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CORRESPONDENCE

Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery. Response to *Br J Anaesth* 2017; 118: 823–33

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Editor—The meta-analysis by Serraino and Murphy[1] on viscoelastic haemostatic assays (VHA) for the diagnosis and treatment of coagulopathic bleeding in cardiac surgery and subsequent comments[2,3] suggest some uncertainty around the association between transfusion of allogeneic red blood cells, fresh frozen plasma, and platelets and final outcomes, as discussed.[1] Kozek and colleagues[2] made two arguments using final outcomes to justify their support of VHA: (i) the observed risk reduction in acute renal failure reported by Serraino and Murphy[1] (odds ratio [OR]=0.42, 95% confidence interval [CI]=0.20–0.86; *P*=0.02; four studies, 424 patients; data taken from supplementary materials provided by the authors) and (ii) the risk reduction in mortality reported by Wikkelsø and colleagues[4,5] (3.9% *vs* 7.4%; relative risk [RR]=0.52, 95% CI=0.28–0.95; *P*=0.033, not specific for cardiac patients). We agree that the reduction of the risk of acute renal failure is an important outcome, but the mortality reduction reported by Wikkelsø and colleagues[4,5] was found through a fixed-effects model combining data from different populations. Heterogeneity was null, but a random-effects model (REM) would be advised regardless.

We therefore conducted our own systematic review with meta-analysis to re-evaluate some of these clinical outcomes and to include recent evidence. We found a statistically and clinically significant reduction in the risk of death with VHA (7.3% *vs* 12.1%; RR=0.64, 95% CI=0.43–0.96, *P*=0.03; I^2=0%, *P*=0.52; 10 studies, 888 patients; REM). This effect is even greater when the meta-analysis includes only patients with coagulation disorders or massive bleeding (14.8% *vs* 26.8%; RR=0.58, 95% CI=0.32–1.07, *P*=0.08; I^2=33%, *P*=0.22; four studies, 315 patients; REM). This analysis did not reach statistical significance at 5% possibly because of the small sample size. The heterogeneity observed is dependent on one study.[6] When removed, the heterogeneity becomes null and the result more favourable to VHA (RR=0.47, 95% CI=0.28–0.80, *P*=0.006; I^2=0%, *P*=0.46; three studies, 255 patients). The subgroup analysis specific for cardiac patients also did not reach statistical significance at 5% in an REM (3.4% *vs* 6.8%; RR=0.55, 95% CI=0.28–1.10; I^2=1%, *P*=0.40; seven studies, 689 patients), but did in a fixed-effects model (RR=0.50, 95% CI=0.26–0.96, *P*=0.04). Considering only studies conducted in cardiac surgery, patients with coagulopathies, or massive bleeding, the meta-analysis showed a significant result favouring VHA (6.6% *vs* 20.6%; RR=0.33, 95% CI=0.12–0.91, *P*=0.03; I^2=0%, *P*=0.34; two studies, 144 patients; REM).

A large trial conducted by Karkouti and colleagues[7] became available in 2016. This trial did not report on mortality, but a subsequent meta-analysis did.[8] They did not report absolute data, but an estimation made with available information was used to include this trial in a meta-analysis (log[RR]=−0.13, standard error [SE]=0.25, RR=0.88, 95% CI=0.54–1.43, 7402 patients).[8] This meta-analysis still showed a significant difference favouring VHA (1.5% *vs* 2.2%; RR=0.73, 95% CI=0.53–0.99, *P*=0.04; I^2=0%, *P*=0.54; 11 studies, 8290 patients; REM). This result is maintained in a fixed-effects model. When we consider only cardiac patients, including Karkouti and colleagues data,[7] the meta-analysis loses its statistical significance (1.0% *vs* 1.4%; RR=0.74, 95% CI=0.48–1.12, *P*=0.15; I^2=2%, *P*=0.40; eight studies, 8091 patients; REM). This result should be read with discretion since the complete data were not available for this study.

We also found results in favour of the VHA in reducing the risk of acute kidney failure (10.5% *vs* 17.6%; RR=0.53, 95% CI=0.34–0.83, *P*=0.005; I^2=0%, *P*=0.43; five studies, 449 patients; REM), but not in terms of thromboembolic events (RR=1.17, 95% CI=0.36–3.81, P=0.80; I^2=0%, *P*=0.41; four studies, 305 patients; REM) and reoperation for bleeding (8.1% *vs* 10.8%; RR=0.82, 95% CI=0.55–1.23, *P*=0.34; I^2=0%, P=0,63; nine studies, 887 patients; REM). The tendency in favour of the

control shown for thromboembolic events might be random, given the imprecision in the meta-analysis.

Similar to Kozek and colleagues,[2] we do not agree with Serraino and Murphy's statement that 'further large trials are unlikely to demonstrate clinical benefits for current viscoelastic point-of-care tests'.[1] There is a tendency in favour of VHA, particularly when considering cardiac surgery patients with coagulopathies or severe postoperative bleeding. More trials specifically designed for this population might show the usefulness of VHA more clearly. Nevertheless, we believe that the data are reasonable to support a recommendation in favour of the technology at least for these patients since clinical benefits were shown and there seem to be no safety concerns.

Declaration of interest

The authors declare that they have no conflicts of interest.

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The halothane hepatitis that was not

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Editor—One of the methods to reduce anaesthetic complications is the identification of risk factors using statistical analysis. Many randomised clinical trials have revealed a variety of risk factors among independent cause variables using multivariate analysis. However, it is impossible for statistical analyses to determine risk factors among unknown and unmeasured variables. Therefore, a critical misunderstanding will occur if the real risk factor is not included among cause variables in a randomised clinical trial.

The National Halothane Study was one of the world's first large-scale multicentre clinical trials conducted over a 4-year period from 1959 to 1962, which reviewed fatal hepatic necrosis cases occurring within 6 weeks of anaesthesia in 34 hospitals in the USA.[1] Among 856 000 administrations of general anaesthesia, 82 unexplained fatal hepatic necrosis cases were identified. The primary objective of the study was to compare halothane with other general anaesthetics, such as nitrous oxide-barbiturate, cyclopropane, ether, and others, regarding the incidence of fatal massive hepatic necrosis. The second objective was to compare operative death rate groups amongst procedures: a low-death rate group involving mouth, eye, herniorrhaphy, and plastic procedures, etc.; a high-death rate group involving craniotomy, open-heart surgeries, laparotomy, etc.; and a middle-death rate group involving all other operations.

The data showed that: (i) the incidence of massive hepatic necrosis after administration of halothane was the same as that after administration of other anaesthetics; (ii) hepatic necrosis occurred more frequently after high-death rate group operations with all anaesthetics; and (iii) repeated exposure to halothane, especially within 2 months, led to a higher incidence of hepatic necrosis.

The National Halothane Study clearly ruled out the existence of halothane hepatitis and halothane as a risk factor of postoperative liver injury. The high risk of repeated exposure to halothane was met with widespread clinical acceptance,