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Pyruvate in Potential Supportive Therapy in Critical Covid-19

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Highlights

Pyruvate protects organ metabolism and function, which anions in current fluids do not.

Clinical studies showed oral or intravenous pyruvate in large doses were safe.

Pyruvate may be a powerful supportive therapy in treating critical care patients.

Oral and intravenous pyruvate solutions may be compassionately used in Covid-19.

Abstract

The focus of present review is on the proposal that pyruvate may be a potential candidate in treating critical care patients with Covid-19 virus infection. The pyruvate anion has beneficial properties to protect organ function by increase of hypoxia/anoxia tolerance, correction of hypoxic lactic acidosis, exertion of anti-oxidative stress/inflammation, protection of mitochondrial function and inhibition of apoptosis. The key effect is reactivation of depressed pyruvate dehydrogenase in various pathogenic insults. These benefits are unparalleled with anions in current medical fluids. Pyruvate in intravenous or oral rehydration salt (ORS) may be a powerful supportive care in treatment of severe virus infection with Covid-19 and critical care patients. Recent studies demonstrate that intravenous pyruvate is superior to regular fluids and pyruvate-enriched ORS (Pyr-ORS) is advantageous over WHO-ORS in organ protection, acidosis correction and survival improvement in severe shock resuscitation in animals. While pyruvate is not yet approved by the FDA, there were many clinical studies on treatment of various diseases with a large dosage of its intravenous or oral form since 1940s. These studies, using the products at the time, indicate pyruvate's clinical effectiveness and absence of adverse effects, which resembled the phase II clinical trial of a novel drug. Therefore, it is logical to consider randomized clinical trials of pyruvate in treatment of Covid-19 or Ebola infection as well as critical care patients as a beneficial supportive therapy, albeit it is not an anti-virus agent, particularly using a low pyruvate dose in Pyr-ORS formulas, under protocols of compassionate use.

Keywords: Hypoxia, Lactic acidosis, Oral rehydration salt, Pyruvate, Resuscitation, Virus, Covid-19

Pyruvate in Potential Supportive Therapy in Critical Covid-19

The treatment of severe novel coronavirus disease (Covid-19) and other virus infection as well as critical illnesses requires an ideal systemic aggressive supportive care, including adequate fluid management [1,2]. The current composition of therapeutic fluids remains unsatisfactory (see below) for meeting clinical requirements in severe Covid-19 infection amid critical care patients.

Pyruvate-enriched oral or intravenous (IV) solutions as a powerful adjuvant or nutrition would be more beneficial for treating severe virus infections.

1, Pyruvate potential effects on cell metabolism and function in severe virus infection

While there is no research regarding pyruvate effects on virus infections with Covid-19, Ebola virus disease (EVD), or MERS, we propose that pyruvate could be ideally one of favorable supportive remedies in fighting severe virus infection, including Covid-19. It is crucial to provide optimized supportive care, including adequate fluids and proper nutrition in EVD patients with diarrhea. The World Health Organization-guided oral rehydration salt/solution (WHO-ORS) is one of regular fluids in EVD fluid management [2,3]. It could be also used in the case of treating critical care patients with or without Covid-19 and would be more appreciated additionally with pyruvate replacement. In 1999, IV hypertonic pyruvate was first demonstrated to improve systemic metabolism and survival in resuscitation from severe hemorrhagic shock in swine [4]. Subsequent studies with regular doses further evidenced pyruvate effects on multi-organ protection, lactic acidosis correction and survival improvement in various animal models with severe shock [5,6].

Experimental pyruvate-enriched ORS (Pyr-ORS) was first proposed in 2012 with equimolar pyruvate to replace the alkalizer: bicarbonate or citrate in WHO-ORS (I, II or III). Pyr-ORS was superior to WHO-ORS in the oral rehydration of lethal shock animals, resulting in significant visceral hemodynamics and vasopermeability improvement, multi-organ protection and robust survival increase [7-9]. Compared to anions in current medical fluids: chloride, bicarbonate, lactate, acetate, citrate, gluconate and even malate, pyruvate replacement does not only avoid Resuscitation Injury induced by some of them (commonly chloride, lactate and acetate), but also provide cell/organ protection as a therapeutic agent in addition to a blood volume expander [10]. Pyruvate confers several significant pharmacologic and therapeutic advantages that benefit critical care patients, particularly targeting the typical clinical features in novel coronavirus pneumonia (NCP) induced with Covid-19: hypoxemia and inflammatory cytokine storm (dyspnoea and lymphopenia) that are key facets of the NCP pathophysiological defects [1]. The main arguments for pyruvate-enriched ORS and IV fluids to be trialed in severe virus infection

diseases along with critical care patients, are as follows. All experimental evidence below is from preclinical studies.

1.1, **Pyruvate increase of cellular anoxia/hypoxia tolerance**

Pyruvate enhances hypoxia tolerance predominantly by improvement of glycolysis via its spontaneous reductive reaction with lactate dehydrogenase (LDH), coupled with NADH oxidation and the enhancement of NAD^+/NADH (nicotinamide adenine dinucleotide: oxidized form/reduced form) ratio that is essential in systemic metabolic pathways. The glycolytic promotion in the step of glyceraldehyde-3-phosphate dehydrogenase (G-3-PD) and pyruvate kinase (PK) stimulation by pyruvate together leads to a sustained glycolytic ATP level, which cellular basic function depends on [10,11]. The LDH reductive reaction is a systemic alkalizing pathway with proton ($[H^+]$) consumption. The pivotal role of LDH reductive pathway is substantiated in its cell-protection of anaerobic metabolism by the fact that the lactate-binding compound consumes $[H^+]$ and converts pyruvate to lactate, leading to a higher NAD^+/NADH ratio and improving acidosis in anoxic conditions [12]. Pyruvate improvement of cellular hypoxia tolerance is also shown in glucose oxidation via the pyruvate dehydrogenase (PDH) reactivation by direct inhibition of PDH kinase (PDK), as dichloroacetate (DCA) and other PDK inhibitors [13-15], and enhance pyruvate carboxylase (PC) activity with favorable anaplerosis (replenishment of tricarboxylic acid (TCA)-cycle substrates), resulting in promotion of oxidative phosphorylation in TCA-cycle and preservation of mitochondrial ATP generation in hypoxic conditions [6,7,15]. Our novel findings demonstrate that pyruvate efficiently reactivates depressed PDH activities through the PDK inhibition in both high glucose-treated HK-2 (human kidney tubular epithelium) cells*, in vitro,* [16] and diabetic *db/db* mice, *in vivo* (data submitted for publication). Both restoration of glycolytic pathways and activation of depressed PDH induced by exogenous pyruvate occur in anoxic conditions. Therefore, increasing PDH flux accompanied with the LDH reduction improves acute hypoxia tolerance [11,13,15]; further, the representative of glucometabolic disorders: Warburg phenomenon (increased glucose uptake and fermentation of glucose to lactate but inhibited oxidative phosphorylation in aerobic conditions) can be reversed by exogenic pyruvate in diabetic *db/db* mice (ibid). Glucometabolic pathways rejuvenation may also be facilitated with hypoxia-inducible factor-1α-erythropoietin (HIF-1α-EPO) signal stimulation by exogenous pyruvate in both hypoxia and normoxia [6,10]. Further, pyruvate preserves red blood cells (RBCs) 2,3-diphosphoglycerate (2,3-DPG), ATP

generation/ATPase activity and oxygen-carrier function (right shift of oxygen dissociation curve) with anoxia and oxidative stress albeit the clinical benefit needs further explored [10,11]. The post-pyruvate metabolic profile has been clearly illustrated previously [10,17].

1.2, **Pyruvate as a superior alkalizer for hypoxic lactic acidosis**

Pyruvate is a superior alkalizer in the correction of hypoxic lactic acidosis, one of fatal complications in critical care patients, which was demonstrated with oral, IV, or peritoneal resuscitation from severe shock in animals and was clinically illustrated at least in one case report on oral pyruvate therapy in a patient with a novel PDH mutation [17-19].

Although clinical lactic acidosis was not concerned, patients with severe Covid-19 infection displayed a high LDH activity [1,20]. The overexpressed LDH reduction may promote the onset and progression of fatal hypoxic lactic acidosis due to concomitant inhibition of oxidative phosphorylation by infection, oxidative stress and hypoxia, while pyruvate inhibits the LDH activity as indicated in a murine transfusion model and diabetic *db/db* mice [21, ibid]. In theory, as the enzymatic substrate of both LDH reduction and PDH oxidative decarboxylation, pyruvate is basically the sole anion responsible for correction of severe hypoxic lactic acidosis. The key underlying mechanism may lie in pyruvate's inherent ability of glucometabolic improvement with optimal [H^+] ions metabolic consumption in processes of LDH reductive reaction, PDH-reactivated oxidative phosphorylation and gluconeogenesis [17,18]. The low dissociation constant of pyruvate *p*Ka value (2.49) with weaker buffering capacity is an additional factor to raise blood pH [6,17].

1.3, **Pyruvate as a powerful anti-oxidative/inflammatory agent**

Pyruvate is a powerful anti-oxidative/nitrosative stress and anti-inflammatory agent. It owns double reactions (direct and indirect) with oxidative agents, leading to increase of GSH/GSSG (glutathione reduced/oxidized form) ratio by restoration of glycolytic pathways besides $NAD(P)^+$/NAD(P)H (nicotinamide adenine dinucleotide (phosphate): oxidized/reduced form) enhancement [10]. It also has a strong inhibitory property of inflammation: secretion of inflammatory mediators (IL-2, IL-6, TNF- α , NF- κ B and HMGB-1) and infiltration of inflammatory cells [5,21-23]. Severe Covid-19 infected patients induce hyper-cytokinemia [1]. Tocilizumab, one of IL-6 blockers, has shown its efficacy in Covid-19 patients [24]. Therefore,

pyruvate may facilitate IL-6 blockers to quickly eliminate systemic inflammatory cytokine storm in Covid-19 infection.

1.4, **Pyruvate protection of mitochondrial structure and function**

Pyruvate also protects mitochondrial structure and function, promoting the inhibition of cellular apoptosis [16,25], which is demonstrated not only with lung, the major target organ with Covid-19 infection [1], but also with liver, kidney and even endothelium and lens by virus infection, ischemic injury, oxidative stress damage or high glucose stimulation as diabetes [1,10,16]. Further, pyruvate may be superior to so-called 'anti-aging Star Molecule': NAD^+ because it spontaneously produces NAD^+ on the equimolar basis by the LDH reduction free of energy in anoxia in addition to direct stimulation of PDH by the PDK inhibition, molecular reaction with oxidants and HIF-1α and to decrease of advanced glycation end products (AGEs) in tissues [10]. A recent study demonstrates pyruvate is more protective than equimolar NAD^+ in cell viability of human skin fibroblast cultures: pyruvate preserved survival of fibroblast cells more than equimolar NAD^+, indicating different underlying protective mechanisms [26].

None of current medical anions have pyruvate's life-saving advantageous characteristics above. Accordingly, pyruvate would efficiently improve systemic metabolisms and protect multi-organ function; it might be a super blood volume expander in care of patients subjected with severe Covid-19 or EVD [17], who are susceptible to multiple organ, including kidney, failure in addition to acute respiratory failure [1]. Further, pyruvate-based hydroxyethyl starch (HES) 130/0.4 also protects kidney in resuscitation of severe shock as pyruvate-based crystalloids in animal studies [27]. Recently, the US authoritative research team in the project also actively recommended to use pyruvate in clinical shock resuscitation [28].

As to pyruvate effect on infection, although intensive studies with pyruvate are still lacking on treatment of bacterial infection and sepsis, preliminary researches have outlooked that pyruvate as a supportive care may favor to control infection and improve survival in clinical scenarios [29,30]. Despite it does not directly affect virus growth, pyruvate inhibits cytokines: IL-1β, IL-2 and TNF-α levels and affects the immune response in mouse macrophages infected with influenza A virus (Abysalamah HM. Sodium pyruvate alters the immune response to influenza A virus infection in macrophages. MSU Graduate Theses 2018; 3301). Further studies are required in this respect.

2, Clinical data support of pyruvate safety

Although sodium pyruvate has been a chemical to be developed as a novel medicine without the FDA approval, many preliminary clinical tests for various diseases were reported with the products at the time since 40s last century, which were cited and focused here on the doses used and any clinical adverse effects.

2.1 **Intravenous pyruvate in humans**

As early as the 1940s, 18.8g of sodium pyruvate (12%) prepared immediately before injection was intravenously infused into 7 schizophrenic patients with/without psychotic symptom [31]. Blood pyruvate rapidly reached the peak 4 min after the injection completed and sustained for 45 min, then returned close to normal in 90 min. Only 2-3% of pyruvate were excreted in the urine. There was no adverse effect released in the paper, which was followed by a subsequent research in patients. Then, in 1996 after half century later, there emerged the first report on IV pyruvate treatment of chronic liver diseases [32]. A large dose of IV pyruvate (54-86.4 g/d) was used for 10-15d; liver function tests and hepato-pathological examinations showed promising outcomes, strongly suggesting that the pyruvate product studied half century ago does not damage liver cells. The resemble reports were released afterwards [33].

In 1999, the Lancet first reported 8 patients with dilated cardiomyopathy treated with pyruvate infusion into the coronary artery. Pyruvate infusion in 1.53g and 3.05g (according to concentrations and volumes used) in 30 min (15 min for each) significantly increased cardiac index and stroke-volume index, however, decreased pulmonary capillary wedge pressure [34]. Myocardial performance and hemodynamics improvements were also released by intracoronary infusion of pyruvate in 9 patients with congestive heart failure and 8 patients subjected to acute myocardial infarction with cardiac shock [35]. The former per patient was infused with pyruvate of 0.495g, 0.990g and 1.980g per 10 min, respectively; the doses in the later per patient were, totally in 5.940g, separately infused in 10 min at 10 min interval for three times. Further, a low dose of pyruvate as cardioplegia also showed promising benefits in cardiopulmonary bypass surgery [36]. Pyruvate cardioprotection with positive inotropic effect has also been extensively studied with failing human heart [37]. In addition, pyruvate loading tests were repeatedly reported with IV infusion of 0.5g/kg for 10 min in children and young adults in the past decades [38].

2.2, **Oral pyruvate in humans**

Recently, a large dose (30-60g/d) of oral pyruvate was also used in treatment of 6 diabetic patients (type I) and 1 mitochondrial diabetes patient; total daily insulin injection was apparently reduced because of its stimulation of insulin secretion and hypoglycemia. Interestingly, oral pyruvate (0.3g/kg/d for 3-6 months) also enhanced fasting insulin secretion in 10 non-diabetic citrin-deficient children without blood sugar changes [39-41].

It was reported that a one-year-old child subjected to myopathic mitochondrial DNA depletion syndrome was improved with the clinical score and life quality by enteral pyruvate of 0.5g/kg for a month. Further, a large dose and long-term therapy with oral pyruvate (0.5g/kg, three times a day for months) also showed clinical improvement and promising decreases of plasma lactate/pyruvate ratio and lateral ventricular lactate in 11 patients subjected to lactic acidosis-accompanied mitochondriopathy without obvious side-effects [42,43].

2.3, **Non-toxic clinical adverse effects**

All reported patients with pyruvate administration, via external application (eye drops, inhalation and skin therapy), oral ingestion or IV infusion, were clinically safe with the absence of toxic side effects [31-43], but one only with myocardiopathy, who might die of acute hyperosmolar status with sodium, other than pyruvate, *per se* [44]. It was reported that LD_{50} of oral pyruvate is 10.0g/kg in rats; LD_{50} of IV pyruvate is 1.25g/kg in mice, which can be classified as a nontoxic substance in humans [32]. All clinical manifestations of adverse effects: gastrointestinal irritation at varying degrees, such as nausea, flatulence and diarrhea, were from oral, instead of IV, administration at a large dosage [10]. Because the pyruvate uses in over 2 hundred patients above strongly indicate its clinical safety and effectiveness, which likely mimicked a phase II clinical trial of a novel drug, the pyruvate clinical trial in treatment of severe Covid-19 and EVD/MERS infection as well as critical care patients as a superior supportive approach should be concerned particularly by oral administration.

3, Clinical approach and implication

3.1, **Clinical options**

Pyruvate is potentially a promising novel drug for protection of multi-organ function and improvement of acid-base disturbance, which is advantageous over current medical anions. The overdose of chloride in normal saline (NS) is an iatrogenic toxin due to hyperchloremia-induced renal failure; regular lactated Ringer's solution (LR) worsens hyperlactemia-inhibited glycolysis and possibility of lethal hypoxic lactic acidosis in critical care patients. Both NS and LR also facilitate systemic inflammatory reactions [6,17,45]. In addition, a large volume of acetate solution may lead to lactic acidosis [46]; although malate may enable to correct lactic acidosis, it cannot be metabolized under anoxia and has no RBCs protection [17]. Use of pyruvate anion in fluids (pyruvate saline: [Na^+] 154 mM; [Cl^-] 104 mM; [Pyr^-] 50 mM [11], or pyruvate Ringer's solution: [Pyr^-] 28 mM [6]) would be the best though the acetate-based solution is the first choice at present, as pyruvate-enriched fluids (oral or IV solution) are not available. It is highly possible in managing severe virus infection, like Covid-19, with fluid therapy that pyruvate substitute is in the hope of decreasing the ICU admission, intubation and stay and increasing survival. Mainly due to enhancement of hypoxia tolerance and inhibition of cytokine storm as well as the absence of clinical toxicity, pyruvate-enriched fluids would illustrate a potential advantageous option in critical care patients under protocols of compassionate use, particularly along with specific pro-antiviral drugs, like Remdesivir or Chloroquine.

Finally, it is worthwhile to select that pyruvate in Pyr-ORS, modified formulas if needed (the standard formula: sodium pyruvate 3.5g, sodium chloride 2.0g, potassium chloride 1.5g and anhydrate glucose 13.5g per liter [18] with flavor additives), is more feasible than pyruvate prepared in IV fluids for severe cases with Covid-19 infection, as ample WHO-ORS used in EVD prevention and treatment. Notably, ingestion of less 20.0g of pyruvate dose not function well in humans instead of animals, but an oral small dose of pyruvate together with appropriate glucose would be beneficial in human beings, according to the principle of WHO-ORS composition [7-10]. In fact, enteral Pyr-ORS is just like a functional drink to rehydrate and supply energy as one of nutrition remedies in patients with Covid-19 or Ebola infection, via a nasogastric tube if needed. Accordingly, its indication may be for all Covid-19 patients subjected to asymptomatic or moderate infection to promote recovery, but mainly for severe or critical NCP patients with or without complicated cardiovascular or hepatorenal parenchymatous diseases, obesity and diabetes and aging to enhance survival. It is also widely suitable for patients from various critical illnesses to diabetes, degenerative/aging and even cancer plenty supported by animal studies

[10,28]. Generally, the majority of these diseases share some common pathophysiological processes in various degrees in humans: hypoxia/ischemia, glucometabolic disorders (commonly Warburg effect), acidosis, oxidative/ nitrosative stress, inflammation and apoptosis, particularly in critical care patients including severe virus infection with multi-organ dysfunction, albeit existing underlying etiological divergence and diverse clinical manifestations. On the other hand, fluid therapy plays one of central roles in the treatment of critical diseases. Up to date, there is not a single drug that simultaneously owns the beneficial behaviors of pyruvate aforementioned [47,48]. To better meet therapeutic requirements, the pyruvate replacement in fluids is apparently an optimal option: avoiding iatrogenic toxicity of current anions and providing organ protection. As to Covid-19, pyruvate enhancement of hypoxia tolerance and counter-effect of cytokines storm would right target its clinical and pathological features, with or without current effective medicine potentially improving survival.

Although numerous studies on ethyl pyruvate (EP, a derivative of sodium pyruvate) has demonstrated its comparable beneficial effects to pyruvate on multi-organ protection in various animal models, which further enforce pyruvate superiority, EP does not work in humans [10]. The detailed approach to administer Pyr-ORS may further refer to previous experiences in critical care patients in the top hospitals [49,50].

3.2, **Limitations**

Despite there was no definite adverse effect in numerous studies of animals and humans with a large dosage of pyruvate used, there is no pyruvate report on animal research or clinical application in patients with Covid-19 virus infection, either. Studies on pyruvate effects on virus infections, particularly on Covid-19 virus, in animals are urgently warranted. Pyruvate aqueous solutions are not stable at room temperature, but a patented simple approach has solved the problem for long-term stability of pyruvate-enriched solutions [10]. Stable pyruvate preparations are not currently available, however, oral and IV pyruvate fluids obtained prior to clinical use from a powder preparation as reported in references are possible in clinical trials under protocols as a compassionate use in Covid-19 patients.

Abbreviations

ATP: adenosine triphosphate, **Covid-19**: 2019-novel coronavirus disease, **EVD**: Ebola virus disease, **GSH/GSSG**: glutathione reduced/oxidized form, **H^+**: hydrogen/proton, **LDH**: lactate dehydrogenase, **MERS**: middle east respiratory syndrome, **$NAD(P)^+$/NAD(P)H**: nicotinamide adenine dinucleotide (phosphate): oxidized/reduced form, **NCP**: novel coronavirus pneumonia, **PDH**: pyruvate dehydrogenase, **PDK**: pyruvate dehydrogenase kinase, **Pyr-ORS**: pyruvate-enriched oral rehydration salt/solution, **WHO-ORS**: World Health Organization-oral rehydration salt/solution, **TCA-cycle**: tricarboxylic acid-cycle.

References

[1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506. doi: 10.1016/S0140-6736(20)30183-5.

[2] Fischer WA 2nd, Crozier I, Bausch DG, Muyembe JJ, Mulangu S, Diaz JV, Kojan R, Wohl DA, Jacob ST. Shifting the paradigm - applying universal standards of care to Ebola virus disease. N Engl J Med. 2019;380:1389-91. doi: 10.1056/NEJMp1817070.

[3] Ansumana R, Jacobsen KH, Sahr F, Idris M, Bangura H, Boie-Jalloh M, Lamin JM, Sesay S. Ebola in Freetown area, Sierra Leone--a case study of 581 patients. N Engl J Med. 2015;372:587-8. doi: 10.1056/NEJMc1413685.

[4] Mongan PD, Fontana JL, Chen R, Bünger R. Intravenous pyruvate prolongs survival during hemorrhagic shock in swine. Am J Physiol. 1999;277:H2253-63. doi: 10.1152/ajpheart.1999.277.6.H2253.

[5] Flaherty DC, Hoxha B, Sun J, Gurji H, Simecka JW, Mallet RT, Olivencia-Yurvati AH.Pyruvate-fortified fluid resuscitation improves hemodynamic stability while suppressing systemic inflammation and myocardial oxidative stress after hemorrhagic shock. Mil Med. 2010;175:166-72. doi:10.7205/milmed-d-09-00161.

[6] Hu S, Bai XD, Liu XQ, Wang HB, Zhong YX, Fang T, Zhou FQ. Pyruvate Ringer's solution corrects lactic acidosis and prolongs survival during hemorrhagic shock in rats. J Emerg Med. 2013;45:885-93. doi: 10.1016/j.jemermed.2013.04.062.

[7] Hu S, Liu WW, Zhao Y, Lin ZL, Luo HM, Bai XD, Sheng ZY, Zhou FQ. Pyruvate-enriched oral rehydration solution improved intestinal absorption of water and sodium during enteral resuscitation in burns. Burns. 2014;40:693-701. doi: 10.1016/j.burns.2013.09.030.

[8] Yu W, Hu S, Xie ZY, He ZJ, Luo HM, Lin HY, Zhou FQ, Sheng ZY. Pyruvate oral rehydration solution improved visceral function and survival in shock rats. J Surg Res. 2015;193:344-54. doi: 10.1016/j.jss.2014.06.037.

[9] Liu R, Hu XH, Wang SM, Guo SJ, Li ZY, Bai XD, Zhou FQ, Hu S. Pyruvate in oral rehydration salt improves hemodynamics, vasopermeability and survival after burns in dogs. Burns. 2016;42:797-806. doi: 10.1016/j.burns.2016.01.012.

[10] Zhou FQ. Pyruvate research and clinical application outlooks a revolutionary medical advance. Int J Nutr. 2020;5:1-8. doi: 10.14302/issn.2379-7835.ijn-20-3159.

[11] Gou D, Tan H, Cai H, Zhou F. Pyruvate effects on red blood cells during in vitro cardiopulmonary bypass with dogs' blood. Artif Organs. 2012;36:988-91. doi: 10.1111/j.1525-1594.2012.01482.x.

[12] Acharya AP, Rafi M, Woods EC, Gardner AB, Murthy N. Metabolic engineering of lactate dehydrogenase rescues mice from acidosis. Sci Rep. 2014;4:5189. doi: 10.1038/srep05189.

[13] Sheeran FL, Angerosa J, Liaw NY, Cheung MM, Pepe S. Adaptations in protein expression and regulated activity of pyruvate dehydrogenase multienzyme complex in human systolic heart failure. Oxid Med Cell Longev. 2019 Feb 7;2019:4532592. doi: 10.1155/2019/4532592.

[14] Wu CY, Satapati S, Gui W, Wynn RM, Sharma G, Lou M, Qi X, Burgess SC, Malloy C, Khemtong C, Sherry AD, Chuang DT, Merritt ME. A novel inhibitor of pyruvate dehydrogenase kinase stimulates myocardial carbohydrate oxidation in diet-induced obesity. J Biol Chem. 2018;293:9604-13. doi: 10.1074/jbc.RA118.002838.

[15] Sato K, Mochida S, Tomimoto D, Konuma T, Kiyota N, Tsuda S, Shiga Y, Omodaka K, Nakazawa T. A pyruvate dehydrogenase kinase inhibitor prevents retinal cell death and

improves energy metabolism in rat retinas after ischemia/reperfusion injury. Exp Eye Res. 2020;193:107997. doi: 10.1016/j.exer.2020.107997.

[16] Zhang XM, Wang YZ, Tong JD, Ning XC, Zhou FQ, Yang XH, Jin HM. Pyruvate alleviates high glucose-induced endoplasmic reticulum stress and apoptosis in HK-2 cells. FEBS Open Bio. 2020 Mar 9. doi: 10.1002/2211-5463.12834.

[17] Wang Y, Huang Y, Yang J, Zhou FQ, Zhao L, Zhou H. Pyruvate is a prospective alkalizer to correct hypoxic lactic acidosis. Mil Med Res. 2018;5:13. doi: 10.1186/s40779-018-0160-y.

[18] Liu R, Wang SM, Li ZY, Yu W, Zhang HP, Zhou FQ. Pyruvate in reduced osmolarity oral rehydration salt corrected lactic acidosis in sever scald rats. J Surg Res. 2018;226:173-80. doi: 10.1016/j.jss.2018.01.018.

[19] Koga Y, Povalko N, Katayama K, Kakimoto N, Matsuishi T, Naito E, Tanaka M. Beneficial effect of pyruvate therapy on Leigh syndrome due to a novel mutation in PDH E1α gene. Brain and Development. 2012;34:87–91. doi:10.1016/j.braindev.2011.03.003.

[20] Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, Liu W, Zhu Y, Lin Q, Mao L, Fang M, Zhang H, Sun Z. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight. 2020 Apr 23. pii: 137799. doi: 10.1172/jci.insight.137799.

[21] Xia S, Chen G, Wang B, Yin Y, Sun Z, Zhao J, Li P, Zhao L, Zhou H. Addition of sodium pyruvate to stored red blood cells attenuates liver injury in a murine transfusion model. Mediators Inflamm. 2016;2016:3549207. https://doi.org/10.1155/2016/3549207.

[22] Liu R, Wang SM, Liu XQ, Guo SJ, Wang HB, Hu S, Zhou FQ, Sheng ZY. Erratum to "Pyruvate alleviates lipid peroxidation and multiple organ dysfunction in rats with hemorrhagic shock" (Am J Emerg Med 34[3]:525-530). Am J Emerg Med. 2016;34:1330. doi: 10.1016/j.ajem.2016.04.035.

[23] Zhang JJ, Deng JT, Shen HQ, Jiang LL, He QW, Zhan J, Zhang ZZ, Wang YL. Pyruvate protects against intestinal injury by inhibiting the JAK/STAT signaling pathway in rats with hemorrhagic shock. J Surg Res. 2020;248:98-108. doi: 10.1016/j.jss.2019.11.012.

[24] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55:105954. doi: 10.1016/j.ijantimicag.2020.105954.

[25] Tanaka KI, Shimoda M, Kawahara M. Pyruvic acid prevents Cu^{2+}/Zn^{2+}-induced neurotoxicity by suppressing mitochondrial injury. Biochem Biophys Res Commun. 2018;495:1335-41. doi: 10.1016/j.bbrc.2017.11.152.

[26] Iannetti EF, Smeitink JAM, Willems PHGM, Beyrath J, Koopman WJH. Rescue from galactose-induced death of Leigh syndrome patient cells by pyruvate and NAD^{+}. Cell Death Dis. 2018;9:1135. doi: 10.1038/s41419-018-1179-4.

[27] Hu S, Dai YL, Gao MJ, Wang XN, Wang HB, Dou YQ, Bai XD, Zhou FQ. Pyruvate as a novel carrier of hydroxyethyl starch 130/0.4 may protect kidney in rats subjected to severe burns. J Surg Res. 2018;225:166-74. doi: 10.1016/j.jss.2018.01.003.

[28] Mallet RT, Olivencia-Yurvati AH, Bünger R. Pyruvate-enriched resuscitation for shock. Exp Biol Med (Maywood). 2018;243:663-4. doi: 10.1177/1535370218773717.

[29] Hamburger T, Broecker-Preuss M, Hartmann M, Schade FU, de Groot H, Petrat F. Effects of glycine, pyruvate, resveratrol, and nitrite on tissue injury and cytokine response in endotoxemic rats. J Surg Res. 2013;183:e7-21. doi: 10.1016/j.jss.2013.01.024.

[30] McCall CE, Zabalawi M, Liu T, Martin A, Long DL, Buechler NL, Arts RJW, Netea M, Yoza BK, Stacpoole PW, Vachharajani V. Pyruvate dehydrogenase complex stimulation promotes immunometabolic homeostasis and sepsis survival. JCI Insight. 2018;3. pii: 99292. doi: 10.1172/jci.insight.99292.

[31] Bueding E, Goldfarb W. Blood changes following glucose, lactate and pyruvate injections in man. J Biol Chem 1943;147:33-40.

[32] Mateva L, Petkova I, Petrov K, Beniozef D, Bojilova M, Vankova L, Thorn W. Ten-Day course of sodium pyruvate infusions in patients with chronic liver diseases (CLD). Jpn Pharmacol Ther 1996;24:2629-39.

[33] Petkova I, Mateva L, Petrov K, Beniozef D, Thorn W. Effects of sodium pyruvate applied in patients with chronic liver diseases (CLD) of different etiology. Comptes rendus de l'Acad´emie bulgare des Sciences: Medecine Clinique 2003;56:107-12.

[34] Hermann HP, Pieske B, Schwarzmuller E, Keul J, Just H, Hasenfuss G. Haemodynamic effects of intracoronary pyruvate in patients with congestive heart failure: an open study. Lancet 1999;353:1321-3. doi:10.1016/s0140-6736(98)06423-x.

[35] Schillinger W, Hünlich M, Sossalla S, Hermann HP, Hasenfuss G. Intracoronary pyruvate in cardiogenic shock as an adjunctive therapy to catecholamines and intra-aortic balloon pump shows beneficial effects on hemodynamics. Clin Res Cardiol 2011;100:433-8. doi: 10.1007/s00392-010-0261-4.

[36] Olivencia-Yurvati AH, Blair JL, Baig M, Mallet RT. Pyruvate-enhanced cardioprotection during surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2003;17:715-20. doi:10.1053/j.jvca.2003.09.007.

[37] Sheeran FL, Angerosa J, Liaw NY, Cheung MM, Pepe S. Adaptations in protein expression and regulated activity of pyruvate dehydrogenase multienzyme complex in human systolic heart failure. Oxid Med Cell Longev. 2019;2019:4532592. doi: 10.1155/2019/4532592.

[38] Van Erven PM, Gabreëls FJ, Wevers RA, Doesburg WH, Ruitenbeek W, Renier WO, Lamers KJ. Intravenous pyruvate loading test in Leigh syndrome. J Neurol Sci. 1987;77:217-27. doi:10.1016/0022-510x(87)90124-9.

[39] ++Petkova I, Hristov V, Petrov K, Thorn W. Oral application of sodium pyruvate in healthy persons and patients with diabetes mellitus type 1. Comptes rendus de l'Acad´emie bulgare des Sciences: Medecine Clinique. 2007;60:579-84.

[40] Inoue T, Murakami N, Ayabe T, Oto Y, Nishino I, Goto Y, Koga Y, Sakuta R. Pyruvate improved insulin secretion status in a mitochondrial diabetes mellitus patient. J Clin Endocrinol Metab. 2016;101:1924-6. doi: 10.1210/jc.2015-4293.

[41] Nagasaka H, Komatsu H, Inui A, Nakacho M, Morioka I, Tsukahara H, Kaji S, Hirayama S, Miida T, Kondou H, Ihara K, Yagi M, Kizaki Z, Bessho K, Kodama T, Iijima K, Saheki T, Yorifuji T, Honda A. Circulating tricarboxylic acid cycle metabolite levels in citrin-deficient children with metabolic adaptation, with and without sodium pyruvate treatment. Mol Genet Metab. 2017;120:207-12. doi: 10.1016/j.ymgme.2016.12.011.

[42] Saito K, Kimura N, Oda N, Shimomura H, Kumada T, Miyajima T, Murayama K, Tanaka M, Fujii T. Pyruvate therapy for mitochondrial DNA depletion syndrome. Biochim Biophys Acta. 2012;1820:632-6. doi: 10.1016/j.bbagen.2011.08.006.

[43] Koga Y, Povalko N, Inoue E, Nashiki K, Tanaka M. Biomarkers and clinical rating scales for sodium pyruvate therapy in patients with mitochondrial disease. Mitochondrion. 2019;48:11-5. doi: 10.1016/j.mito.2019.02.001.

[44] Matthys D, Van Coster R, Verhaaren H. Fatal outcome of pyruvate loading test in child with restrictive cardiomyopathy. Lancet. 1991;338:1020-1. doi:10.1016/0140-6736(91)91884-w.

[45] Wu XQ, Li ZB, Chen WX, Wen DL, Zhang ZH, Xiong XM. The influence of different resuscitation solution on lactic acid accumulation after hemorrhagic shock: a network meta-analysis. Eur Rev Med Pharmacol Sci. 2019;23:6707-17. doi:10.26355/eurrev_201908_18562.

[46] McCague A, Bowman N, Wong DT. Lactic acidosis after resuscitation with sodium acetate. J Surg Res. 2012;173:362-4. doi: 10.1016/j.jss.2010.10.028.

[47] Webster KA. Hypoxia: life on the edge. Antioxid Redox Signal 2007;9:1303-7. doi:10.1089/ars.2007.1730.

[48] Minko T, Wang Y, Pozharov V. Remediation of cellular hypoxic damage by pharmacological agents. Curr Pharm Des 2005;11:3185-99. doi:10.2174/1381612054864948.

[49] Milner SM, Greenough WB 3rd, Asuku ME, Feldman M, Makam R, Noppenberger D, Price LA, Prosciak M, van Loon IN. From cholera to burns: a role for oral rehydration therapy. J Health Popul Nutr 2011;29:648-51. doi: 10.3329/jhpn.v29i6.9902.

[50] Patiño AM, Marsh RH, Nilles EJ, Baugh CW, Rouhani SA, Kayden S. Facing the shortage of IV fluids - A hospital-based oral rehydration strategy. N Engl J Med 2018;378:1475-7. doi: 10.1056/NEJMp1801772.