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COMMENTARY

Fibrinogen concentrate in surgery

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Fibrinogen is a plasma glycoprotein synthesised by the liver which plays a critical role in haemostasis by acting as an endogenous substrate for fibrin formation and by inducing clot formation and platelet aggregation[1]. A deficiency in fibrinogen may be inherited or acquired, the latter condition developing predominantly in association with trauma-related or peri-operative major bleeding[2,3]. Fibrinogen supplementation can be achieved using fresh-frozen plasma, cryoprecipitate or plasma-derived, virally-inactivated, fibrinogen concentrate[4-8].

Although a number of studies have reported the use of fibrinogen concentrate for the treatment and prevention of acquired bleeding, its beneficial effect is still debated, mainly due to the low quality of the published clinical evidence[9]. For instance, a Cochrane review published in 2013 by Wikkelsø and Colleagues[10], which evaluated fibrinogen concentrate in 248 bleeding patients enrolled in six randomised controlled trials, concluded that, besides an apparent effect on the reduction of transfusion requirements, the heterogeneity and the high risk of bias of these studies prevented a proper evaluation of any beneficial effect of fibrinogen concentrate.

The topic of the beneficial effects of fibrinogen concentrate in surgical patients was recently reviewed by another meta-analysis published by Fominskiy and Colleagues[11]. This review paper pooled 14 original studies[12-24], all with a prospective, randomised controlled design. The end-points focused on in the meta-analysis were all-cause mortality, volume of bleeding, and red blood cell units transfused. Data regarding the first end-point, which were drawn from ten studies, showed a consistently lower cumulative rate of fatal events in the pooled arm of fibrinogen-treated patients than in the placebo-treated control arm, as evaluated by the risk ratio (0.26) with a 95% confidence interval (95% CI) of 0.09 to 0.78 (p=0.02). The authors, however, included data on all-cause mortality obtained in a multicentre study conducted by Rahe-Meyer (oral presentation during the 2015 Annual Congress of the European Society of Anaesthesiology, Berlin, May 30-June 2, 2015), still unpublished on the date of submission of the meta-analysis. These data were subsequently published by the same author, albeit with minor changes (a total of 152 patients enrolled instead of 142)[25].

The use of fibrinogen concentrate was also associated with a significantly less bleeding (nine studies included) and a lower number of red blood cell units transfused (nine studies included), but the mean differences of these quantitative indices were modest (−127 mL and −0.93 units, respectively). Differences in other indices were of borderline statistical significance, but were not significant when Bonferroni's correction was applied (the number of patients receiving red blood cell transfusions and the number of patients receiving any blood components). Moreover, the number of surgical revisions for bleeding, the rate of thrombotic events, and the incidence of myocardial infarction were not statistically significantly different between the patients who received fibrinogen concentrate and those who did not.

Considering this meta-analysis[11] in greater detail, a number of criticisms can be levelled against it. The first is that it seems improper to put together studies dealing with different clinical diseases, with patients being submitted to a very wide variety of surgical procedures. Most patients had coronary artery disease and were submitted to cardiopulmonary shunting with anticoagulant treatment. Two studies concerned paediatric patients with severe congenital heart disease[12,14], one study collected liver transplant recipients (in whom the basal severe liver failure could have caused deficient synthesis of clotting factors)[21], one study was on women with severe post-partum haemorrhages[24], and one study was on patients undergoing total cystectomy[13]. In addition, two studies used active comparators, in one instance platelet transfusion[23], and in the other cryoprecipitate[14].

Another concern is the use of "all-cause mortality at the longest follow-up available" as a proper index of efficacy in the context of surgery. Fibrinogen is a clotting factor, and in a surgical context a pro-haemorrhagic effect in the control arm is expected to happen early. So, early deaths (in the first 7-10 days after surgery) would have been a more suitable index than later mortality, which seems due mostly to the

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baseline clinical condition. Unfortunately, only the study by Rahe-Meyer and Colleagues published in 2016 distinguished early deaths from later ones[25], whereas most studies neither indicated the time of deaths, nor mentioned the time limits of surveillance for untoward events. Interestingly, while this latter study reported one death in the fibrinogen arm and five deaths in the control arm, the early deaths ("between 1 and 10 days after study medication") as well as the treatment-related adverse events were balanced (1:1 and 4:4, respectively). Notably, most of the deaths in the review[11] were reported in the two subsequent studies published by Rahe-Meyer and Colleagues in 2013 and 2016[19,25]. The all-cause mortality appeared significant. However, this large effect size (reducing the risk by almost three-quarters in fibrinogen-treated patients) was hardly justified by the modest reduction in the fibrinogen arm of the other two quantitative end-points reported in detail: post-operative bleeding (mean difference, −127 mL), and number of transfused red blood cell units (mean difference, −0.93 units). Differences in the latter end-points were statistically significant, but quantitatively modest. A likely explanation for this incongruity could be the comparative index chosen for mortality cumulative incidence, relative risk. First, this choice of index excludes all eventless studies from the quantitative evaluation (6 studies out 10)[26]. Moreover, since the relative risk is a ratio between incidences, it masks the substantive rareness of deaths. Indeed, fatal events were uncommon, with 19 deaths among 872 patients (about 2.2%). We would have preferred another comparative index, the risk difference, which does not suffer from these drawbacks. In addition, the risk difference enables calculation of an important pharmaco-economic index, the number-needed-to-treat. We calculated the pooled inverse-variance risk difference on the same ten papers considered in the meta-analysis. Using the method of Mantel-Haenszel the index was significant, with a mean −2.5% (95% CI: −4.7% to −0.3%, p=0.024). However, with the inverse variance method, a lower mean was found, 0.07% (95% CI: −2% to 0.7%, p: not significant). Clearly, these estimates suffer of a degree of instability. Indeed, all classical meta-analytical methods are less than satisfactory with rare events[27,28]. A remedy could consist in logistic or Poisson regression for hierarchical data, taking into account the studies as grouping variable[29,30]. With the former method, the estimated mean risk difference was −1.4% (95% CI: −5.0% to −0.4%, p=0.016), and the results were very similar with the latter. The estimates were statistically significant, but the effect sizes were low. Another method that appears suitable for determining risk difference when events are rare was recently developed by Tian and Colleagues[31]. This method is based on the combination of the study-level risk difference distributions[32,33]. Using this procedure, the mean risk difference was estimated as −1.6% (95% CI: −5.8% to 0.1%, p=0.086) and the corresponding number-needed-to-treat (i.e., the number of patients who need to be treated with fibrinogen in order to save one life) was 61.

In conclusion, for a series of methodological aspects, the evidence collected by the above-cited meta-analysis[11] seems weak and insufficient as a basis for therapeutic or prophylactic guidelines, as highlighted in the previously published Cochrane meta-analysis[10].

Disclosure of conflicts of interest

GML is the Editor-in-Chief of Blood Transfusion and this manuscript has undergone additional external review as a result. The other Authors declare no conflicts of interest.

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