

Differential Diagnosis of Seizure and Syncope by the Means of Biochemical Markers in Emergency Department Patients

Abstract

Background: Seizure and syncope have similar clinical symptoms but different etiologies. Hence, differential diagnosis is crucial prior to intervention. This study evaluates the diagnostic importance of neuron specific enolase (NSE), creatine phosphokinase (CPK), and serum lactate dehydrogenase (LDH) for admitting patients with seizure medical history to emergency department (ED) in order for differential diagnosis between syncope and seizure. **Methods:** Patients with a short-lasting loss of consciousness admitted to the ED were recruited. All patients with a short-lasting loss of consciousness were eligible and EEG was conducted several times and was taken over a long period. Patients were then divided into two groups of seizure and syncope. The biochemical markers levels of all the eligible patients were measured by a reputable laboratory. **Results:** In order to define specificity and sensitivity of different levels of biomarkers and the optimal cut-off points, ROC curves for each biomarker of syncope and seizure patients admitted to ED were performed. AUC for NSE, CPK, and LDH were 0.973 ± 0.023 , 0.827 ± 0.047 , and 0.836 ± 0.043 respectively in 95% confidence level. Cut-off points for NSE, CPK, and LDH were determined 25.12, 218.09, and 193.88 respectively. **Conclusions:** It was concluded that NSE, CPK and LDH levels were different significantly in seizure patients compared to syncope ones. The seizure group showed an increase in NSE, CPK and LDH level. Determining biomarkers level for differential diagnosis of seizure and syncope can be applied as a supplementary test in addition to tests like EEG.

Keywords: Biomarkers, emergencies, seizures, syncope

Introduction

Syncope, as a transient loss of consciousness associated with cerebral hypo perfusion, can be improved by recumbent posture without any residual deficits.^[1] Seizure, on the other hand, is one of the most important symptoms of neurological disorders.^[2] In addition to epilepsy, head trauma,^[3] and some drug toxicity such as tramadol poisoning^[4] can cause seizure. Thus, diagnosis and treatment of seizure play an essential role in patients' health.^[5] However seizure and syncope have similar clinical symptoms, they have different etiologies.^[6,7] Since there are various pathophysiology for syncope and seizure, different treatments and prophylaxis are available for them. Hence, differential diagnosis of them is crucial prior to intervention.^[7] In case patients experience vivid clinical symptoms, differentiation and diagnosis of the seizure and syncope are

not difficult.^[8,9] Nevertheless, differentiation between these disorders based on medical history can be confusing.^[9] On the other hand, tongue biting and urinary incontinency can also be observed in syncope. Therefore, electroencephalography (EEG) is considered as one of the most important methods for seizure diagnosis. Although, referring to its results can cause problems in diagnosis and treatment of the disease.^[6,10] Other probable symptoms observed in seizure are heart problems including arrhythmia, bradycardia, hypotension^[8,9,11] which lead to confusion in diagnosis of disorder. Therefore, more objective tests are needed for differential diagnosis of syncope and seizure. Using S-100 protein, neuron specific enolase (NSE), creatinine phosphokinase isoenzyme BB (CPK-BB) and myelin basic protein (MBP) as some biochemical markers could be applied in diagnosis of traumatic brain injury (TBI)^[12] in addition to EEG results.

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How to cite this article: Masoumi B, Mozafari S, Golshani K, Heydari F, Nasr-Esfahani M. Differential diagnosis of seizure and syncope by the means of biochemical markers in emergency department patients. *Int J Prev Med* 2022;13:58.

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Access this article online

Website:
www.ijpvmjournal.net/www.ijpvm.ir

DOI:
10.4103/ijpvm.IJPVM_129_20

Quick Response Code:



Neuron-specific Enolase (NSE) is one of the proteins playing a role in transferring neural messages which are naturally found in neurons and neuroectodermal cells rather than in Extracellular fluid (ECF).^[13-16] An increase in serum NSE level has been reported in cerebral venous thrombosis (CVT),^[17] cerebral infarction,^[18-20] TBI,^[21-24] Creutzfeldt – Jakob disease,^[25-27] and status epilepticus.^[27,28] Lee *et al.* evaluated serum enolase level in patients suffering from seizure and syncope.^[6] It was also shown NSE level increased after fever and seizure in pediatrics.^[29]

Creatine phosphokinase (CPK) has a distinct isoenzyme-specific localization in brain and plays an important role for brain energetics.^[30] The increasing value of CPK after tonic-clonic seizures has been confirmed.^[31] Willert *et al.*^[32] studied serum NSE, prolactin, and CPK levels in epileptic and psychogenic non-epileptic patients after seizure. Their results showed these levels had differential diagnosis capability. Brigo *et al.*^[33] evaluated diagnostic capability of CPK in seizure and pseudo-seizure and approved its positive impact.

Serum lactate dehydrogenase (LDH), which is an indicator of disease and tissue injury, catalyzes the interconversion of lactate and pyruvate.^[34] Wong^[35] showed patients with an acute illness with seizure as one of their clinical manifestations, had elevated serum LDH above the upper limit, before, during, or after a period of seizure. Khosroshahi *et al.*^[36] showed that spinal fluid lactate dehydrogenase level can contribute to differentiate structural and metabolic causes of altered mental status in children. The levels of LDH in the cerebrospinal fluid (CSF) have been used to evaluate a variety of neurologic disorders. However, few studies have been performed on CSF LDH in febrile convulsion patients. Ehsanipour *et al.*^[37] compared CSF LDH in children with simple and complex febrile convulsion. They showed that LDH level was the highest in complex febrile convulsion. Rash *et al.*^[38] studied endothelin and copeptin for diagnostic significance of syncope and seizure patients. Their results showed no significant difference in the level of these two chemical biomarkers for the patients.

The levels of chemical biomarkers are being studied in syncope and seizure diagnostic significance. The aim of this study is to evaluate diagnostic importance of NSE, CPK, and LDH for admitting patient with seizure medical history to emergency department (ED) in order for differential diagnosis between syncope and seizure. Presented method can be beneficial to confirm seizure in patients.

Methods

Population and sampling strategy

Patients with short-lasting loss of consciousness admitted to the emergency department of Al-Zahra and Kashani university hospitals of Isfahan during February 2017 to September 2018 were recruited in the study. The sample

size was calculated according to the equation presented by Charan and Biswas.^[39] In this study the minimum sample size was calculated 44 per group according to the above-mentioned equation.

Inclusion and exclusion criteria

Patients, 18- to 70-year-old, with a short-lasting loss of consciousness admitted to Al-Zahra and Kashani hospitals ED were recruited in this study. In addition to the patients who were either unwilling to participate in the study, or not able to give consent, patients with cardiac ischemia, trauma history in the past week, cerebrovascular accident (CVA) in the last three months, rhabdomyolysis, polymyositis (PM), dermatomyositis (DM), hemolysis, hypothyroidism, and muscular injection in the past week were also excluded since the above mentioned disorders affect CPK, LDH, and NSE levels. Also, patients receiving antiepileptic treatment were excluded due to effect of antiepileptics on EEG.

Methods

This study was carried out after ethic committee approval (IR.MUI.REC.1396.3.761). All patients with a short-lasting loss of consciousness admitted to the emergency department were eligible for the present work. All patients' demographic characteristics such as age, sex, history of underlying diseases, were recorded. Patients with exclusion criteria were eliminated.

Electroencephalography (EEG) was conducted several times and was taken over a long period for the eligible patients. Patients whose EEG test showed abnormalities were classified in seizure group (group A). Since the presence of a seizure discharge on EEG depends on how likely the EEG is capable of detecting the part of brain, where the excessive and synchronous neuronal discharge take place, and in some seizure cases it is invisible on scalp EEG,^[40] patients with normal EEG must be screened according to syncope guideline management.^[41] The patients with normal EEG approved by syncope guideline management, were categorized in syncope group (group B). The biochemical markers (LDH, CPK, and NSE) levels for all the eligible patients were measured by a reputable laboratory at the time of admission. A control group of people having no short-lasting loss of consciousness history was considered.

Statistical analysis

Statistical analysis of the raw data achieved from all subjects was carried on by SPSS software. Statistical significance for continuous data was determined by one-way ANOVA and the multiple comparison method of Tukey. Different sex groups were analyzed by Chi-square test. Diagnostic performance of the markers measurements to discriminate diseased from normal cases was evaluated using Receiver Operating Characteristic (ROC) curve analysis. ROC curve analyses were performed for the

true-positive rate and sensitivity was plotted in the function of the false-positive rate (1-specificity) for different cut-off values.

Results

A total of 111 patients were screened with a short-lasting loss of consciousness. EEG test was conducted several times and was taken over a long period for eligible patients ($n = 103$). 44 patients had syncope with a mean age of 47.11 ± 14.9 , 55 patients had seizure with a mean age of 42.86 ± 11.4 . The control group ($n = 44$) had a mean age of 41.36 ± 12.1 . No meaningful difference between the age groups was observed.

ANOVA test was applied to show the effect of each biomarker serum level on seizure and syncope. The results showed that seizure or syncope had effect on each biomarker ($P < 0.0001$). Tukey test was conducted for comparison of biomarkers levels between the groups of A, B, and control. Accordingly, it was concluded that CPK and LDH level were different significantly in each group at 95% confidence level ($P < 0.0001$). These biomarkers level increased more in seizure patients compared to syncope ones [Figure 1]. However, NSE serum level had no meaningful difference for syncope and control group ($P = 0.485$). On the contrary, NSE level had a significant difference for seizure group in comparison with the other ones ($P < 0.0001$). The seizure group showed an increase in NSE level. The results are shown in Table 1.

In order to define specificity and sensitivity of different levels of biomarkers and the optimal cut-off points, ROC curves for each biomarker of syncope and seizure patients admitted to ED were performed [Figure 2]. Area

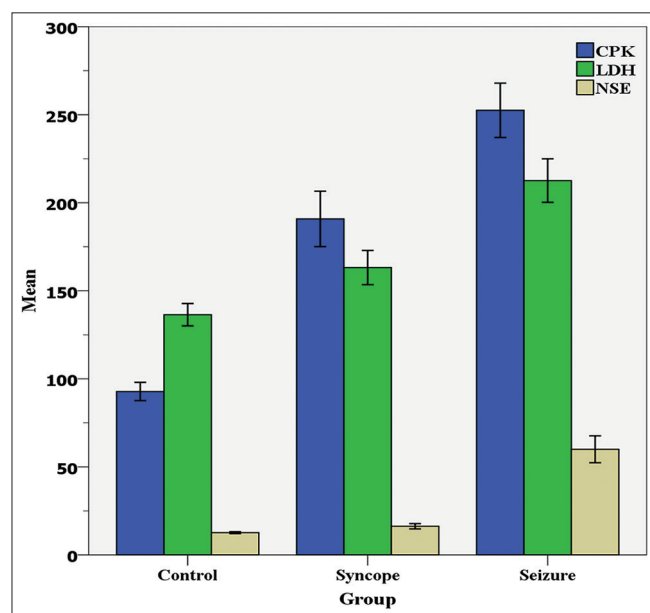


Figure 1: Comparison of biomarkers for control, syncope and, seizure groups

under Curve (AUC) determines differential diagnosis capability or accuracy^[42] which approves biomarker in differentiating syncope and seizure. According to an optional classification, AUC can be defined as follows, 1-0.9 Excellent, 0.9-0.8 Good, 0.8-0.7 Fairly Good, 0.7-0.6 Weak, and 0.6-0.5 Useless.^[43] AUC for NSE, CPK, and LDH were 0.973 ± 0.023 , 0.827 ± 0.047 , and 0.836 ± 0.043 respectively in 95% confidence level which means they were excellent parameters for recognition. Cut-off points for NSE, CPK, and LDH were determined 25.12, 218.09, and 193.88, respectively. Sensitivity for NSE, CPK, and LDH were 0.932, 0.795, and 0.705 and specificity were 0.955, 0.818, and 0.841, respectively.

Discussion

Seizure and syncope cause loss of consciousness with different etiologies, treatments, and prognoses. Therefore, various objective tests were needed for differential diagnosis of syncope and seizure. EEG was considered as one of the most important treatments for diagnosis of seizure. However, referring to its results can cause problems in diagnosis of it. Determining the level of biomarkers such as NSE, CPK, and LDH can be a reliable method for differential diagnosis of seizure and syncope. The results showed that serum NSE, CPK, and LDH level increased in seizure group in comparison with syncope and control group. AUC result suggested that determining NSE level had excellent diagnostic capability while it was good for CPK and LDH.

Limitations

There were several potential limitations for this study. One limitation was the small sample size and restricted number of centers which led to limited number of patients. It was also possible that some inclusion criteria were missed that could affect the results.

Conclusion

In the present study patients with seizure medical history admitted to the emergency department were recruited. Eligible patients were divided in two groups of seizure and syncope based on their EEG results. The biochemical markers (LDH, CPK, and NSE) levels were measured for the two groups by a reputable laboratory and statistically compared with each other and with control group.

The results showed that CPK and LDH level were higher in seizure compared to syncope group and both were higher than control group. NSE serum level had no meaningful difference in syncope and control group while it was higher in seizure group. Therefore, determining biomarkers level for differential diagnosis of seizure and syncope can be applied as a supplementary test in addition to tests like EEG. It is also recommended to conduct more comprehended researches with broader range of samples in different centers in near future.

Table 1: The characteristics of patients and control group

Variables\Group	Syncope (n=44)	Seizure (n=55)	Control (n=44)	P
Age (year)	47.11±14.9	42.86±11.4	41.36±12.1	0.10
male (female)	23 (21)	32 (23)	25 (19)	0.84
Serum NSE (ng/dl)	16.27±5.02	59.98±25.13	12.63±1.78	<0.0001
CPK (U/l)	190.85±51.73	252.53±50.76	92.79±17.12	<0.0001
LDH (U/l)	163.21±31.95	212.60±40.71	136.42±20.87	<0.0001

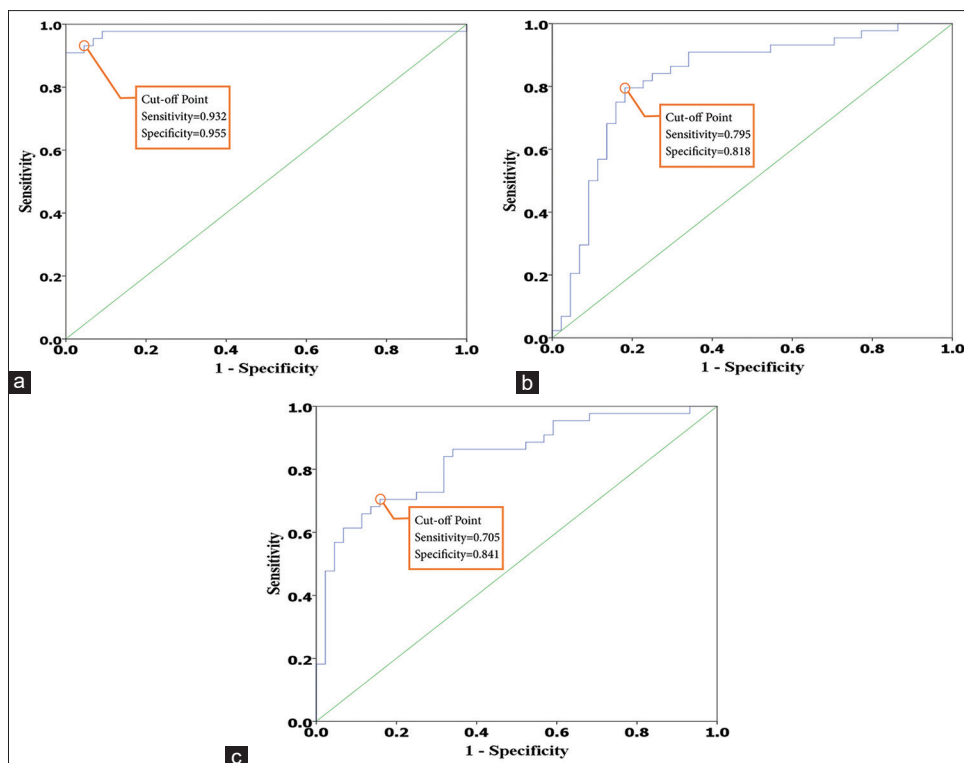


Figure 2: ROC curve and cut-off points of NSE (a), CPK (b), and LDH (c) with relative sensitivity and specificity

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgments

Herein, the authors would like to express their gratefulness to vice chancellor of research of Isfahan University of Medical Sciences for sponsoring this paper, and the respected personnel of the emergency departments of Kashani and Al-Zahra hospitals for their kind contributions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 19 Mar 20 **Accepted:** 04 Aug 20

Published: 08 Apr 22

References

- Ma J-F, Zeng R. Syncope. In: Handbook of Clinical Diagnostics. Singapore: Springer; 2020. p. 89-90.
- Habibabadi JM, Zare M, Naghibi SN, Afzali M, Adibi I, Tabrizi N, *et al.* Frequency of seizure clusters and their associated risk factors in adult patients with epilepsy referred to epilepsy center of Kashani Hospital in Isfahan from 2011 to 2016. *Int J Prev Med* 2020;11:19.
- Hamilton K, Parko K. Epileptic and nonepileptic seizures after traumatic brain injury. In: *Traumatic Brain Injury*. Cham: Springer; 2020. p. 181-96.
- Eizadi-Mood N, Ghandehari M, Mansourian M, Sabzghabae AM, Samasamshariat S, Sadeghi E. Risk of seizure after naloxone therapy in acute tramadol poisoning: A systematic review with meta-analysis. *Int J Prev Med* 2019;10:183.
- Lee SCM, Lueck CJ. Cerebrospinal fluid pressure in adults. *J Neuroophthalmol* 2014;34:278-83.
- Lee SY, Choi YC, Kim JH, Kim WJ. Serum neuron-specific enolase level as a biomarker in differential diagnosis of seizure and syncope. *J Neurol* 2010;257:1708-12.
- Sabu J, Regeti K, Mallappallil M, Kassotis J, Islam H, Zafar S,

- et al.* Convulsive syncope induced by ventricular arrhythmia masquerading as epileptic seizures: case report and literature review. *J Clin Med Res* 2016;8:610-5.
8. Bergfeldt L. Differential diagnosis of cardiogenic syncope and seizure disorders. *Heart* 2003;89:353-8.
 9. Ghearing GR, Munger TM, Jaffe AS, Benarroch EE, Britton JW. Clinical cues for detecting ictal asystole. *Clin Auton Res* 2007;17:221-6.
 10. Mckeon A, Vaughan C, Delanty N. Erratum: Seizures versus syncope (*Lancet Neurology* (2006) 5 (171-180)). *Lancet Neurol* 2006;5:293.
 11. Britton JW, Benarroch E. Syncope and seizures. *Clin Auton Res* 2004;14:148-59.
 12. Sahu S, Nag DS, Swain A, Samaddar DP. Biochemical changes in the injured brain. *World J Biol Chem* 2017;8:21-31.
 13. Francis A, Rivett AJ, Roth JA. Activity of neuron-specific enolase in normal and lesioned rat brain. *Brain Res* 1983;263:89-95.
 14. Marangos PJ, Schmechel DE. Neuron specific enolase, a clinically useful marker for neurons and neuroendocrine cells. *Annu Rev Neurosci* 1987;10:269-95.
 15. Naeimi ZS, Weinhofer A, Sarahrudi K, Heinz T, Vécsei V. Predictive value of S-100B protein and neuron specific-enolase as markers of traumatic brain damage in clinical use. *Brain Inj* 2006;20:463-8.
 16. Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S, Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): Report of the quality standards subcommittee of the American academy of neurology. *Neurology* 2006;67:203-10.
 17. Hu Y, Meng R, Zhang X, Guo L, Li S, Wu Y, *et al.* Serum neuron specific enolase may be a marker to predict the severity and outcome of cerebral venous thrombosis. *J Neurol* 2018;265:46-51.
 18. Göksülük H, Güleç S, Özyüncü N, Kürklü ST, Vurgun VK, Candemir B, *et al.* Comparison of frequency of silent cerebral infarction after coronary angiography and stenting with transradial versus transfemoral approaches. *Am J Cardiol* 2018;122:548-53.
 19. Cunningham RT, Young IS, Winder J, O’Kane MJ, McKinstry S, Johnston CF, *et al.* Serum neurone specific enolase (NSE) levels as an indicator of neuronal damage in patients with cerebral infarction. *Eur J Clin Invest* 1991;21:497-500.
 20. Oh SH, Lee JG, Na SJ, Park JH, Choi YC, Kim WJ. Prediction of early clinical severity and extent of neuronal damage in anterior-circulation infarction using the initial serum neuron-specific enolase level. *Arch Neurol* 2003;60:37-41.
 21. Thelin EP, Jeppsson E, Frostell A, Svensson M, Mondello S, Bellander B-M, *et al.* Utility of neuron-specific enolase in traumatic brain injury; relations to S100B levels, outcome, and extracranial injury severity. *Crit Care* 2016;20:285.
 22. Wolf H, Krall C, Pajenda G, Hajdu S, Widhalm H, Leitgeb J, *et al.* Preliminary findings on biomarker levels from extracerebral sources in patients undergoing trauma surgery: Potential implications for TBI outcome studies. *Brain Inj* 2016;30:1220-5.
 23. Glushakova OY, Valadka AB, Hayes RL, and Glushakov AV. The potential of brain specific blood biomarkers for TBI patient management, diagnosis, and clinical research. In: Wang KKW, editors. *Neurotrauma: A Comprehensive Textbook on Traumatic Brain Injury and Spinal Cord Injury*. Oxford University Press; 2018. p. 189-99.
 24. Honda M, Tsuruta R, Kaneko T, Kasaoka S, Yagi T, Todani M, *et al.* Serum glial fibrillary acidic protein is a highly specific biomarker for traumatic brain injury in humans compared with S-100B and neuron-specific enolase. *J Trauma* 2010;69:104-9.
 25. Gmitterová K, Heinemann U, Krasnianski A, Gawinecka J, Zerr I. Cerebrospinal fluid markers in the differentiation of molecular subtypes of sporadic Creutzfeldt-Jakob disease. *Eur J Neurol* 2016;23:1126-33.
 26. Crowell JL, Wooten GF, Barrett MJ. MM1-Type sporadic Creutzfeldt-Jakob disease with early behavioral changes and prolonged symptom duration. *J Neuropsychiatry Clin Neurosci* 2016;28.2:e31-2.
 27. Samancı Y, Samancı B, Şahin E, Altıokka-Uzun G, Küçükali Cİ, Tüzün E, *et al.* Neuron-specific enolase levels as a marker for possible neuronal damage in idiopathic intracranial hypertension. *Acta Neurol Belg* 2017;117:707-11.
 28. Backman S, Westhall E, Dragancea I, Friberg H, Rundgren M, Ullén S, *et al.* Electroencephalographic characteristics of status epilepticus after cardiac arrest. *Clin Neurophysiol* 2017;128:681-8.
 29. Atici Y, Alehan F, Sezer T, Tuycun N, Haberal A, Yazici AC, *et al.* Serum S100B levels in children with simple febrile seizures. *Seizure* 2012;21:175-7.
 30. Hemmer W, Wallimann T. Functional aspects of creatine kinase in brain. *Dev Neurosci* 1993;15:249-60.
 31. Petramfar P, Yaghoobi E, Nemati R, Asadi-Pooya AA. Serum creatine phosphokinase is helpful in distinguishing generalized tonic-clonic seizures from psychogenic nonepileptic seizures and vasovagal syncope. *Epilepsy Behav* 2009;15:330-2.
 32. Willert C, Spitzer C, Kusserow S, Runge U. Serum neuron-specific enolase, prolactin, and creatine kinase after epileptic and psychogenic non-epileptic seizures. *Acta Neurol Scand* 2004;109:318-23.
 33. Brigo F, Igwe SC, Erro R, Bongiovanni LG, Marangi A, Nardone R, *et al.* Postictal serum creatine kinase for the differential diagnosis of epileptic seizures and psychogenic non-epileptic seizures: A systematic review. *J Neurol* 2015;262:251-7.
 34. Rho JM. Inhibition of lactate dehydrogenase to treat epilepsy. *N Engl J Med* 2015;373:187-9.
 35. Wong KC. Correlation between serum lactate dehydrogenase (LDH) and seizure—an observation in clinical cases. *Int J Adv Sci Eng Inf Technol* 2016;4:99-103.
 36. Khosroshahi N, Alizadeh P, Khosravi M, Salamati P, Kamrani K. Spinal fluid lactate dehydrogenase level differentiates between structural and metabolic etiologies of altered mental status in children. *Iran J Child Neurol* 2015;9:31-6.
 37. Ehsanipour F, Mo’adabi H, Shayanfar N. A comparison of CSF lactic dehydrogenase in children with simple and complex febrile convulsion. *Razi J Med Sci* 2008;15:7-12.
 38. Rash A, McRae M, Fatehi J, Richie D, Solbiati M, Pillay N, *et al.* Assessment of endothelin and copeptin as biomarkers for vasovagal syncope. *Eur J Clin Invest* 2016;46:141-5.
 39. Jaykaran C, Tamoghna B. How to calculate sample size for different study designs in medical research? *Indian J Psychol Med* 2013;35:121-6.
 40. Jean G. A few thoughts on “What is a seizure?”. *Epilepsy Behav* 2011;22(Suppl 1):S2-3.
 41. Bringnol M, Moya A, de Lange F, Deharo J, Elliott P, Fanciulli A, *et al.* "Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope." *European heart journal* 2018;39:21:e43 e80.
 42. Ambrosius WT. *Topics in Bio Statics*. New York, Humana Press; 2007.
 43. Kumar R, Indrayan A. Receiver operating characteristic (ROC) curve for medical researchers. *Indian Pediatr* 2011;48:277-87.