Bleeding news

Restrictive versus liberal fluid administration strategy (refill study) in postpartum hemorrhage and its effects on thromboelastometry (Rotem®) values: A randomized, controlled trial.

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At first sight, the title of the article sounds very appealing, not only because of the topic, but because it deals with a randomized clinical trial (RCT). As the article advances, it is made clear that this is a **subanalysis of the REFILL RCT** *(restrictive vs liberal fluid resuscitation strategy, influence on blood loss and haemostatic parameters in mild obstetric hemorrhage: an open-label randomized controlled trial)*, published in 2021. In this subanalysis, only 72 patients (36 in each arm) got a ROTEM, and so the subanalysis **lacks statistical power**, and its results and conclusions may be a product of chance.

WHY CARRYING OUT THIS SUBANALYSIS?

Because of the **importance of secondary maternal mortality in postpartum hemorrhage** (PPH), and the effect of **coagulopathy** in it. This article reports a 4-8% mortality, but it is based on old articles and just the first-world population. In fact, mortality is still very high worldwide (16-27%).

WERE INCLUSION CRITERIA, RANDOMIZATION, TREATMENT, AND SAMPLE ANALYSIS APPROPRIATE?

Patients with blood loss between **500 and 1500 mL** were **included**. As is widely known, the higher the blood loss, the higher the likelihood of a coagulopathy, and the more significant the effect of the serum therapy used. I believe it would have been more informative to include more severe patients, although the RCT is clear about that: "mild obstetric hemorrhage". Since the study covers mild patients, where the incidence of the coagulopathy is lower, the required number of patients would be much higher.

As for **randomization**, patients were randomized to receive a **restrictive fluid administration (RFA) (0.75-1 times the blood losses) or liberal fluid administration (LFA) (1.5-2 times the blood losses).** Apparently, patients who received 1-1.5 times the blood losses were excluded from the analysis, probably to ensure the administration of a restrictive volume and a liberal one.

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Was fluid resuscitation really different between the groups? The analysis of the final results shows that patients randomized to RFA received 1214 ± 1250 mL, whereas those randomized to LFA received 1588± 982 mL. Is this difference, barely over 300 mL, relevant to justify alterations in the coagulopathy? In critical hemorrhages maybe, in mild ones, probably not. Furthermore, in the description of patients randomized to the RFA group, can the standard deviation (1250 mL) be above the average (1214 mL)? No, there should be two medians, since it proves the study population is not normal.

The **replacement of serum therapy in this RCT may also be discussed,** since they use saline 0.9%, combined or not with Ringer's lactate. Currently, hemorrhage treatment guidelines recommend using isotonic crystalloids (evidence 1A) (Saline 0.9% has a much higher tonicity than plasma), and avoiding the use Ringer's lactate, since it is a hypoosmolar serum (evidence 1B).

The **drawing of the study coagulation samples** for ROTEM and conventional coagulation was performed at the time of diagnosing a blood loss of 500 mL, and 45-60 min thereafter, regardless of the amount of blood lost. No significant differences were observed in the analyzed parameters between groups, but as discussed, the difference in blood loss was small and the PPH mild, so that was to be expected. It must be noted that the coagulation tests used were aPTT and PT, although it is known that, in order to compare these values with laboratories in other sites, the aPTT and INR ratio must be analyzed. Therefore, in terms of conventional coagulation, are not comparable to other sites.

In conclusion, although this RCT reviews a very relevant health issue, its design presents some very debatable points, and the performance of a subanalysis with no statistical power invalidates the results. Therefore, it cannot be categorically concluded that there are no differences in conventional coagulation tests or ROTEM. According to other published studies, a moderate-severe blood loss with a liberal resuscitation could make the coagulopathy worse.

In its defense, it must be said that designing and carrying out RCTs in these clinical settings is extremely complex.