Commentary

Pyruvate-enriched resuscitation for shock

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Impact statement

This commentary addresses the recent retraction of a clinical report of significant benefits of intravenous pyruvate resuscitation in septic patients, including sharply lowered mortality and decreased circulating pro-inflammatory cytokines, which was cited in the authors' minireview in *Experimental Biology and Medicine*. The potential implications of the retraction, and the extensive preclinical evidence supporting the use of pyruvate-enriched resuscitation for shock states, are summarized and discussed.

Abstract

This commentary addresses the recent retraction of an article which reported favorable outcomes in septic patients treated with intravenous pyruvate. The retracted report was cited in the authors' recent minireview on the cellular mechanisms and clinical application of pyruvate to improve cardiac performance. Because the retracted article reports pyruvate-enhanced resuscitation of critically ill patients, the authors wish to inform the readership, especially critical care providers, that this particular clinical application of pyruvate is not now supported by robust evidence. After discussing the retraction's implications for the clinical application of pyruvate-enriched resuscitation for sepsis, this commentary summarizes the extensive preclinical evidence of the efficacy and mechanisms of pyruvate resuscitation in animal models of hemorrhagic and septic shock, which argues for renewed clinical investigation of pyruvate-enriched resuscitation.

Keywords: Hemorrhage, inflammation, pyruvate, sepsis, septic shock

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A minireview by the authors, presenting the cellular mechanisms and clinical implications of pyruvate-enhanced cardiac performance, recently appeared in this journal.[1] An article[2] cited in that review, reporting favorable effects of pyruvate-enriched resuscitation of patients in septic shock, has subsequently been retracted. Because the retracted study cannot now be taken as evidence supporting expanded clinical application of pyruvate resuscitation for sepsis and other shock states, we wish to alert the readership of the retraction. Here also we briefly summarize evidence demonstrating favorable effects of pyruvate resuscitation in animal models of septic and hemorrhagic shock, to ensure the retraction does not stifle scientifically and clinically rigorous efforts to test and validate pyruvate-enriched resuscitation for shock states.

The retracted article[2] reported a clinical trial comparing pyruvate-enriched Ringer's to NaCl solution for resuscitation of septic shock. Pyruvate- versus NaCl resuscitation was found to exert several clinically important effects in these patients, including improved pulmonary and renal function and decreased circulating activities of pro-inflammatory cytokines, culminating in a reduction in mortality from 20 to 4.4%. Although the specific reasons for the retraction are not stated, it is particularly disappointing because the report seemed to confirm in critically ill patients the favorable effects of pyruvate revealed by extensive preclinical research.

In a porcine model of hemorrhagic shock, sodium pyruvate delayed cardiovascular decompensation and systemic acidemia, slowed cerebrocortical ATP degradation and sustained cerebrocortical electrical activity for 75 min longer than isotonic or hypertonic NaCl infusions.[3] In male rats subjected to severe hemorrhage, resuscitation with pyruvate-fortified Ringer's solution prevented post-resuscitation base deficit, augmented renal ATP content and lowered pro-apoptotic Bax/Bcl-2 ratio in lung, in a manner superior to racemic Ringer's lactate.[4] Similarly, in rats subjected to hemorrhagic shock, pyruvate Ringer's increased survival 2.5-fold versus lactated Ringer's, while stabilizing arterial blood pressure and mitigating

acidemia.[5] Relative to lactated Ringer's, pyruvate Ringer's also suppressed lipid peroxidation and augmented glutathione/glutathione disulfide redox ratios in myocardium, lung, liver, and jejunum of these hemorrhaged rats.[6] Also, in severely hemorrhaged rats, hypertonic sodium pyruvate resuscitation suppressed inflammatory cytokines, augmented hepatic ATP content and suppressed pro-apoptotic caspase-3 and poly(ADP-ribose)polymerase (PARP) activation in a manner superior to lactate- or ethyl pyruvate (EP)-enriched Ringer's.[7] In goats subjected to hemorrhage and hindlimb ischemia-reperfusion, hypertonic pyruvate infusion stabilized arterial pressure while preserving oxidant-susceptible enzymes and preventing PARP activation and tyrosine nitration in myocardium and post-ischemic hindlimb muscle.[8–10] Thus, pyruvate-enriched resuscitation has proven effective in a variety of preclinical hemorrhagic shock models.

Numerous reports in animal models of severe sepsis, the condition addressed in the retracted report,[2] have demonstrated hemodynamic stabilization by a pyruvate derivative, EP. In dogs subjected to lipopolysaccharide-induced sepsis, addition of EP to lactated Ringer's increased tissue O_2 delivery, mixed venous O_2 saturation and urine output[11] while lowering intestinal permeability and mucosal inflammation.[12] EP-fortified versus conventional Ringer's lactate suppressed circulating pro-inflammatory cytokines and increased anti-inflammatory interleukin-10, while blunting lipid peroxidation and ATP depletion in mice made septic by cecal ligation and puncture.[13] In endotoxemic pigs, EP-enriched lactated Ringer's stabilized arterial pressure, minimized acidemia and better sustained urine output versus control Ringer's resuscitation.[14] In rats made septic by intravenous *Escherichia coli* injection, EP-enhanced versus conventional lactated Ringer's more effectively suppressed leukocyte-endothelial interactions and microvascular expression of adhesion molecules.[15] Nevertheless, until unmodified pyruvate is tested in sepsis, these many favorable effects cannot be ascribed specifically to EP's pyruvate moiety.

Collectively, pyruvate and its derivative EP have been found to stabilize hemodynamics and suppress inflammation, oxidative stress and apoptosis in several different animal models of hemorrhagic shock and sepsis. It remains to be demonstrated if these favorable preclinical effects of pyruvate-enriched resuscitation will translate to meaningful clinical outcomes in patients suffering from sepsis and septic shock.

DECLARATION OF CONFLICTING INTERESTS

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