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Pyruvate Application Indicates an Important Medical Advance

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Abstract: On the occasion of the 50th anniversary of WHO-guided oral rehydration salts (ORS) clinical application, this review mainly discussed recent findings in ORS, a novel pyruvate-enriched ORS (Pyr-ORS), in animal experiments. Since past several decades, numerous pieces of evidence have shown that pyruvate owns superior biological and pharmacological characteristics that benefit critical care patients: enhancement of anoxia/hypoxia tolerance, correction of hypoxic lactic acidosis, antagonism of oxidative stress and inflammation, protection of mitochondrial structure and function and anti-apoptosis, etc. Therefore, pyruvate prevents from multi-organ dysfunction and corrects disturbances of glucose metabolism and acid-base balance in patients subjected with various pathogen insults. In recent years, investigations of intravenous pyruvate and oral pyruvate in ORS demonstrated properties above and a double increase of survival in animals subjected to hemorrhagic or burn shock. In the review, biological properties of pyruvate and the high efficiency, underlying mechanisms and vast potential clinical indications of Pyr-ORS were illustrated. The review points out that pyruvate-enriched fluids may be the third generation of fluid therapy, not only a volume expander, but also a therapeutic agent for organ dysfunction and metabolic disturbance; pyruvate may be the first-line drug for fluid therapy: Pyr-ORS may become the first choice for patients who require fluid rehydration alone or in combination with intravenous pyruvate. Pyruvate applications would improve overall clinical outcomes of various diseases, particularly critical illnesses, potentiating a new most important medical advance this century.

Keywords: Fluid Therapy, Hypoxic Lactic Acidosis, Oral Rehydration Salts, Pyruvate, Resuscitation, Shock

丙酮酸钠的临床应用将预示又一重大医学进展

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摘要：在‘世界卫生组织-口服补液盐’（口服盐）临床应用50周年之际，本文着重讨论我们应用丙酮酸钠改进现有口服盐中的碱剂(碳酸氢钠或枸橼酸钠)，在动物实验中的发现。半个多世纪来，众多实验证据显示丙酮酸盐具有提高细胞无氧/缺氧耐受性，纠正缺氧型乳酸性酸中毒，抗氧化/抗炎作用，保护线粒体结构和机能及抗细胞凋亡等功能。因此，拥有在多致病因子作用下，保护周身器官和纠正糖代谢与酸碱平衡紊乱的作用，这些正是重症医学中迫切需求的药物性能。近数年来，实验性‘丙酮酸钠-口服补液盐’和丙酮酸钠注射液在大出血和烧伤休克动物复苏实验中反复论证了以上特性，并成倍提高了生存率。本文就丙酮酸钠的生物学特性，动物实验和临床试验疗效和机理，丙酮酸钠-口服盐潜在的广泛临床适应症，及其临床意义等作了探讨，指出：丙酮酸钠的临床应用将创建人类第三代静脉输液:不仅是容量

扩充剂，同时也是器官功能异常和代谢紊乱的治疗剂；丙酮酸钠的口服盐和静脉制剂可能成为液体治疗的一线药物，它们的研发和临床应用将全面提高疾病，尤其是危重病的基础治疗水平，成为新世纪又一最重要医学进展。

关键词：丙酮酸钠，口服补液盐，缺氧型乳酸性酸中毒，复苏，液体治疗，休克

1．前言

著名医学期刊The Lancet在1978年指出，世界卫生组织(World Health Organization, WHO)指导开发的口服补液盐(Oral Rehydration Salts, ORS，口服盐)及口服补液疗法(Oral Rehydration Therapy, ORT)，每年拯救了约2百万人的生命，是上世纪医学的最重要进展[1]。值此纪念口服盐/口服补液疗法临床应用半个世纪之际，Lancet和JAMA都发表了纪念文章，回顾其成功的经验和展望[2,3]。其中，经验之一是‘在临床治疗中不断创新’[2]。为提高口服盐的临床效果和扩大适应症，近来，我们应用丙酮酸钠(Sodium Pyruvate)改进了现有口服盐和静脉输液，创新的丙酮酸钠制剂在动物实验中获得了显著效果，新制剂可能成为人类历史上第三代危重病复苏的液体，预计其临床应用将全面改观现有的基础医疗局面[4]，丙酮酸钠的研发与临床应用值得深切关注。

2．丙酮酸钠的优异生物学活性和药理特性

丙酮酸钠是已研究半个多世纪而尚待开发的一类新药。近20多年来，众多动物实验和少量临床试验充分显示其优异的生物学特性，适用于临床众多方面。丙酮酸存在于正常动物和人体的各组织/细胞内，它位于葡萄糖无氧酵解和有氧氧化通路交接处，是三大物质代谢中枢，连接糖、脂肪和蛋白质代谢，其独特的生化代谢和性能显示了其特有的药理学性能，保护细胞免受多致病因子的损伤。

2.1．提高细胞无氧/缺氧耐受性

内源和外源性丙酮酸盐在无须能量参与下，自发经乳酸脱氢酶(LDH)还原反应，在生成乳酸的同时，提高了NAD^+/NADH(辅酶 I：氧化型/还原型)比例，并消耗胞浆中游离氢离子($[H^+]$),前者为糖酵解在3-磷酸甘油醛脱氢酶(G-3-PD)一步有效代谢所必须，后者提高细胞内pH,防治了细胞内酸化(图1)；LDH还原反应发生在哺乳类动物和人体内各组织/细胞，是周身的碱化反应[5]。因此，丙酮酸盐在无氧下仍有助糖酵解的进行，维持‘糖酵解-三磷酸腺苷(Glycolytic ATP)’生成，以最大程度保持细胞依赖于此的基本生物学功能，如细胞膜完整性和细胞浆pH等内环境的稳定。不久前，丙酮酸盐保护狗体外红细胞ATP生成的观察进一步论证了这一认识[6-8]；它也有助恢复受抑制的磷酸戊糖支路和抑制亢进的山梨醇支路[9,10]。此外，它在缺氧下直接刺激缺氧诱导因子-1 (HIF-1)活性和HIF-1α-EPO (erythropoietin，促红细胞生存素)通路，进而提高下游诸多糖代谢相关酶活性[11,12]，也经直接抑制丙酮酸脱氢酶激酶(PDK)活性，增强受多种致病因子，包括缺氧、氧化应激、炎症和创伤等作用而抑制的关键酶：丙酮酸脱氢酶(PDH)活性[13,14]，并促进三羧酸循环(TCA cycle)的回补反应(Anaplerosis)。因此，丙酮酸盐能在缺氧下有力逆转受抑制的氧化代谢，促成和维持‘线粒体-三磷酸腺苷(Mitochondrial ATP)’生成；

2.2．纠正缺氧型乳酸性酸中毒

缺氧型乳酸性酸中毒(Hypoxic lactic acidosis, LA)是多病因危重病的致命性并发症之一，因缺乏有效纠酸制剂[15]，在成人和儿童的监护病房内发生率可高达30-50%，病死率在50-75%。其中，血乳酸水平的升高与病死率成正比，是衡量休克严重度与可逆性的可靠单一指标[16,17]。1999年，在小样本动物实验中首次显示静脉注射大剂量丙酮酸盐能成功纠正缺氧型LA的资料，并提高生存率[18]，此后应用常规剂量也论证了这一结果[19,20]。2012年，在对比丙酮酸钠与乳酸钠二种林格氏液用于大鼠严重失血性休克复苏中进一步证实：血浆丙酮酸根浓度升高了近10倍(1.68 vs. 0.21 mmol/L)，缺氧型LA在3小时内全面纠正，并成倍提高生存率，首次确立了这一概念[21-23]。而二氯醋酸盐 (DCA) 的二期临床试验，尽管纠正血生化异常，但并不提高患者生存率而告失败[24]。丙酮酸根因有力维持糖酵解，促进三羧酸循环氧化代谢和氧化磷酸化过程，促使推积的乳酸氧化，并大力消耗胞内$[H^+]$，因此，独特有效地快速清除升高的血乳酸和纠正严重酸中毒；其耗$[H^+]$途径是无氧下经LDH还原反应和有氧下的氧化磷酸化过程，以及丙酮酸根作为最佳碳原的糖原异生的胞浆内途径(图1)[21-23]，而非化学的酸碱中和。此外，因其低解离系数所显示的有限缓冲容量也有利酸中毒的纠正[22]；

2.3．天然抗氧化/抗炎剂

丙酮酸根是体内外强有力抗氧化剂，除了直接在无酶下自发与氧/氮自由基结合清除氧化剂外，也间接经体内二大氧化还原势能:$NAD(P)^+$/NAD(P)H 和GSH/GSSG(辅酶II：还原型/氧化型)的作用发挥抗氧化功能，而且，它经改善糖酵解经典途径也调节了糖酵解的二支路，从而逆转$NAD(P)^+$/NAD(P)H和 GSH/GSSG 比例下降，增强抗氧化效率[25]。此外，它也是强抗炎剂：抑制炎症细胞的激活与组织侵润，及炎症因子的分泌水平和活性，如IL-2、IL-6、NF-kB、TNF-α和高迁移率族蛋白-1 (HMGB-1)等，但提高IL-10水平[26,27]，而呈强力抗炎性能；

2.4．保护线粒体的结构与功能

它有效抑制线粒体内膜通透性转运孔(mPTP)的开放，抑制NADH等大分子及离子的流失，维持线粒体内环境稳定；抑制促凋亡基因，而防治细胞凋亡[28-30]。

以上代谢途径和特性是传统碱剂和静脉输液中阴离子：氯离子，碳酸氢根，乳酸根，醋酸根，枸橼酸根和苹果酸根等所不具备，或难以媲美的。此外，又以丙酮酸根氧化产能的氧耗最低[4]。因此，丙酮酸盐具备多致病因子下周

身多器官(包括脑/神经[6,31,32]，心[20,33,34]，肝肾和肠道[35-37]，及血细胞[8,38,39]等)功能保护和纠正代谢紊乱(如糖尿病及其器官并发症和严重酸中毒等[40-43])的作用，这整是危重病医学中防治药物需具备的理想性能。外源性丙酮酸根的代谢特性和优异功能不可取代。但是，相关研究还局限在动物实验阶段，少量临床试验虽然也显示优异结果[34,35,40]，但还需与其他输液中阴离子做更多对比观察，其在病患体内的作用和机理有待进一步证实和探讨。

3．丙酮酸钠口服盐的优越性

口服盐为含氯化钠，氯化钾，葡萄糖和碱剂的混合粉剂，临用前溶解在可饮用水口服，是上世纪60年代末始用于防治小儿腹泻与霍乱流行的有效方法。半个世纪来，世卫组织-口服盐(WHO-ORS)配方不断改进：先是改标准配方中含碳酸氢钠(ORS I, 331 mOsm/L)为等分子量枸橼酸钠(ORS II, 311 mOsm/L)，后又改进为含等量枸橼酸钠，而较少氯化钠和葡萄糖的低渗透压第三代产品(ORS III, 245 mOsm/L)。低渗配方有利于肠道对水盐的吸收，提高了产品质量和疗效[44,45]。口服盐也被推广用于各类烧伤的复苏和防治尚无有效病原学治疗的严重失水和盐的保守支持治疗，如Ebola 病毒感染，获得明显效果[46,47]。鉴于丙酮酸盐特有的生物学性能，我们以等分子量丙酮酸钠取代WHO-ORS中碳酸氢钠或枸橼酸钠，构成新型丙酮酸钠口服补液盐(Pyruvate-ORS, Pyr-ORS)，动物实验显示其优异性能和疗效。

3.1．改善多器官功能

2013年首次报道渗透压相似的实验性Pyr-ORS在大鼠失血性休克中，较含碳酸氢钠的ORS I 提高肠道对水和盐的吸收量约30%，并显示对肠道屏障结构与功能的良好保护：维持钠-钾泵活性和水通蛋白-1，及增强屏障结构蛋白(紧密连接蛋白：ZO-1)的表达，抑制肠脂肪酸结合蛋白(肠道屏障结构完整性的血清学指标)水平；降低多个氧化酶活性而抑制氧化应激反应；也明显改善内脏:肝，肾和肠道粘膜表面的血流量及其器官功能，尤其在肠道方面更显著。这些可能为防治肠源性感染提供了有效途径，并成倍提高失血性休克大鼠生存率[48,49]。以后的发现证实在口服盐中，丙酮酸钠(Pyr-ORS)也较枸橼酸钠(ORS II)更有效保护内脏器官的血流量和器官功能，降低血浆血管内皮生长因子和血小板激活因子水平，抑制周身血管通透性和组织水肿，同样成倍提高严重烫伤狗的生存率[50]。此外，它也直接激活肠谜走神经活性[51]；经肠道摄取的丙酮酸盐还激活肠道组织HIF-1α-EPO信息系统[12]，这可能是其显著的细胞保护作用分子机理之一；

3.2．纠正乳酸性酸中毒

无论在大鼠或狗严重失血性或烧伤休克口服复苏中，Pyr-ORS 都能快速有效纠正缺氧型LA，而不同配方WHO-ORS都无效，甚至恶化[49,50,52]。新近证实：在大鼠50%烫伤休克口服盐复苏中，低渗Pyr-ORS (247 mOsm/L)也较ORS III (245 mOsm/L)更有效改善心血管动力学和内脏器官血流量和功能，如同经静脉给药显著提高血浆中丙酮酸根浓度近10倍 (1.14 mmol/L vs. 0.13 mmol/L)，并在24小时内全面纠正严重的LA，成倍提高生存率[21,52]。Pyr-ORS与WHO-ORS具有等分子量碱剂，都含相当30 mmol/L碳酸氢根，但是，只有Pyr-ORS具备纠正LA效力，可见丙酮酸根经代谢耗[H^+]和保护肝肾功能的能力是其他碱剂所不及。Pyr-ORS应更适用于各类病因所致危重病，尤其并发LA者的液体复苏；也可望明显提高作为支持治疗用于Ebola, SARS 和 HIV等病毒性疾病的疗效[47]；

3.3．符合口服盐开发理论基础

近来已明确单纯一次性口服丙酮酸钠，即使较大剂量(7-25克)对纠正酸中毒作用甚微，甚至并不提高血浆丙酮酸盐浓度[53,54]。但是，在含糖的Pyr-ORS中，低浓度丙酮酸钠(0.35%)却显著提升其血浆浓度，取得优异疗效，这进一步论证了开发口服盐的理论基础：肠道上皮存在的糖-钠共同转运体(Sodium/Glucose Co-transporter)'是其疗效的病理生理基础[55]。这一特性和临床效果为进一步改进ORS的配方提供了强有力的实验证据和理论依据。
同样，以上发现还只来自动物实验，急待临床试验的论证。

4．丙酮酸钠口服盐的潜在应用与重大临床意义

丙酮酸钠口服盐的优异特性和功效，提示它和丙酮酸钠注射剂都具备潜在的广泛临床适应症，至少包括以下诸方面, 在主要方面也同样适用于兽医学的临床治疗。

4.1．危重病和围手术期的液体治疗

Pyr-ORS可首先推广应用于烧伤，提高临床复苏效果，也适用于创伤，失血性或败血症性休克等复苏和保守支持治疗[47,56]；口服盐用于围手术期液体治疗的优点，尤其在保持水与盐的平衡及防治酸碱紊乱上已受到关注[57,58]，Pyr-ORS应更适用；在院前现场救护中，尤其在大规模或无力提供常规输液条件下，如地震和战场等，它将提供有力的防治手段，为后续治疗赢得时间；

4.2．保护多器官功能

口服常规剂量Pyr-ORS也能发挥显著的多器官保护作用，尤其对脑/神经，心脏，肝肾和肠道功能[52,59]，因此，可能适用于心肌梗塞/心脏骤停的复苏及低血糖脑损伤的防治[59-61]。慢性给药还可能控制神经退行性病变，如Alzheimer's病[32]，推测口服或灌肠还适用于慢性肠道炎症性疾病，如坏死性结肠炎[62-65]，也应适用于急性胰腺炎的治疗[66]等；

4.3．糖尿病及器官并发症

饭后口服大剂量(30-60克/日，共7-10日)单纯丙酮酸盐能显著改善糖尿病者高血糖状态，甚至诱发低血糖反应而须减少胰岛素用量，可能与它调节胰岛功能有关；患者的血浆丙酮酸盐浓度明显升高，但胃肠道刺激症状严重[40,41]；动物实验显示口服低浓度丙酮酸钠(1-2%)也能防

治糖尿病器官并发症，如视网膜病变，并降低血糖水平[30,42,43]。以上提示糖尿病患者口服含糖的Pyr-ORS是可行的：提高血浆浓度，并避免大剂量丙酮酸盐的肠道副作用。推测Pyr-ORS也适用于糖尿病性肾病或心肌病变及皮肤病变等；

4.4．肾脏疾病和肾前性肾功能不全

丙酮酸盐的肾保护作用有众多实验证据，Pyr-ORS经胃肠道给药同样显示良好的防治作用[49,50,52]。丙酮酸盐的优异碱化作用有利于防治横纹肌溶解综合症(挤压综合症)的肾损伤，应胜于常用的碳酸氢钠：不仅更好碱化血液，也直接保护肾功能[67,68]。同样，它应适用于防治造影剂肾损伤，优于常规输液和碳酸氢钠的作用[69]；

4.5．在老年医学，高原医学和运动医学中作用

丙酮酸盐具有拮抗老龄化病理过程：缺氧，氧化/炎症反应，酸中毒和细胞凋亡等的性能，可望保护周身器官功能，尤其是脑神经退行性病变[70]；它也特异地提高细胞缺氧/无氧耐受性，并有效防治缺氧型 LA,因此，预期能在高原医学和运动医学领域发挥重要作用。‘低氧与健康’是个日益受关注的重大医学课题，其生化基础离不开维持糖酵解和促进缺氧下的氧化代谢，也总与丙酮酸盐有关。Pyr-ORS 就是功能性饮料原型，稍加改进应能发挥运动饮料的功效，缓解运动所致的缺氧型 LA，真正达到提高剧烈运动耐力和技能的目的；也适用于高山地区或酷暑下的旅游饮料，防治高原病和中暑等。
此外，丙酮酸盐还具有一定条件下的抗肿瘤作用[71,72]。

丙酮酸钠粉剂是成熟而稳定的产品，动物毒理实验显示并无临床毒性[35]，市场上曾用于减肥，多个人体静脉负荷试验(0.5g/kg)显示耐受而安全[73]，预期其临床应用应有效，无毒和可行。基于稳定的丙酮酸钠水溶液专利[74]，丙酮酸钠水溶液可能有效取代传统静脉输液中适量阴离子：氯离子，乳酸根，醋酸根等，开创人类输液历史上继生理盐水和乳酸钠平衡液后真正的第三代输液，如丙酮酸钠-氯化钠盐水([Na^+] 154, [Cl^-] 104, [Pyr^-] 50 mmol/L)和丙酮酸钠林格氏液([Pyr-] 28 mmol/L)等[75-77]。其特征是不仅扩充血容量，也防治器官功能不全与严重酸中毒，尤其是缺氧型 LA；它在胶体溶液中也显示了器官保护[78]。因此，丙酮酸钠制剂能克服传统输液的严重缺陷：只是容量扩张剂，还有导致高氯性酸中毒和LA及炎症反应等‘复苏损伤’毒性作用[52,78]。新近的临床经验表明：随着口服盐疗效的提高，推广和调整适用于不同临床适应症的配方，Pyr-ORS可能成为液体治疗的一线药物[80]，即：全部需要补充水和盐的病患，首选Pyr-ORS单独经胃肠道(口服，经胃管或灌肠)给药或合并静脉输液，其中，又以含丙酮酸钠制剂为优。这一策略将创新世纪中液体治疗的基本原则，预计可提高各类疾病，尤其是危重病的基础治疗效果，减少并发症和副作用，缩短危重病的监护和住院时间，全面提高医疗质量。因此，开展丙酮酸钠口服盐或粉针剂的临床试验，尤其首个针对缺氧型LA适应症，是十分迫切的，值得大力投入。

结论：丙酮酸盐具有常用医用阴离子无可比拟的优异药理特性，尤其是提高细胞缺氧耐受性和纠正缺氧型LA而无毒性，推测可广泛适用于临床医学诸多领域，特别在危重病的救治中，它可望成为液体治疗的首选药物，革新液体治疗的基本局面。但现有研究尚局限在动物实验阶段，急需开展临床试验，得到临床的验证和应用。丙酮酸钠制剂的研发和应用显示半个世纪来ORT的不断创新经验，预示着本世纪又一重大医学进展。

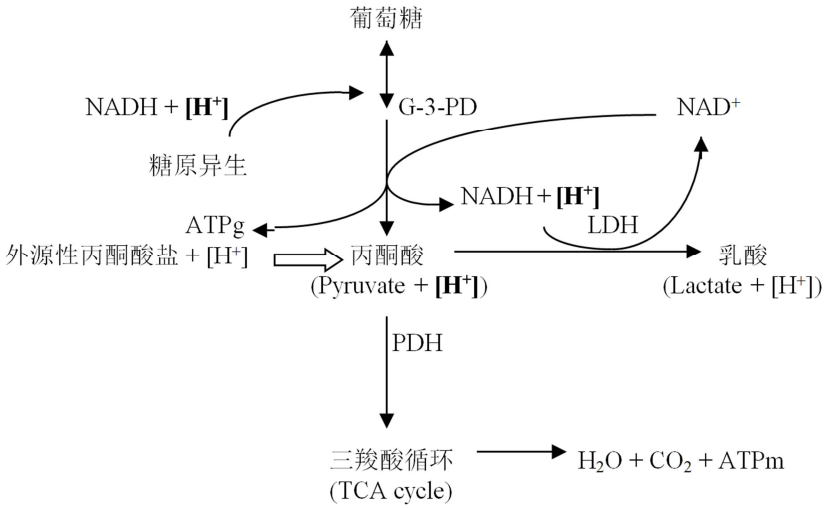

图1 外源性丙酮酸盐和糖酵解产物丙酮酸代谢中[H^+]的消耗途径。

丙酮酸是LDH还原反应与PDH氧化脱羧反应的唯一底物，不可取代；前者在无氧下发生在机体每一细胞内，后者在有核细胞内缺氧下也能有效进行；
外源性丙酮酸盐结合血浆中游离[H^+]在单羧酸转运体作用下进入细胞内；
糖原异生：仅显示细胞浆内部分；
LDH:乳酸脱氢酶；PDH:丙酮酸脱氢酶；NAD^+/NADH:辅酶I(氧化型/还原型)；
G-3-PD:3-磷酸甘油醛脱氢酶；ATPg:糖酵解-三磷酸腺苷;ATPm:线粒体-三磷酸腺苷；
[H^+]：体内代谢产生的氢离子；**[H^+]**：经代谢消耗的氢离子

说明

本文内容和观点并不代表Fresenius Medical Care, USA的意见；本文并未接受任何方来源的资助。

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