction in mean lactate levels at various time points between the babies who survived and expired, with more reduction in babies who survived. Lactate correlates better than pH with severity of encephalopathy. No correlation established between lactate levels and length of NICU stay.

Limitation: Smaller sample size and shorter study period was the limitation of this study.

Acknowledgement

The author would like to thank Dr. Vijay Kulkarni, MD, Professor, and head of the Department of Pediatrics SDM College of Medical Sciences and Hospital, Dharwad. Affiliated to Shri Dharmasthala Manjunatheswara University, Dharwad, Karnataka, India 580009.

References

1. *Cady Jr LD, Weil M H, Afifi AA, Michales SF, Liu VY, Shubin H. Quantitation of severity of critical illness with special reference to blood lactate. Crit Care Med 1973; 1:75-80*
2. *Newborns: Improving survival and well-being: world health organisation.19 September 2020.Available at https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality*
3. *Beena B. Kamath-Rayne, Alan H. Jobe. Birth Asphyxia. Clinics in Perinatology 2016; 43(3):395-620.*
4. *MacLennan A. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. BMJ 1999; 319:1054-1059.*
5. *National Neonatal Perinatal Database. Human Reproduction Research Centre Network. Neonatology Forum NNPD Network, India: report for 2002-2003. Available at https://www.newbornwhocc.org/pdf/HRRC-Report_2002-03.pdf*
6. *Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976; 33(10):696-705*
7. *Sankar MJ, Natarajan CK, Das RR, Agarwal R, Chandrasekaran A, Paul VK. When do newborns die? A systematic review of timing of overall and cause-specific neonatal deaths in developing countries. J Perinatol 2016; 36(Suppl 1):S1-S11*
8. *Neacsu A, Herghelegiu CG, Voinea S, Dimitriu MCT, Ples L, Bohiltea RE, Braila AD, Nastase L, Bacalbasa N, Chivu LI, Furtunescu F, Ioan RG. Umbilical cord lactate compared with pH as predictors of intrapartum asphyxia. Exp Ther Med 2021; 21(1):80.*
9. *Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. Pediatr Res 1990; 27:372-8*
10. *da Silva S, Hennebert N, Denis R, Wayenberg JL. Clinical value of a single postnatal lactate measurement after intrapartum asphyxia. Acta Paediatr Int J Paediatr 2000; 89(3):320-323*
11. *Frey B, Pfenninger J, Bachmann D. Prognostic value of hyperlactatemia in neonates. J Pediatr 1995; 127(2):334*
12. *Revathy Natesan S. Routine measurements of cord arterial blood lactate levels in infants delivering at term and prediction of neonatal outcome. Med J Malaysia 2016; 71(3):131-3*
13. *Dhita Ayu Permatasari, Dede Mahdiyah, Erni Yuliastuti. The Correlation between the Type Of Childbirth With Neonatal Asphyxia. Proceedings of the 2nd Sari Mulia International Conference on Health and Sciences 2017. Advances in Health Sciences Research, volume 6. Published by Atlantis Press.ISBN 978-94-6252-468-2*
14. *Singh N, Gupta AK, Arya AK. A Study on Correlation of Umbilical Cord Arterial Blood pH with Perinatal Asphyxia & Early Neonatal Outcome. AJCPN 2020; 8(2):30-5*
15. *Wiberg N, Källén K, Herbst A, Olofsson P. Relation between umbilical cord blood pH, base deficit, lactate, 5-minute Apgar score and development of hypoxic ischemic encephalopathy. Acta Obstet Gynecol Scand 2010; 89(10):1263-9*
16. *Simalti AK, Negi V, Kumar A, Pramanik SK. Cord blood lactate levels as marker for perinatal hypoxia and predictor for hypoxic ischemic encephalopathy. Acta Med Int 2020; 7:93-6*
17. *Heljic S, Hukeljic L, Terzic S, Spahovic R (2018) Serial measurements of blood lactate and early outcome of neonatal hypoxic ischemic encephalopathy after therapeutic hypothermia. Clin Res Trials 2018; 4(3):1-4*
18. *Choudhary R, Sitaraman S, Choudhary A. Lactate clearance as the predictor of outcome in pediatric septic shock. J Emerg Trauma Shock 2017; 10(2):55-59*
19. *Dettmer M, Holthaus CV, Fuller BM. The impact of serial lactate monitoring on emergency department resuscitation interventions and clinical outcomes in severe sepsis and septic shock: an observational cohort study. Shock 2015; 43(1):55-61.*

Conflict of interest: Nil

Source of funding: Nil

Date received: Oct 18, 2022

Date accepted: Dec 25, 2022