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Starch solutions for volume resuscitation in intensive care units

Amidos para ressuscitação volêmica na UTI: ao vencedor, as batatas!

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Conflicts of interest: None.

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Fluid resuscitation is a fundamental part of the care of a critically ill patient.⁽¹⁾ Most patients admitted to intensive care units will eventually undergo volume challenge. The optimum type of fluid resuscitation product has been debated for the last four decades.^(1,2)

Crystalloid solutions are widely available and affordable and are therefore used as the basis of the standard volume expansion strategy in many intensive care units (ICUs). The most commonly used colloid solutions include human albumin, synthetic starches, dextrans and gels;⁽³⁾ of these types, starch solutions are preferred.⁽³⁾ Starch solutions are more commonly used in European countries than in the United States of America.⁽⁴⁾ Colloids offer the theoretical advantage of a longer intravascular time, which would result in better fluid expansion, therefore requiring lower infusion volumes.⁽⁴⁾ However, colloid administration is not without risk, and serious concerns regarding the effects of colloids on coagulation and renal function should be considered.⁽⁴⁾

Starches (hydroxyethyl starches – HES) are becoming popular and are preferred by several clinical services.⁽⁴⁾ Starches are corn- or potato-derived glycogen-like polysaccharides, composed of polymerized D-glucose with branches for 20 glucose monomers. Hydroxyl groups are replaced by hydroxyethyl groups to prevent degradation by blood amylase. These hydroxyethyl groups are bound to variable carbon chain positions (mainly C2, C3 and C6). The more substituted and more C2 carbon substitutions (instead of C6), the longer the circulating starch half-life will be.⁽⁴⁾ In addition, degradation will be slower for starches with higher molecular weights. The starch name includes its molecular weight and its substitution rate (e.g., 6% 130/0.40).

The first available starch products had high molecular weights (between 480-670 kDa) and were highly substituted (above 0.7); these starches are referred to as hetastarches. These were long half-life products and had significant coagulation effects.⁽⁴⁾ The last decades witnessed the development of progressively lower mean molecular weight and less substituted modern starches. ‘Modern’ starches (referred to as tetrastarches) have molecular weights of approximately 130 kDa and are approximately 0.40 substituted (6% HES 130/0.40).

Possible harmful effects of starches include coagulation effects and renal injury, in addition to anaphylactic reactions and itching due to subcutaneous deposits.⁽⁴⁾ Starch-induced coagulation effects appear to

be worse with older solutions, particularly those with high molecular weights and high substitution rates. More recently developed compounds theoretically lead to fewer coagulation effects.⁽⁵⁾ Renal injury is also an important concern related to the use of starch solutions. The VISEP trial⁽⁶⁾ was a multi-center and factorial trial (2 x 2) comparing the use of strict blood glucose control versus conventional crystalloid volume expansion (using Ringer's lactate) versus pentastarch (HES 200/0.5) in patients with sepsis. The trial was discontinued early due to safety issues; the preliminary results show that pentastarch had a dose-dependent association with renal injury and the use of renal replacement therapies. This trial was criticized both for the use of high starch doses and the use of older generation starch compounds instead of more recently developed products, which are apparently associated with lower renal dysfunction rates.

Therefore, given the uncertainties regarding the safety of these colloid products and their higher costs, their advantages over crystalloids are disputable. A recent meta-analysis by the Cochrane group⁽²⁾ concluded that there is no evidence that the use of starch products after trauma or in the postoperative period is associated with lower mortality rates and they questioned the use of these compounds outside of the clinical trials setting.

The Australian and New Zealand Intensive Care Society (ANZICS), in association with the George Institute for National Health, started the CHEST (Crystalloid versus Hydroxyethyl Starch Trial) trial in April 2010. This trial is intended to broaden the knowledge about the effectiveness and safety of starch.⁽⁷⁾ This is a multi-center, randomized, double-blind protocol involving 33 sites in Australia and New Zealand. The trial seeks to include 7,000 patients over 21 months. This sample size will assure a 90% power to detect a 3.5% mortality difference or 1.5-fold increase in the relative risk of renal dysfunction between the study groups. In this protocol, patients who, after ICU admission, are identified to meet the criteria for volume expansion (tachycardia, low filling pressures, hypotension, and reduced urinary output, among others) will be randomized to receive either 0.9% saline or HES

130/0.4. If additional volumes are required, 0.9% saline will be administered until the end of the 24-hour period. The same fluid will be used for all required volume challenges for the next 90 days or until death, and the study's primary endpoint will be the mortality rate at 90 days. Important secondary endpoints will be analyzed, including the incidence of renal injury (evaluated by the RIFLE or SOFA criteria or based on the requirement of renal replacement therapy), other organ dysfunctions, the length of the ICU stay, and quality of life after ICU discharge. Subgroup analyses are planned for head trauma, severe sepsis, and non-head trauma patients in addition to chronic renal failure patients who do not require ambulatory dialysis. An economic analysis will include the treatment costs.

In parallel with the CHEST trial, a European trial, the 6S (Scandinavian Starch for Severe Sepsis/Septic Shock) trial⁽⁸⁾ is currently ongoing to evaluate the safety and effects of HES 130/0.4 in septic ICU patients. In contrast to the Australian trial, the 6S will include only septic patients who require volume challenge.

Both above mentioned trials are expected to broaden our knowledge of the effectiveness and safety of starches. The economic analysis included in the CHEST trial is very welcome. However, both the CHEST and 6S trials are subject to an important criticism: exclusive starch volume replacement is uncommon. When used, starches are part of a strategy that usually includes different proportions of crystalloids and colloids. Reanimation using exclusively starches may, therefore, not reflect the usual practice, and such exclusive use may increase the substance's possible adverse effects. Studies involving resuscitation with balanced crystalloids and colloids would more closely resemble clinical practice. However, we should acknowledge that a trial with such complex interventions would hardly be feasible.

Therefore, there is no doubt that the CHEST trial will become a landmark in the already long history of the use of colloids in critically ill patients. However, this study will not be able to answer the question as to whether mixed reanimation, using both crystalloids and colloids, can influence a patient's outcome.

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