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Pyruvate-Enriched Fluids as a Novel Medical Solution and Beverage

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Abstract

Pyruvate has been extensively and intensively studied since a half century ago. An abundance of experimental researches, *in vitro* and *in vivo*, in both animals and humans demonstrate that pyruvate is an unique anion, which is more beneficial in protection of multiple cell/organ metabolism and function than anions in commercial medical fluids and health beverages. The robust advantages of pyruvate action are mainly enhancement of anoxia/hypoxia tolerance, correction of hypoxic lactic acidosis and improvement of glucometabolic disorders in addition to anti-oxidative stress and anti-inflammation and protection of mitochondria, leading to reversal of the Warburg effect in various pathogenic attacks, including severe hypoxia/ischemia, hypo/hyperglycemia, trauma/burn and sepsis. Many investigations in animals and humans, *in vivo*, reveal pyruvate protections with absence of clinical adverse effects. Innovative pyruvate-enriched fluids, both crystalloids and colloids, would be more favorable than current fluids in clinical resuscitation due to therapeutic effects in addition as a volume expander. Pyruvate-enriched oral rehydration salt (Pyr-ORS, equimolar pyruvate replacement of alkalizers in WHO-ORS) also would be more beneficial than WHO-ORS in oral rehydration, peri-operative fluid management and prehospital rescue. Alternatively, oral Pyr-ORS-based beverages may be helpful in plateau tourism, diabetes care and anti-aging. This review cited most important animal experiments and human tests with pyruvate dosages applicated, suggesting the effectiveness and clinical safety and recommending innovative Pyr-ORS-based beverages as both medical care when short of medical supply and functional drinks in endurance exercises. Pyruvate, as a novel nutritional componence, applications in clinical scenarios would be another most important medical advance this century.

Keywords: Beverage; Endurance; Pyruvate; Oral Rehydration Salt; Resuscitation

Introduction

Pyruvate is a key metabolite in glucose metabolism, which holds several beneficial biomedical and pharmacological properties superior to current medical anions in cell/organ metabolism and function. Pyruvate-enriched fluids have been demonstrated to be advantageous over commercial fluids in resuscitation from various severe injuries in many animal models. Pyruvate-enriched oral rehydration salt/solution is a novel ORS that cannot be only a therapeutic solution, but also a health functional beverage. However, sodium pyruvate is non-FDA approved for medical uses to date. This review mainly focuses on the possibility and feasibility of pyruvate-enriched ORS as a novel functional beverage.

Pyruvate-Enriched ORS Protection Against Various Injuries in Animals

In 2012, sodium pyruvate (SP, pyruvate)-enriched oral rehydration salt/solution (Pyr-ORS) was first innovated by equimolar pyruvate replacement of alkalizers in World Health Organization-guided ORS that contains salts and glucose for controlling children diarrhea. WHO-ORS saved a couple of million young lives worldwide per year. It was

discovered that enteral Pyr-ORS is advantageous over traditional bicarbonate-based WHO-ORS (I) in intestinal absorption of sodium and water and protection of barrier structure and function in severe shock rats [1]. Then, Pyr-ORS was further demonstrated with more protection of intestinal energy metabolism, additionally via hypoxia-inducible factor-1 activation, inhibition of oxidative stress/inflammation, increase of systemic and visceral blood flow and preservation of multiorgan (brain, heart, liver, kidney and intestine) function, resulting in severe acidemia correction and significant survival improvement than WHO-ORS (I; II and III: citrate-based) in severe shock-injured models with hemorrhage, burns or cardiac arrest [2-6]. Notably, even the buffer capacity is equal (30 bicarbonate mmol/L) in both Pyr-ORS and WHO-ORS, neither bicarbonate-, nor citrate-based WHO-ORS corrected hypoxic lactic acidosis (one of lethal complications in critical care patients), but did Pyr-ORS, robustly prolonging survival in animal studies [2,3,5]. That is because only can pyruvate consume hydrogen ($[H^+]$) in three metabolic pathways as a prospective alkalizer: 1) the pyruvate reduction coupled with the nicotinamide adenine dinucleotide reduced form (NADH) oxidative reaction by stereo-specific lactate dehydrogenase (LDH) to raise the oxidized form NAD^+/NADH ratio throughout the body, 2) the reactivation of pyruvate dehydrogenase (PDH) activity to promote oxidative phosphorylation in the tricarboxylic acid (TCA) cycle of almost all organs and tissues and 3) pyruvate-based cytosolic gluconeogenesis mainly in liver and kidney [2,5,7], reversing the Warburg effect in glucometabolic disorders [8,9]. The post-pyruvate metabolic profile was previously illustrated [7-9]. Oral pyruvate in Pyr-ORS multifaceted protection of organ metabolism and function above was supported by many previous studies with intravenous (IV) pyruvate and further evidenced by pyruvate peritoneal resuscitation in shock resuscitation of rats [8,10,11]. It is worthy of comment that pyruvate of sodium salt in animal shock resuscitation displays superiorities to anions in current medical fluids and commercial beverages: chloride, bicarbonate, lactate, acetate, citrate, phosphate and gluconate in the correction of hypoxic lactic acidosis and improvement of glucose metabolic disorders [5,8,9]. Although malate exerts in these respects [12], it still cannot protect red blood cells (RBCs) without aerobic metabolism, compared to pyruvate [13]. Alternatively, oral ingestion of Pyr-ORS and simple pyruvate also clearly provided ergogenic effects on protection of multiorgan (brain, eye and kidney) function against aberrant glucose metabolisms in diabetic cataract, retinopathy and nephropathy and aging [9,14-17].

Pyruvate Protection Against Multiorgan Dysfunction in Humans

Albeit non-FDA approved and no studies on Pyr-ORS yet in the clinical setting, clinical investigations of IV pyruvate even started as the 1930s. In 12% concentration, 18.8g sodium pyruvate was intravenously injected for exploring its metabolism in 7 psychologic patients [18]. About 2 decades late, 18 non-diabetic subjects and 19 diabetes patients were infused with IV10.0g (10% in 100 ml) SP over one hour period to exam pyruvate metabolism, accompanied with another mimetic report [19]. In 1996, the first clinical therapeutic investigation of pyruvate effects on chronic liver diseases in 10 patients was reported with a large dose of IV pyruvate (54.0-86.4g/d for 10 days) and followed by additional case reports, showing promising clinical and pathological improvements, clinical tolerance and safety without toxic adverse effects [20,21]. Further, the Lancet first released a clinical study on 8 patients subjected with dilated cardiomyopathy in 1999. A total of 4.58g pyruvate was infused in 30 min via the coronary artery per patient, leading to an immediate significant improvement of cardiac function [22]. Subsequent studies were followed with a similar approach in 9 patients subjected to congestive heart failure and 8 patients with acute myocardial infarction with cardiac shock, resulting in promising outcomes [23]. Furthermore, a small dose of pyruvate in cardioplegia was also demonstrated with a robust cardio-protection against surgical cardiac arrest in 15 patients underwent bypass surgery [24]. The only side effect is vascular pain in locations injected with hypertonic pyruvate solutions [19]. Pyruvate is rapidly metabolized, *in vivo*, in both animals and humans: the peak level in blood after pyruvate infusion can be down close to normal in about 30 min [19,25], suggesting its rapid systemic metabolism. However, the pyruvate effects can prolong for at least several hours probably due to its stimulation of hypoxia-inducible factor-1α (HIF-1α) [4].

On the other hand, oral ingestion of a large amount of SP products (30-60g/d for 7-10d) showed significant therapeutic effects in treatment of 6 Type 1 diabetic patients and 1 mitochondrial diabetic patient (0.5g/kg thrice daily for 10 months) with a remarkable reduction of total daily dose of insulin injection due to hypoglycemia and the stimulation of insulin secretion [26,27]. Interestingly, oral pyruvate with 0.3g/kg/d for 3-6 month also increased fasting insulin secretion in 10 non-diabetic children [28]. Further, a large dose with long-term oral pyruvate therapy indicates the clinical effectiveness on mitochondrial dysfunction in dozens of patients [29]. Despite the small size of patients in each report, a total of released data strongly suggests that oral pyruvate protects systemic metabolism and multiorgan function in absence of clinical adverse effects except gastrointestinal irritation. The clinical safety is further reinforced with several IV pyruvate loading tests (SP 10.0g over 4 min or 0.5g/kg over 10 min) with a well clinical acceptance in several dozens of young and adult patients during past decades [30,31].

In all, extensive and intensive studies in animals and humans, both *in vitro* and *in vivo*, explicitly illustrate the pyruvate superiority in various routes of its administration, including IV infusion, peritoneal injection, oral taking and inhalation, with a diverse range of doses in past decades [20,24,32-34]. Therefore, pyruvate beneficial protection of cell/organ metabolism, function and survival is an acknowledged concept in the biomedical area to date.

Pyruvate Potential Advantages In Beverages

Pyruvate Superior Biomedical Features in Medical Fluids: The biomedical features demonstrated from a huge of studies above substantiate that pyruvate is a specific anion that holds pharmacological beneficial properties: increase of hypoxia tolerance and redox potentials, exertion of anti-oxidative stress and anti-inflammation, correction of hypoxic lactic acidosis and protection of mitochondrial function and against apoptosis [9,15,32-35]. These characteristics are unparallel with current anions in medical fluids. Therefore, pyruvate-enriched fluids, such as pyruvate saline ([Na^+] 154 mM, [Cl^-] 104 mM, [Pyr^-] 50 mM), pyruvate Ringer's solution ([Pyr^-] 28 mM), Pyr-ORS (sodium pyruvate 3.5g/L) and hypertonic pyruvate saline (NaPyr 0.5-1.0 M) as well as pyruvate-based peritoneal dialysis solution ([Pyr^-] 40 mM) revealed the superiority in fluid resuscitation and dialysis to current commercial fluids [5,13,35,36]. Pyruvate-enriched fluids in both crystalloids and colloids will be not only volume expanders, but also therapeutic agents to directly improve organ metabolism and function additionally as a nutritional therapy, compared to current fluids basically as a volume expander only [8,37], in critically ill patients.

Pyruvate-Enriched ORS as Medicine and Functional Beverages: Pyr-ORS as the prototype (the formula that consists of sodium, chloride, and pyruvate as a superior alkalizer and glucose can be improved by adding favorable components, if needed) is an innovative medicine as well as pyruvate-enriched functional beverages as a phenotype of drinks.

Even though Pyr-ORS has not yet been employed in clinical settings, in Critical Medicine, better outcomes of its rehydration of children diarrhea and cholera as well as burn injury would be convincible, relative to WHO-ORS (Ceralyte®90: US Cera products, or Pedialyte: US product) [38]. In addition, in oral peri-operative fluid management Pyr-ORS may be more beneficial, compared to lactate-based OS-1® (Japan product) [39]. In Par/enteral Nutrition, additions of pyruvate as a nutritional ingredient may enhance the clinical efficient of current products. In Disaster Medicine, Pyr-ORS-based fluids can provide a feasible approach in a large scale of prehospital rescue scene without sufficient medical supply, like earthquake and terrorist attack, just as a novel functional drink to win the golden window for saving lives. In Sports and Altitude Medicine, Pyr-ORS or pyruvate-enriched beverages may show its advantages predominantly because of improving hypoxia tolerance, energy metabolism and lactic acidosis reversal in strenuous exercises and high attitude hypoxia. Although the famous drink like Red-Bull (taurine and caffeine) is popular, it is still controversial to enhance endurance performance [40,41]. It is well known that alkalizers like bicarbonate can improve endurance performance by affecting buffering capacity and lactic acidosis may be a critical factor in limiting performance in exhaustive sports [42,43]. Pyruvate-enriched beverages may improve endurance performance and prevent from mountain sickness responses and heatstroke by eliminating severe metabolic acidosis and improving energy metabolism. In Diabetes, a beverage based on Pyr-ORS formula may prevent and treat diabetes and its organ complication in a large population [9,14-16]. Most likely, pyruvate-enriched fluids are favorable in Geriatric Medicine and Pyr-ORS as a beverage may be helpful in anti-aging, as demonstrated in the protection against acute or chronic brain injury like traumatic brain injury and Alzheimer's disease [6,17,44,45]. Interestingly, it is recently proposed that oral pyruvate in ORS, like melatonin, potentially facilitates the prophylaxis and intervention of Covid-19 and other severe viral infections with or without specific anti-virus agents [46]. The pyruvate clinical application was recently encouraged in shock therapy and is potentially another important advance in medical history [47].

Notably, exogenous pyruvate can spontaneously provide NAD^+ on the equal molecular basis via the spontaneous LDH reductive reaction with free of energy throughout the whole body in anoxia. It is a well acknowledged discovery that NAD^+, a molecule of youth, is essential for most enzymatic reactions associated with diseases and aging [47,48]. At least, a clinical trial with nicotinamide riboside (NR, a precursor of NAD^+) in patients with Covid-19 infection is recruiting, indicating that pyruvate in Pyr-ORS has potential modulation of immune function in fighting Covid-19 [46]. Nevertheless, preliminary investigations, *in vitro*, displayed that pyruvate more protected cell survival than equimolar NAD^+ in selected insults and cell lines [49,50]. Pyruvate, at least, is theoretically better in the reactivation of PDH activity and correction of hypoxic lactic acidosis, oxidative stress and hypo/hyperglycemia than equimolar NAD^+ though direct comparable evidence is lack, *in vivo*, yet.

Currently, no pyruvate as an ingredient is involved in almost all commercial beverages in exception of a couple of drinks (Hansen's Slimdown™ and Pyru Force™) with unfavorable formula, so that both show no ergogenic effects

[51]. Although taurine, which is considered as a semi-essential amino acid with insulin-like activation, has recently been indicated with supplemental effects in endurance exercises [52], it holds no property to improve the PDH activity and correct hypoxic lactic acidosis, as pyruvate expected in animal shock resuscitation. To compare taurine with pyruvate in exhaustive exercises may be attractive. Therefore, those with Pyr-ORS as a prototype of functional pyruvate-enriched beverages are innovative efficient products for both health and diseases.

Feasibility of Pyruvate-Enriched Beverages

Clinical data above in several hundred patients suffered from various diseases including chronic cirrhosis suggest its clinical safety. Early animal acute toxicity tests showed that the LD_{50} of oral pyruvate is 10.0g/kg in rats [20]. However, a large dose of oral pyruvate is gastrointestinal irritative, such as flatulence and diarrhea [20,25], which is prevalently unacceptable if used in a population, while a single dose less than 25g neither raises blood pyruvate levels, nor functions well [53,54]. On the contrast, a small amount of oral pyruvate in Pry-ORS (3.5g/L) robustly enhances pyruvate levels in plasma and exerts functionally [1-6]. Hence, the improvement of pyruvate supplementation regime is essential by a small dose of pyruvate together with sufficient glucose in Pyr-ORS formula, which is optimal for intestinal absorption of water and salts along with pyruvate, according to the physiology of intestinal epithelium with 'Na^+-glucose cotransporter' that right is the basis for WHO-ORS development, as functioned in shock resuscitation [1,2,5]. Prospectively, most of current beverages (commonly containing salts and glucose) may create a new brand with the pyruvate addition.

Although pyruvate dimers (para-pyruvate) spontaneously generated in pyruvate aqueous solutions at room temperature are cytotoxic, *in vitro*, no toxic side effects have been appeared to date in humans [47]. Enteral pyruvate in a relatively small dose as Pyr-ORS even containing a trace of para-pyruvate should be acceptable in clinical scenarios, not to mention the fact that IV pyruvate products were applied in patients suffered from parenchymatous diseases, which contained around 1.0% para-pyruvate, at the time several decades ago. In fact, appropriate acidic pyruvate solutions are long-term stable at room temperature with the patent protection [47]. Accordingly, commercial pyruvate-enriched beverages based on Pyr-ORS formula are feasible in near future.

Calcium pyruvate is available in food supplement markets. However, the calcium salt is poor dissolvable in water and malabsorptive from intestines. Studies in exercises with oral calcium pyruvate indicate its ineffectiveness in humans [54,55]. However, the rise of its dissolvability in water by sufficiently acidic pH adjusting may raise the possibility to partially replace sodium salt of pyruvate in the pyruvate-enriched beverage products.

It is worthy of note that ethyl pyruvate (EP) is not allowed to replace SP here. Albeit numerous studies, including oral EP, showed its pharmacological effects as SP on various animal models in the last decade [56], EP did not correct severe acidosis because of $[H^+]$ generation after its hydrolysis with or without the esterase, separating pyruvate moiety, whereas accumulated blood lactate was eliminated in septic rats [57]. Importantly, EP does not work in humans [47].

Interestingly, recent findings showed that oral lactate favored oxidative metabolism of endurance training in mouse muscle, but a pyruvate counterpart was not compared [58]. The LDH reaction is bidirectional with preferable lactate generation; exogenous pyruvate reduction is more favorable with the LDH (A isoenzyme) than the lactate oxidation with the LDH (B isoenzyme) in cytosol, so that lactate infusion raises less blood pyruvate than blood lactate rises after equimolar pyruvate infusion [7]. Despite both pyruvate and lactate as energy substrates, they are quite opposite in the last step of glycolysis, acid-base balance, redox potential and oxidative stress by the LDH reaction and pyruvate oxidizes with a less oxygen consumption rate, compared to lactate.

The impact of ingredients in functional drinks on metabolic and physiological adaptations has been concerned in endurance training [59], but their clinical implications have been less examined in a young and adult population [60]. Clinical trials with pyruvate-enriched fluids are urgently warranted in critical care patients and Pyr-ORS-based functional beverages require comparative controlled tests in sports medicine.

Conclusions

Pyruvate owns superior biomedical and pharmacological characteristics to anions in current medical fluids and beverages in cell metabolism and function. Pyruvate-enriched beverage based on Pyr-ORS formula will be an innovative nutritional product as a health drink as well as a medicine when needed. Further studies and clinical trials are warranted.

Declarations

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