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Essay

Fibrinogen and postpartum hemorrhage – Association or causality?☆

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ABSTRACT

Postpartum hemorrhage (PPH) is the leading cause of maternal death worldwide, accounting for one in four maternal deaths. Despite efforts in public health policy, the incidence of massive PPH has increased in recent years even in first world countries. In Colombia, PPH is the second leading cause of maternal death. Multiple observational studies have provided evidence about the association between the concentration levels of fibrinogen in blood plasma and the severity of PPH, proposing the systematic use of fibrinogen concentrates as a prophylactic or therapeutic measure in patients with obstetric hemorrhage. However, the statistical relationship demonstrated in such studies should not necessarily be interpreted as a cause-effect relationship. Traditionally, we have used the criteria postulated by Sir Arthur Bradford Hill to establish a causal relationship. Therefore, the most pragmatic way to evaluate a possible causal relationship is through a randomized placebo-controlled experiment. Experiments of this kind available to date have methodological deficiencies or have been criticized for internal validity. As a result, the statistical relationship (association) between low levels of fibrinogen and PPH cannot be certainly interpreted as a cause-effect relationship and the use of fibrinogen concentrates may only be justified in the context of new clinical trials.

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Fibrinógeno y hemorragia posparto – ¿Asociación o causalidad?

Palabras clave:
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RESUMEN

La hemorragia posparto (HPP) es la primera causa de muerte materna en el mundo, siendo responsable de una de cuatro muertes maternas. A pesar de los esfuerzos en políticas de salud pública, la incidencia de la HPP masiva ha aumentado en los últimos años incluso en países del primer mundo. En Colombia, la HPP es la segunda causa de muerte materna. Múltiples estudios observacionales han proporcionado evidencia sobre la asociación entre la concentración plasmática de fibrinógeno y la severidad de la HPP, por lo que se ha planteado el uso sistemático de concentrados de fibrinógeno como medida profiláctica o terapéutica en pacientes con hemorragia obstétrica. Sin embargo, la relación estadística demostrada en este tipo de estudios no necesariamente se debe interpretar como una relación causa-efecto. Tradicionalmente, se han usado los criterios postulados por Sir Arthur Bradford Hill para establecer una relación causal, a la luz de los cuales la manera más pragmática para evaluar una eventual relación causal sea a través de un experimento aleatorizado controlado con placebo. Los experimentos de esto tipo disponibles a la fecha poseen deficiencias metodológicas o se ha criticado su validez interna. Por lo pronto, la relación estadística (asociación) entre los niveles bajos de fibrinógeno y la HPP no se puede interpretar como una certeza de relación causa-efecto y el uso de concentrados de fibrinógeno solo estará justificado en el contexto de nuevos experimentos clínicos.

Postpartum hemorrhage (PPH) is the leading cause of maternal death in the world (defined as maternal death during gestation, delivery or during the first 42 days after birth).[1] Although the incidence of PPH is variable, it is estimated to be the cause of one in four maternal deaths.[2] Despite public health policy efforts, the incidence of massive PPH has increased over the last ten years in countries such as the United Kingdom and the United States, with no evidence of improvement in outcomes.[3–5]

PPH along with hypertensive disorders of pregnancy and maternal sepsis are the cause of more than half of the maternal deaths in the world.[6] The vast majority of deaths occur in the immediate postpartum in countries with medium or low *per capita* income.[7] In Colombia, PPH is the second cause of maternal death after hypertensive disorders of pregnancy, although it is leading cause of death in obstetric patients in the department of Antioquia.[2] In a cohort studied retrospectively between 2006 and 2011, PPH was the leading cause of death in obstetric patients admitted to the intensive care unit.[8]

In Colombia, regional analyses of deaths from PPH have identified some aspects that are likely to have a favorable impact on the incidence of maternal mortality due to PPH, for example, the implementation of active management of labor, early diagnosis and aggressive treatment of shock and resuscitation.[9] "Red code" guidelines have emerged as tools that permit the planning of an organized, systematic, timely and relevant treatment of obstetric hemorrhage.[2,10] Although efforts have been made to implement these unified management guidelines involving obstetricians, nurses, anesthesiologists and others, problems related to the appropriation of knowledge of the "red code" have been identified, possibly interfering with their effective implementation.[11]

Recently in the Colombian Journal of Anesthesiology, García Velásquez and collaborators reported the results of an observational study with 79 patients diagnosed with severe PPH in which they found that the concentration of fibrinogen at the onset of bleeding is associated with severity and morbidity produced by bleeding.[12]

Fibrinogen is a coagulation glycoprotein involved in primary hemostasis (inducing platelet activation and aggregation binding to IIb/IIIa receptors on the platelet surface) and secondary (through thrombin-induced fibrin polymerization).[13] The concentration of fibrinogen is higher in pregnant women than in non-pregnant women. These concentrations increase progressively during pregnancy reaching their highest level in the third trimester.[14] Changes in the concentration of fibrinogen during pregnancy are probably due to the increase in the blood concentration of estrogens.[13] In the postpartum period, the fibrinogen concentration decreases after delivery and may remain low during the immediate puerperium.[15] Although the reason for the decrease in fibrinogen concentration after birth is not fully understood, it has been postulated that an increase in intravascular fibrin deposits occurs after delivery, increasing fibrinogen consumption.[16] This mechanism could also explain the observed increase in venous thromboembolism in the puerperium.[17] On the other hand, it has been proposed that the pathological increase in fibrinogenolysis and fibrinolysis may decrease fibrinogen levels and contribute to PPH. For this reason it has been proposed that tranexamic acid (a synthetic derivative of lysine) through its antifibrinolytic action may reduce the risk of PPH.[13,18,19]

A plasma fibrinogen concentration <100 mg/dL had been previously considered to be a suitable threshold to initiate its replacement, which is often done by transfusion of fresh

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frozen plasma (FFP) that has an approximate fibrinogen concentration of 200 mg/dL or cryoprecipitate which can reach up to 400 mg per unit.[13] Recent studies have suggested that the limiting concentration of fibrinogen to maintain adequate hemostasis is 200 mg/dL.[20] This threshold value of plasma fibrinogen coincides with that found by García-Velásquez in his study.[12] Some authors have expressed objections to the use of FFP and cryoprecipitate for fibrinogen replacement given the possibilities of circulatory overload, immune reactions or the transmission of infections.[21] This has led to the widespread use of fibrinogen concentrates.[22]

In addition to the García-Velásquez study,[12] other research has provided evidence on the association between plasma fibrinogen concentration and HPP severity.[16,23–28] Although Garcia-Velásquez and collaborators present a judicious and conservative discussion regarding the use of fibrinogen concentration as a useful measure to quantify the impact of PPH, the results of this type of observational studies have naturally led other authors to raise that supplementary administration of fibrinogen may be a therapeutic measure for the prevention of PPH.[21,29,30] However, the demonstrated statistical relationship between plasma fibrinogen concentration and clinical outcomes in patients with PPH should not be necessarily interpreted as a cause-effect relationship.[31,32]

The criteria postulated in 1965 by Sir Austin Bradford Hill have been used traditionally to establish a causal relationship: strength of association, temporality, consistency, theoretical plausibility, coherency, specificity, dose-response relationship, experimental evidence, and analogy.[33,34] In light of these criteria, it is possible that the most pragmatic way to assess a possible causal relationship between fibrinogen concentration and PPH is through the findings of a randomized placebo-controlled trial, in which the therapeutic intervention is the administration of a fibrinogen concentrate. In a systematic review, which included six experimental studies and studied a total of 248 non-obstetric patients, it was found that the administration of fibrinogen concentrate decreased the need for allogeneic transfusion, although all the studies analyzed had methodological deficiencies.[35] The first experimental study performed in obstetric patients, in which the use of fibrinogen concentrate has been studied to reduce the need for allogeneic transfusion in patients with PPH was the FIB-PPH trial.[36] In this placebo-controlled experiment 249 obstetric patients with severe PPH were randomized (average blood loss close to 1500 ml before inclusion in the study) to receive 2 g of fibrinogen or saline solution as a control. The need for transfusion from inclusion to study and up to 42 days postpartum was 20.3% in the group of patients receiving fibrinogen and 21.5% in patients receiving placebo (relative risk 0.95, confidence interval 95% from 0.58 to 1.54).[37] Despite the experimental methodology of this study, there have been critics of the external validity of its findings due to the possibility that the most relevant population has been excluded, since the majority of patients included in the study had no hypofibrinogenemia and also because the dose used barely achieved a marginal increase in plasma levels of fibrinogen.[38]

In light of the evidence accumulated in experimental studies, the cause-effect relationship between plasma fibrinogen concentration and the incidence or severity of PPH cannot yet be established or dismissed. For the time being, it can be theorized that blood fibrinogen levels could be lowered as a consequence of the severity of bleeding and as such could represent an objective measure of the magnitude of bleeding. This possible tool could be very interesting and promising, as Garcia-Velásquez puts it in the discussion of his study, considering the inaccuracy of visual estimation of bleeding[39,40] and poor correlation between blood loss and clinical signs.[41]

In conclusion, the statistical relationship (association) between low levels of fibrinogen and PPH can not be certainly interpreted as a cause-effect relationship in which the natural conclusion would be the widespread and systematic use of fibrinogen concentrates as a prophylactic or therapeutic measure in patients with obstetric hemorrhage. Possibly the use of such interventions would only be justified in the context of new clinical trials.[42]

Declaration

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Conflict of interest

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