VIEW POINT

Synthetic Colloids should not be Put out of the Shelves of Intensive Care Unit

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Medicine is a science of uncertainty and the art of probability as quoted by William Osler. The applicability of modern medicine has become highly dependent on randomized control trials (RCTs) which is the pinnacle of evidence. However, in critical care patients such trials are very difficult to conduct due to large heterogenicity of the population, timing of the study, and selection of endpoints. This has resulted in many negative trials. Individual observations have now no value in modern clinical practice. Thus, certain medicines, which were widely used in critical care and were found to be useful by clinicians have gone into oblivion. One of such victims is synthetic colloids.

Even more than 190 years have passed since the first use of fluids for resuscitation by Dr Thomas Latta, clinicians are still undecided as to which fluid would be the best one for resuscitation of critically ill patients in intensive care. Synthetic colloids have an excellent volume sparing effect needing less fluids to resuscitate patients and preventing overhydration. It rapidly brings in hemodynamic stability. However, they are blamed for the increase in incidence of renal replacement therapy (RRT). Three studies, VISEP,[1] 6S,[2] and CHEST,[3] in the earlier part of the century, were conducted to arrive at this conclusion.

The VISEP[1] trial was a multicenter, two-by-two factorial trial. Here, patients were randomly assigned with severe sepsis to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either 10% pentastarch or modified Ringer's lactate for fluid resuscitation. The rate of death at 28 days and the mean score for organ failure were coprimary endpoints. The trial was stopped early for safety reasons. The rate of severe hypoglycemia (glucose level, ≤40 mg/dL) was higher in the intensive-therapy group than in the conventional-therapy group (17.0% vs 4.1%, $p < 0.001$), as was the rate of serious adverse events (10.9% vs 5.2%, $p = 0.01$). Hydroxyethyl starch (HES) therapy was associated with higher rates of acute renal failure and RRT than was Ringer's lactate. There are several limitations of this study. The fact known since the year 2001 that high molecular weight, poorly biodegradable HES preparations can present an independent risk factor for acute kidney failure in patients with sepsis or septic shock was ignored. The hyperoncotic colloid solution should have been employed for a brief period instead of prolonged usage thus avoiding its culminative effect. The dose limit for HES (20 mL/kg per day) was exceeded by more than 10% on at least 1 day in 100 of 262 patients in the HES group. A total of 315 out of the 537 patients included in the VISEP[1] trial (59%) had already received colloids before randomization. In spite of all these loopholes this study was one of the diagnostics rocks against the colloids.

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The second study was the 6S[2] study. In this multicenter, parallel-group, blinded trial, patients with severe sepsis were randomly assigned to fluid resuscitation in the intensive care unit (ICU) with either 6% HES 130/0.42 or Ringer's acetate at a dose of up to 33 mL/kg of ideal body weight per day. The primary outcome measure was either death or end-stage kidney failure (dependence on dialysis) 90 days after randomization. Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 (51% vs 43%, $p = 0.03$) and were more likely to require RRT (22% vs 16%, $p = 0.04$), as compared with those receiving Ringer's acetate. This study has a fragility index of 2 making it unreliable for any logical conclusion. Also, strict compliance is not maintained. Also, 411 out of the 798 patients included in the 6S trial (52%) had already received colloids before randomization, irrespective of group assignment and the risk of renal failure. But this study was again taken as an important evidence against use of colloids.

The third trial, supposed to be the Holy Grail to be used against colloids was the CHEST[3] trial. A total of 7000 patients were randomly assigned, who had been admitted to an ICU, in a 1:1 ratio to receive either 6% HES with a molecular weight of 130 kg and a molar substitution ratio of 0.4 (130/0.4, Voluven) in 0.9% sodium chloride or 0.9% sodium chloride (saline) for all fluid resuscitation until ICU discharge, death, or 90 days after randomization. The primary outcome was death within 90 days. Secondary outcomes included acute kidney injury and failure and treatment with RRT. There was no significant difference in 90-day mortality, but the number of cases of RRT was significantly increased in colloid group. The careful observation of the study revealed that patients who were on the saline group had significantly more risks (RIFLE-R, $p = 0.007$) and injuries (RIFLE-I, $p = 0.005$) compared to colloids. Patients in the colloid group was having more failure than saline though it was not statistically significant (RIFLE-F, $p = 0.12$). The cases of RRT, however, reached statistical significance ($p = 0.04$). The explanation

for this may be the decision of RRT was kept in clinical discretion, and it is not clear that at which stage RRT was started, or whether RRT was undergone completely due to other indications apart from acute kidney injury (AKI). Moreover, 15% patients received colloids prior to randomization. Parallel studies in favor of colloids like the CRISTAL,[4] CHRYSTMAS,[5] FIRST,[6] and BaSES[7] trials were largely ignored while formulating guidelines.

CRISTAL[4] trial is a multicenter, randomized clinical trial stratified by case mix (sepsis, trauma, or hypovolemic shock without sepsis or trauma). Colloids ($n = 1,414$; gelatins, dextrans, hydroxyethyl starches, or 4% or 20% of albumin) or crystalloids ($n = 1,443$; isotonic or hypertonic saline or Ringer's lactate solution) were used for all fluid interventions other than fluid maintenance throughout the ICU stay. Among ICU patients with hypovolemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality (25.4% vs 27%, $p = 0.26$). Also, 90-day mortality was lower among patients receiving colloids (30.7% vs 34.2%, $p = 0.03$), and there was no increase in RRT in the colloid group (11% vs 12.5%, $p = 0.19$). The CRISTAL trial never received prior fluids for resuscitation as compared to 6S and CHEST trials. Also, the hemodynamic monitoring was precise to select patients for resuscitation. And thirdly, it never exceeded the recommended dose of colloids.

The CRYSTMAS[5] trial compared the hemodynamic efficacy and safety of 6% HES 130/0.4 and NaCl 0.9% for HDS in patients with severe sepsis, in a prospective, multicenter, active-controlled, double-blind, randomized study in intensive care units. A total of 174 out of 196 patients reached HDS (88 and 86 patients for HES and NaCl, respectively). Significantly less HES was used to reach HDS (hemodynamic stability) vs NaCl ($p = 0.0185$). Acute renal failure occurred in 24 (24.5%) and 19 (20%) patients for HES and NaCl, respectively ($p = 0.454$). There was no difference between AKIN and RIFLE criteria among groups and no difference in mortality, coagulation, or pruritus up to 90 days after treatment initiation.

The FIRST[6] trial was a randomized control double blind trial comparing HES 140/0.4 with 0.9% normal saline in severe trauma patient. There was no mortality difference and better lactate clearance, less renal injury, and less fluid requirement in penetrating trauma patients.

It is important to perceive that it is not what you do but how you do it. Meybohm et al. in critical care 2013, re-evaluated the prospective RCT[8] from four meta-analyses published in 2013 that compared the effect of HES with crystalloids in critically ill patients, focusing on the adherence to "presumably correct indication". Regarding the definition of "presumably correct indication", studies were checked for the following six criteria (maximum six points): short time interval from shock to randomization (<6 hours), restricted use for initial volume resuscitation, use of any consistent algorithm for hemodynamic stabilization, reproducible indicators of hypovolemia, maximum dose of HES, and exclusion of patients with pre-existing renal failure or RRT trials taken into consideration were the VISEP, 6S CHEST, CRYSTMAS, BaSES, and FIRST trials. The negative trials faltered in these indications (CHEST satisfied two criteria whereas BaSES and 6S satisfied one criterion only). The proponents of colloids satisfied four out of six criteria and outscored the trials which negated colloids.

A recent Cochrane database[9] systematic review of 69 studies with 30,020 participants failed to find any difference in mortality across all types of starches when compared to crystalloids.

The ideal resuscitation fluid should be one that produces a predictable and sustained increase in intravascular volume, has a chemical composition as close as possible to that of extracellular fluid, is metabolized and completely excreted without accumulation in tissues, does not produce adverse metabolic or systemic effects, and is cost-effective in terms of improving patient outcomes. Currently, there is no such fluid available for clinical use.

The value of experience is not in seeing much, but in seeing wisely—William Osler.

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