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

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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 alkali ion: 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-1\(\alpha\)-erythropoietin (HIF-1\(\alpha\)-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 pKa 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-κB 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 LD50 of oral pyruvate is 10.0g/kg in rats; LD50 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 anhydride 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.
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

References


