DOI: 10.14744/ejmi.2021.15575
EJMI 2021;5(1):39–44

Research Article

Association between Beta-Hydroxybutyrate Levels and Survival in Sepsis Patients

Ramazan Acar,[1] Ismail Erturk,[1] Gurhan Taskin,[2] Metin Uyanik,[3] Ilker Tasci,[4] Bilgin Bahadir Basgoz,[4] Serhat Ozer,[2] Levent Yamanel,[2] Halil Kiziloz,[5] Murat Emrah Mavis,[6] Canan Porucu,[1] Erdim Sertoglu[7]

[1]Department of Medical Oncology, Unıversity of Health Science, Gulhane Faculty of Medicine, Ankara, Turkey
[2]Department of Intensive Care, University of Health Science, Gulhane Faculty of Medicine, Ankara, Turkey
[3]Department of Biochemistry, Corlu Government Hospital, Tekirdag, Turkey
[4]Department of Internal Medicine, University of Health Science, Gulhane Faculty of Medicine, Ankara, Turkey
[5]Department of Urology, Nevsehir Government Hospital, Nevsehir, Turkey
[6]Sem Laboratory Devices Marketing Industry and Trade Inc., R&D Center, Istanbul, Turkey
[7]Department of Biochemistry, University of Health Science, Gulhane Faculty of Medicine, Ankara, Turkey

Abstract

Objectives: Sepsis is a systemic inflammatory response. Beta-hydroxybutyrate is a product of ketogenesis that develops after the formation of coenzyme A from fatty acids.We aimed to evaluate the association between survival and beta-hydroxybutyrate in sepsis patients.

Methods: This is a single-center, prospective, cross-sectional study. Between May 2018 and May 2019, 51 patients diagnosed with sepsis or septic shock in Gulhane Education and Research Hospital were included in the study. Patients, grouped as non-survivors (Group I) and survivors (Group II) were included in the study and followed for 28 days after their initial blood samples obtained. Plasma beta-hydroxybutyrate level analyses were measured by using Liquid Chromatography Tandem Mass Spectrometry (LC-MS-MS).

Results: Within 28 days, 22 patients died (Group I); 29 patients survived (Group II). The SOFA scores were 12.45±4.22 in Group I and 9.97±3.30 (p=0.022) in Group II, and the APACHE-2 scores were 38.05±6.23 in Group I and 34.10±7.22(p=0.046) in Group II. Beta-hydroxybutyrate levels were 20.4 μM (IQR=9.2-29.98 μM) in Group I and 54.9 μM (IQR=13.55–120.83 μM) in Group II (p<0.05).

Conclusion: Our study is the first showing the clinical significance of beta-hydroxybutyrate in sepsis patients. Our findings on beta-hydroxybutyrate may illuminate a reasonable positive effect.

Keywords: APACHE-2 score, beta-hydroxybutyrate, sepsis, SOFA score

Cite This Article: *Acar R, Erturk I, Taskin G, Uyanik M, Tasci I, Basgoz BB, et al. Association between Beta-Hydroxybutyrate Levels and Survival in Sepsis Patients. EJMI 2021;5(1):39–44.*

According to current data, sepsis is a systemic inflammatory response triggered by infection that affects 6% of all patients admitted to the hospital.[1,2] There are two phases of sepsis: the inflammatory and anti-inflammatory phases.[3,4] Through the struggle of the inflammatory and anti-inflammatory mechanisms, a balance condition can be restored. If this balance, which the body aims to establish, is disrupted in favor of inflammation and oxidative stress, it causes undesired, destructive results.[5]

In the literature, many molecules and scoring systems have been used to predict mortality in patients with sepsis. There are several studies about the development and pre-

Address for correspondence: Ramazan Acar, MD. Saglik Bilimleri Universitesi, Gulhane Tip Fakultesi, Tıbbi Onkoloji Anabilim Dali, Ankara, Turkey
Phone: +90 312 304 41 57 **E-mail:** dr_racar@yahoo.com

Submitted Date: November 15, 2020 **Accepted Date:** January 19, 2021 **Available Online Date:** January 22, 2021

diction of prognosis of sepsis in the literature.[6,7] Compared with survival group APACHE II score, SOFA score, lactate and 24 hours lactate clearance were observed increased in 478 septic shock patients in a cohort study. These biochemical analyses and scoring indices are being used for assessing the severity and predicting prognosis in sepsis.[8] And human antibacterial peptide LL-37 was used for predicting prognosis in 67 elderly sepsis patients comparing with SOFA and APACHE II scores in a different study.[9] These types of studies aiming early detection and more intensive treatment of patients who will progress badly, or less intensive treatment to patients who will progress better and provide less health spending.

In addition to all these, the decrease in β-hydroxybutyrate (BHB) levels in patients with sepsis has been demonstrated to diminish lipolysis and glucose production in recent studies.[10] As is known, BHB is a product of ketogenesis that develops after the formation of coenzyme A from fatty acids in liver mitochondria.[11] Also, indirect effects of BHB on other metabolites with signaling functions including acetyl-CoA, succinyl-CoA and NAD + implicated previously.[12] However, beside this, it is assumed to possess a variety of signaling functions that might provide for broad regulation of cellular functions with implications for metabolic disorders through alterations in post-translational protein function and cell surface receptor activation.[13] Thus, as a signaling molecule, BHB is thought have anti-inflammatory and autophagy-stimulating actions and can induce mTOR-mediated protein synthesis and muscle regeneration.[14,15] Even so, studies evaluating the relationship between BHB and sepsis severity are still insufficient.

Based on all this information, we aimed to conduct an observational analysis to evaluate the clinical significance and relationship between BHB levels, APACHE II and SOFA score calculations, and mortality in sepsis patients.

Methods

This study is a single-center, prospective, cross-sectional study. Between May 2018 and May 2019, 51 patients diagnosed with sepsis or septic shock in Gulhane Training and Research Hospital were included in the study. Sepsis diagnosis was determined according to the Third Sepsis Consensus (Sepsis-3) Report, published by European Society of Intensive Care Medicine (ESICM) in 2016 and updated by the same institution in the 2017 International Sepsis and Septic Shock Management Guide. The Ethics Committee of Gulhane Education and Research Hospital approved the study. All procedures were carried out according to the Helsinki Declaration of 1975 (revised in 2008) and all procedures adhered to the ethical standards of the responsible committee on human experimentation (institutional and national). All of the patients were over 18 years old and were admitted to the clinic with a diagnosis of sepsis. APACHE II and SOFA calculations were performed. Accompanying diseases and medicines were recorded. Serum beta-hydroxybutyrate analyses were performed on the blood samples taken on the first day of hospitalization.

Determination of Serum Levels of BHB Using LC-MS/MS

Analyzes of BHB were performed on 6470 Triple Quadrupole LC/MS system (Agilent Technologies, Santa Clara, CA, USA). For the measurement of BHB concentrations in urine and serum specimens, CE-IVD certified validated Jasem Organic acids LC-MS/MS analysis kit was used (Sem Laboratuar Cihazları Pazarlama San. ve Tic. Inc., Istanbul, Turkey). Before LC-MS/MS analysis, serum samples were prepared concerning the kit sample preparation procedures. In addition to the sample treatment protocols, the analysis kit covers six calibration standards (calibrators) for both matrices in order to establish calibration curves, stable isotope labeled organic acid solution (consisting of methylmalonic acid-2H3) as internal standard (IS), mobile phases (mobile phase A and B), dilution reagent for urine (reagent 1), protein precipitation reagent for serum (reagent 2) analytical column specified for the analysis of organic acids, chromatographic and mass detection parameters of the analytical method. Negative electronic spray ionization (-ESI) in multiple reaction monitoring (MRM) mode was implemented for the MS/MS detection of the analytes. MRM transitions, optimum fragmentation voltages (FV), and optimum collision energies (CE) of the organic acids and assigned IS are presented in Table 1. Data acquisition and quantification were carried out using Agilent MassHunter Acquisition and Quantitative Analysis software programs, respectively. MRM transitions of analytes and LC-MS/MS conditions are presented in Table 1.

Statistical Analysis

The mean (standard deviation) was performed to represent parametric continuous variables, and the median (interquartile ranges and/or minimum–maximum) was used to represent nonparametric variables. Kolmogorov–Smirnov test were used to differentiate parametric and nonparametric variables from continuous data of the patients. The Student's t-test (independent t-test) was used for normally distributed variables and Mann–Whitney U test was used for nonparametric variables. Chi-square test was used for categorical variables. We performed Spearman correlation analysis to assess correlations between beta-hydroxybutyrate levels and SOFA and APACHE II

Table 1. MRM transitions of analytes, IS and MS/MS conditions

Compound Name	Precursor Ion (m/z)	*Product Ion(s) (m/z)	FV (V)	*CE(s) (V)	Polarity
3-OH-Isobutyric acid	103	73	80	5	Negative
2-OH-Butyric acid	102.9	57-44.9	50	8-6	Negative
3-OH-Butyric acid	103.1	59.1	80	4	Negative
**Methylmalonic acid-$^{2}H_{3}$	120	76-58	70	4-26	Negative

*In case of more than one mass transition as product ion, they are shown respectively with corresponding CE value. **Assigned as internal standart (IS). MRM: Multiple reaction monitoring; MS: Tandem mass spectrometry; FV: Fragmentor voltage; CE: Collision energy; V: Voltage.

scores. P<0.05 was considered statistically significant. SPSS Ver.23.0 commercial software was used for the statistical analyzes described.

Results

51 patients were included in the study. 22 patients were non-survivors (43.1%) defined as group I, and 29 survivors (56.9%) defined as group II. When the demographic and comorbid conditions of the two groups were compared, there was no statistical difference in terms of age, gender and body mass index (BMI).

The calculated SOFA and APACHE-II scores were statistically higher in group I than group II. Mean beta-hydroxybutyrate levels of Group I patients with comorbidities such as hypertension (HT), diabetes mellitus (DM), chronic kidney disease (CKD), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), dementia and cerebrovascular disease (CVO) were not significantly different from Group II patients with any accompanying disease (Table 2).

The mean BHB level of Group I was statistically significantly lower than the mean BHB level of Group II. (Table 1). No statistical significances were observed between the two groups in terms of procalcitonin, high sensitive CRP (hs CRP), albumin, neutrophil-lymphocyte ratio (NLR), and white blood cell count levels studied on the first day of hospitalization (Table 3).

While there was a statistically significant negative correlation between APACHE II score and beta-hydroxybutyrate levels in whole patient group (Group I, and Group II); there was no significant correlation between SOFA score and beta-hydroxybutyrate levels (Fig. 1). A significant positive correlation was observed between SOFA and APACHE II scores as expected in all patient groups (Group II and Group II) (Fig. 1). No significant correlations were observed among

Table 2. Dermographic features and comorbid conditions

	Total (n=51)	Non-survivors n=22 (43.1%)	Survivors n=29 (56.9%)	p
Dermographic features				
Age, Avg.±SD	72.49±14.03	74.31±13.48	71.10±14.50	0.463[d]
Gender, women, n (%)	21 (41.2)	9 (40.9)	12 (41.4)	0.973[a]
BMI	27.37±4.63	25.18±3.97	27.34±4.97	0.105[c]
SOFA score, Avg.±SD	11.04±3.89	12.45±4.22	9.97±3.30	**0.022***,[c]
APACHE-II score, Avg.±SD	35.80±7.03	38.05±6.23	34.10±7.22	**0.046***,[c]
Comorbid Dideases, n (%)				
HT	32 (62.7)	12 (54.5)	20 (69.0)	0.291[a]
DM	13 (25.5)	6 (27.3)	7 (24.1)	0.799[a]
CKD	12 (23.5)	7 (31.8)	5 (17.2)	0.224[a]
CHF	19 (37.3)	7 (31.8)	12 (41.4)	0.484[a]
CAD	9 (17.6)	4 (18.2)	5 (17.2)	1.000[b]
COPD	9 (17.6)	4 (18.2)	5 (17.2)	1.000[b]
Demantia	9 (17.6)	5 (22.7)	4 (13.8)	0.474[b]
CVO	5 (9.8)	0 (0)	5 (17.2)	0.062[b]

Avg.±SD: Mean±standard deviation; HT: Hypertension; DM: Diabetes mellitus; CKD: Chronic kidney disease; CHF: Congestive heart failure; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CVO: Cerebrovascular disease; BMI: Body mass index; SOFA: Sequential [Sepsis-related] organ failure assessment; APACHE-II: Acute physiologic and chronic health evaluation. [a]: Pearson chi square test; [b]: Independent sample t test; [c]: Independent sample t test; [d]: Mann- whitney U test.

Table 3. Comparison of major laboratory findings related to sepsis

	Total (n=51)	Non-survivors n=22 (43.1%)	Survivors n=29 (56.9%)	p
Beta-hydroxybutyrate (m/z)*	29.0 (10.28-102.14)	20.4 (9.2-29.98)	54.9 (13.55-120.83)	**p<0.013**
NLR*	12.9 (7.03-22.75)	13 (11.13-29.86)	11.4 (5.75-20.43)	0.149
Procalsitonin(ng/ml)*	3.5 (1.45-21.70)	8.7 (1.34-36.35)	2.7 (1.60-9.55)	0.202
hsCRP (milligram)**	160.41±98.15	178.28±85.03	148.09±105.95	0.295
Albumin (g/dl)**	2.54±0.52	2.48±0.46	2.58±0.56	0.548
White blood count(mm^3)**	16.10±9.81	15.16±10.46	16.78±9.45	0.570

* The values are given as median and interquartile ranges. **The values are given as Mean ± standard deviation; NLR: Neutrophil lymphocyte ratio.

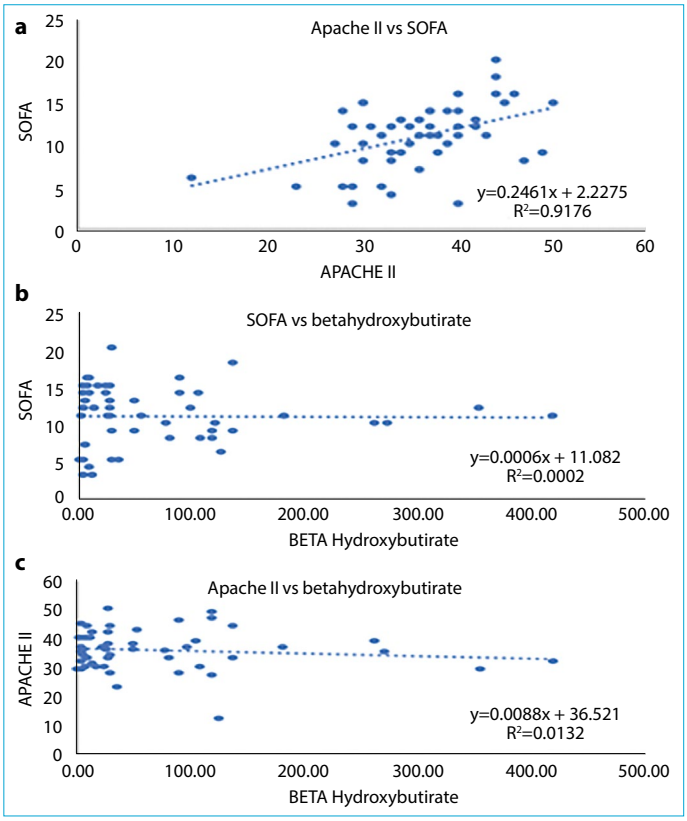

Figure 1. Correlation analysis **(a)** between Apache II and SOFA, **(b)** between SOFA and β-hydroxybutirate, **(c)** between Apache II and β-hydroxybutirate.

APACHE-II: Acute physiologic and chronic health evaluation; SOFA: Sequential [Sepsis-related] organ failure assessment; BETA: Beta-hydroxybutirate.

APACHE II, SOFA, and beta-hydroxybutyrate levels in non-survivor group.

Receiver operating characteristic (ROC) curves were plotted to define discriminative value of beta-hydroxybutyrate, APACHE II and SOFA scores as a prognosis of survival. Figure 2 shows the comparison of BHB, APACHE II and SOFA scores by ROC curves. The area under the ROC curve (AUC) for beta-Hydroxybutyrate to discriminate survival in sepsis patients, was 0.688 (95% confidence interval [CI], 0.543-0.810) (p value=0.0126 for AUC vs 50%). For detecting survival in sepsis patients, beta-hydroxybutyrate cut off value of 50.7 yielded sensitivity of 86.4%, and specificity of 55.2% (Fig. 2).

Discussion

To our knowledge, prior literature has not addressed the comparison of BHB between non- survivors and survivors of sepsis. The levels of BHB in non-survivor sepsis patients were significantly lower than in the survivors, in our study. Additionally, the SOFA and APACHE II scores of the non-survivors were significantly higher than the survivors, as expected.

Karakike et al.[16] showed the SOFA score calculated on day 7 of sepsis as an early prognostic indicator of 28-day mortality and was associated with higher mortality. Godinjak et al.[17] showed that the APACHE II score was predictive of 28-day mortality too. In the current study, both SOFA and APACHE II scores were found to be higher in the non-survivor patients, in accordance with the literature. Both are effective to describe organ dysfunction or failure in critically ill patients. APACHE II score is calculated by physicians in first 24 hours of admission of patients in ICU. It bases upon parameters about comorbidities, laboratory findings of organ functions, age, glaskow coma score and surgery history. SOFA score also has similar parameters like laboratory findings of organ functions and glaskow coma score. APACHE II has more extensive parameters than SOFA. A systemic review of the SOFA and APACHE-II scoring systems found that the APACHE score was slightly superior to the SOFA score in predicting ICU mortality.[18]

Wang X and colleagues tested the effects and underlying mechanisms of exogenous BHB on post-sepsis cognitive impairment. In their study, BHB was identified as a potential pharmacological agent for preventing cognitive impairment.[19] Beylot et al.[20] determined that lipolysis and glucose production decreased due to the infusion of exogenous ketone bodies in septic patients. Lanzo Jacoby and colleagues suggested that plasma ketone bodies remain low during gram-negative sepsis, which was supported by

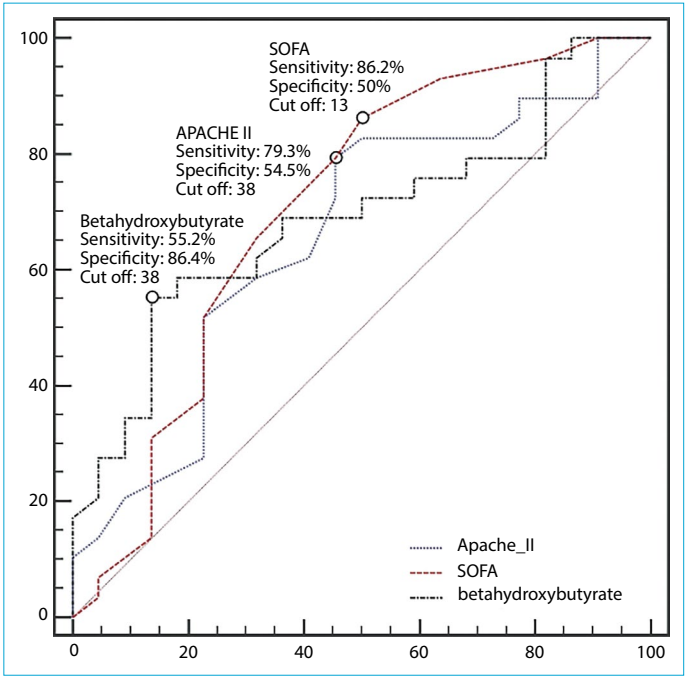

Figure 2. Comparison of beta-hydroxybutyrate, APACHE II and SOFA scores by ROC curves. Receiver operating characteristic (ROC) curves were plotted to define discriminative value of beta-hydroxybutyrate, APACHE II and SOFA scores as a prognosis of survival. Figure 1 shows the comparison of beta-hydroxybutyrate, APACHE II and SOFA scores by ROC curves.

our results regarding hunger status. Also, the BHB levels of the survivor sepsis patients were lower than the non-survivors.[21] Conversely, Gallet D et al.[22] demonstrated an increased lactate/pyruvate ratio with standard BHB/acetoacetate ratios and a lack of oxygen supply dependency in a case study of a patient with fatal septic shock. In the light of these results, we hypothesized that decreased BHB levels should predict survival. And as the result we observed significantly diminished levels of BHB in non-survivors compared to survivors while there was also a negative correlation between BHB levels and APACHE II scores. Considering higher APACHE II score is assumed to predict bad prognosis and mortality in sepsis patients, taking together, decreased BHB and increased APACHE II score, may be more valuable in following the prognosis of sepsis patients.

Regarding the relationship between STD and sepsis process, BHB is well known to have inhibitory effects on insulin glication and glycolysis end products.[23,24] It also has a protective effect on microglial apoptosis. Considering this information, it is thought to be similarly protective in patients with sepsis. Studies have been performed with different biomarkers (paraxonase1, HDL level) to investigate this relationship, and essential data have been obtained.[25] Similarly, high levels of BHB in survivors suggest that this chemical is related to protection in sepsis patients.

In prolonged catabolism, ketone metabolism has evolved to protect against muscle atrophy. The hypercatabolic condition worsens the clinical course in patients with sepsis. BHB prevents lipolysis via PUMA-G receptor.[26] It reduces energy consumption by inhibiting short-chain fatty acid signal via GPR 41.[27] Most importantly, it reduces inflammation with NLRP3 blockade.[14] It protects muscle mass through these mechanisms. In addition, hyperglycemia is one of the most prominent features of sepsis and is associated with mortality. With BHB monoester supplement, hyperglycemia decreases thanks to the specified pathways. Therefore, mortality decreases in patients with high BDH levels.[10]

The present study has some limitations. Firstly, our study is limited to the analysis of the limited number of patients. It has been studied in sepsis patients and we had no healthy control group. However, we think that our study is meaningful and valuable with the reason that it has not been studied before in the literature and it is a clinical study. In this context, BHB should be used in sepsis both in predicting survival and in the treatment of patients with sepsis. This study is based on a limited number of patients and thus cannot ascertain whether these findings apply to other patients with sepsis. The diagnostic predictive values of all parameters in ROC results are low. Accordingly, more extensive clinical studies will be necessary for confirmation of these findings.

Conclusion

SOFA based scores are widely used for predicting mortality in ICU. They contain many parameters. We showed that only one parameter-BHB level is enough for predicting mortality. This may cost effective and sooner than calculating APACHE or other scoring systems. Time is important due to quick treatment decision is essential in evaluation of ICU patients.

Disclosures

Acknowledgement: We thank to Management of the University of Health Science, Gulhane Training and Research Hospital and our patients and their families who participated in the research devotedly.

Ethics Committee Approval: The study protocol was approved by Gulhane Education and Research Hospital Ethics Committee with 26/04/2018 dated and 18/118 numbered decision.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Authorship Contributions: Concept – R.A.; Design – R.A.,E.S.; Supervision – L.Y., E.S.; Materials – C.P., R.A., S.O., G.T.; Data collection &/or processing – R.A., C.P., S.O., B.B.B.; Analysis and/or interpretation – E.S., M.U., H.K., M.E.M.; Literature search – R.A., I.E., I.T.; Writing – R.A., İ.E., E.S.; Critical review – R.A., İ.E., E.S.

References

1. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. Jama 2017;318:1241–9.
2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive care medicine 2017;43:304–77.
3. Galley HF. Oxidative stress and mitochondrial dysfunction in sepsis. British journal of anaesthesia 2011;107:57–64.
4. Pinsky MR. Dysregulation of the immune response in severe sepsis. The American journal of the medical sciences 2004;328:220–9.
5. Andrades ME, Ritter C, Dal-Pizzol F. The role of free radicals in sepsis development. Front Biosci (Elite Ed) 2009;1:277–87.
6. Na L, Ding H, Xing E, Zhang Y, Gao J, Liu B, et al. The predictive value of microRNA-21 for sepsis risk and its correlation with disease severity, systemic inflammation, and 28-day mortality in sepsis patients. Journal of Clinical Laboratory Analysis 2020;34:e23103.
7. Jobin S, Maitra S, Baidya DK, Subramaniam R, Prasad G, Seenu V. Role of serial lactate measurement to predict 28-day mortality in patients undergoing emergency laparotomy for perforation peritonitis: prospective observational study. Journal of Intensive Care 2019;7:58.
8. Zhao M, Duan M. Lactic acid, lactate clearance and procalcitonin in assessing the severity and predicting prognosis in sepsis. Zhonghua wei Zhong Bing ji jiu yi xue 2020;32:449–53.
9. Guo W, Wang C, Huo F, Li H, Yan Y, Xu S, et al. Evaluation value of human antibacterial peptide LL-37 on the prognosis of elderly patients with sepsis. Zhonghua wei zhong bing ji jiu yi xue 2018;30:1011–6.
10. Soto-Mota A, Norwitz N, Clarke K. Why a d-β-hydroxybutyrate monoester? Biochemical Society Transactions 2020;48.51–9.
11. Akram M. A focused review of the role of ketone bodies in health and disease. Journal of medicinal food 2013;16:965–7.
12. Quant PA, Tubbs PK, Brand MD. Treatment of rats with glucagon or mannoheptulose increases mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase activity and decreases succinyl-CoA content in liver. Biochemical Journal 1989;262:159–64.
13. Newman JC, Verdin E. β-hydroxybutyrate: much more than a metabolite. Diabetes research and clinical practice 2014;106:173–81.
14. Youm Y-H, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease. Nature medicine 2015;21:263–9.
15. Vandoorne T, De Smet S, Ramaekers M, Van Thienen R, De Bock K, Clarke K, et al. Intake of a ketone ester drink during recovery from exercise promotes mTORC1 signaling but not glycogen resynthesis in human muscle. Frontiers in physiology 2017;8:310.
16. Karakike E, Kyriazopoulou E, Tsangaris I, Routsi C, Vincent JL, Giamarellos-Bourboulis EJ. The early change of SOFA score as a prognostic marker of 28-day sepsis mortality: analysis through a derivation and a validation cohort. Critical care 2019;23:387.
17. Godinjak A, Iglica A, Rama A, Tančica I, Jusufović S, Ajanović A, et al. Predictive value of SAPS II and APACHE II scoring systems for patient outcome in a medical intensive care unit. Acta medica academica 2016;45:97–103.
18. Minne L, Abu-Hanna A, de Jonge E. Evaluation of SOFA-based models for predicting mortality in the ICU: A systematic review. Critical care 2008;12:R161.
19. Wang X, Song Y, Chen J, Zhang S, Le Y, Xie Z, et al. Subcutaneous administration of β-hydroxybutyrate improves learning and memory of sepsis surviving mice. Neurotherapeutics 2019;27:616–26.
20. Beylot M, Chassard D, Chambrier C, Guiraud M, Odeon M, Beaufrère B, et al. Metabolic effects of a D-beta-hydroxybutyrate infusion in septic patients: inhibition of lipolysis and glucose production but not leucine oxidation. Critical care medicine 1994;22:1091–8.
21. Lanza-Jacoby S, Rosato E, Braccia G, Tabares A. Altered ketone body metabolism during gram-negative sepsis in the rat. Metabolism 1990;39:1151–7.
22. Gallet D, Goudable J, Vedrinne J-M, Viale J-P, Annat G. Increased lactate/pyruvate ratio with normal b-hydroxybutyrate/acetoacetate ratio and lack of oxygen supply dependency in a patient with fatal septic shock. Intensive care medicine 1997;23:114–6.
23. Kashiwaya Y, Takeshima T, Mori N, Nakashima K, Clarke K, Veech RL. d-β-Hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. Proceedings of the National Academy of Sciences 2000;97:5440–4.
24. Lim S, Chesser AS, Grima JC, Rappold PM, Blum D, Przedborski S, et al. D-β-hydroxybutyrate is protective in mouse models of Huntington's disease. Plos one 2011;6:e24620.
25. İnal V, Yamanel L, Taşkın G, Tapan S, Cömert B. Paraoxonase 1 activity and survival in sepsis patients. Balkan medical journal 2015;32:183–8.
26. Taggart AK, Kero J, Gan X, Cai T-Q, Cheng K, Ippolito M, et al. (D)-β-hydroxybutyrate inhibits adipocyte lipolysis via the nicotinic acid receptor PUMA-G. Journal of Biological Chemistry 2005;280:26649–52.
27. Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). Proceedings of the national academy of sciences 2011;108:8030–5.