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Fluid Resuscitation in Acute Pancreatitis — Going over the WATERFALL

Timothy B. Gardner, M.D.

Acute pancreatitis, responsible for approximately 300,000 hospital admissions in the United States annually, is characterized by intense inflammation of the pancreas that leads to severe disease in approximately one third of affected patients.[1] Because no proven pharmacologic therapy for acute pancreatitis exists, treatment is largely supportive.[2] Intravenous fluid resuscitation is recommended as a fundamental component of initial supportive therapy in acute pancreatitis, owing largely to observations that untreated pancreatic hypoperfusion contributes to poor outcomes such as pancreatic necrosis and death.[3]

For the past three decades, multiple studies — but few randomized, controlled trials — have investigated the effects of crystalloid fluid type, rate of infusion, or infused total volume on important clinical outcomes in patients with acute pancreatitis. Although lactated Ringer's solution is firmly established as the crystalloid of choice because of its antiinflammatory properties, controversy exists regarding the rate and volume of fluid resuscitation.[4] Most major society guidelines recommend aggressive early fluid resuscitation on the basis of data showing the clinical determinant of underresuscitation, but there is contradictory evidence from randomized, controlled trials arguing that overaggressive early resuscitation leads to poor clinical outcomes, including greater rates of sepsis and death.[5-7] In essence, a well-designed, prospective trial to answer the question "How much lactated Ringer's solution is too much?" needed to be performed.

In this issue of the *Journal*, de-Madaria and colleagues[8] present the results of a landmark multicenter, randomized trial — WATERFALL (the Early Weight-Based Aggressive vs. Nonaggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis: an Open-Label Multicenter Randomized Controlled Trial) — which definitively provides the answer. The trial is so clinically relevant because of its choice of real world–appropriate aggressive-resuscitation and moderate-resuscitation treatment groups, its use of pancreatitis severity as the main clinical outcome, and its reliance on the carefully defined variable of fluid overload as the main safety outcome. Unlike in most other randomized, controlled trials of fluid resuscitation in acute pancreatitis, patients with varying baseline pancreatitis severity were included, and changes in the rate of resuscitation were determined on the basis of a dynamic assessment of hemodynamic testing, imaging, and clinical factors.

Although statistical significance was not observed with regard to any of the clinically important outcomes, the results generally favored the moderate-resuscitation group. The data and safety monitoring board terminated the trial at the first interim safety analysis on the basis of the development of fluid overload in 20.5% of the patients in the aggressive-resuscitation group, as compared with 6.3% of those in the moderate-resuscitation group. The smaller-than-planned sample size may have contributed to the lack of significant findings with respect to the primary outcome. In addition, the total volume of fluid given over the 72-hour trial period was higher in the aggressive-resuscitation group than in the moderate-resuscitation group (8.3 vs. 6.6 liters) — a finding that indicates that not only should the rate of resuscitation be slower but the total infused volume should be lower. These results are stunning and, given the carefully crafted trial methods, irrefutable.

What can we conclude therefore from this trial? First, clinicians should focus on a steady rate of initial resuscitation — no more than 1.5 ml per kilogram of body weight per hour — and should administer a bolus of 10 ml per kilogram only if there are signs of initial hypovolemia. Second, careful clinical and hemodynamic monitoring are essential during the first 72 hours after admission to make sure that patients remain euvolemic and to avoid fluid overload. Third, diuresis in patients with fluid overload in the first 72 hours is most likely beneficial and certainly not detrimental to important clinical outcomes.

Finally, a main conclusion of this trial is that medical pancreatologists as a specialty now need to focus on trials evaluating other pharmacologic therapies instead of crystalloid fluids. Although this trial showed a greater clinical benefit in the moderate-resuscitation group, the incidence of moderately severe or severe pancreatitis was still 17.3%, the incidence of local complications was 16.5%, and organ failure occurred in 3.9% of the patients in that group. Performing randomized, controlled trials in acute pancreatitis is notoriously difficult, and the limited human and financial resources that are available for appropriately powered trials in this field post-WATERFALL are much better spent on comparative-effectiveness and placebo-controlled trials evaluating new therapeutic agents. Now that we have gone over the WATERFALL, it is time to look downstream at new targets to treat this challenging disease.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Section of Gastroenterology and Hepatology, Dartmouth–Hitchcock Medical Center, Lebanon, NH.

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