Editorial to accompany 20394 Stein

Major trauma and the need for massive transfusion

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In this issue of the journal, Stein et al report a retrospective study of the effect of changes in the management of major trauma patients on the incidence of massive transfusion [1]. They collected data on all injured adults admitted to the University Hospital of Zurich over two time periods. The first spanned 2005 and 2007, and the second ran from 2012 to 2014. The intervention, introduced in 2009, was an 'individualised, goal-directed transfusion and coagulation algorithm'. The authors used the Trauma- Associated Severe Haemorrhage (TASH) score [2] to predict the likely incidence of massive transfusion in both patient groups. The algorithmic approach is described in detail in the paper. Essentially, an initial rotational thromboelastometry (ROTEM) assay was performed by the anaesthesia team in the Emergency Department as soon as the patient arrived. Depending on the specific values provided by ROTEM and the concurrently performed laboratory tests of coagulation, patients might receive fibrinogen concentrate, protamine, tranexamic acid, platelets or prothrombin complex concentrate.

There were a number of baseline differences between the averages in the two patient groups. Patients in the later time period were significantly more likely to be older and have a higher Glasgow Coma Scale score at scene. The incidence of massive transfusion decreased from 12% (the rate predicted by the TASH scores) to around 4%, an effect which persisted even after correction for the changed patient and trauma epidemiology. The data also suggested a reduction in mortality, and a shorter ICU stay in the later group.

However, we need to be cautious as we interpret the improvements detailed in the report, real though they undoubtedly are. Standards of care in general, not simply in coagulation management, improved between the two time periods captured in the study. Casualty evacuation procedures, pre-hospital care, targeted temperature control, the whole-body computed tomographic scan, the wider use of tranexamic acid after the CRASH2 trial [3] and the greater use of damage control surgery probably all contributed. (Previously, prolonged attempts at immediate definitive surgery, for instance, often led to coagulopathy after major trauma). Some sense of some of these changes can be gleaned from the authors' data, as patients in the second group showed higher temperatures on admission to hospital, and displayed a smaller average fall in Glasgow coma scale core between the scene of injury and admission. Other factors, such as pre-hospital distance travelled, pre-hospital transfusion (including volume transfused) and whether patients were sedated and underwent tracheal intubation, are not fully accounted for in the analysis. Finally, there are, moreover, no data on adverse effects such as the complications of transfusion.

The retrospective nature of the work must also make us pause for thought. Despite the rise to cultural supremacy of the randomised controlled trial as the preferred study design for assessing the effects of interventions, researchers continue to conduct, and journals continue to publish, retrospectively collected data. For instance, in the last few months, Anasthesia has published two such papers [4,5], the second being accompanied by an editorial by Doherty and Shenkin [6] revisiting Bradford Hill's criteria for determining causation in associations in scientific findings. This is worth re-reading with the paper of Stein et al in mind. Why do we continue to use a study design which is in some way 'inferior'? One reason is that some research questions simply cannot be tackled using the randomised controlled format [7,8] . There is also much to gain from initial analyses, for instance of routinely-collected data, as these can make initial sense of what is held, help establish trends and formulate hypotheses for further testing [9, 10]. We should also remember that the systematic review, much vaunted as the highest level of clinical research evidence, has a retrospective character too. Whilst it is prospective in intent, and the process of preparation contains many elements to guard against some of the possible biases that can bedevil it, the systematic review is at its heart a backward-looking, observational exercise whose subjects are not patients, but rather other researchers' trials [11, 12].

As Doherty and Shenkin note [6], in order to be able to make causal inferences, random selection of patients and random allocation of treatment is required. Though random selection of patients may be possible in a retrospective, observational study, random allocation of treatment (or exposure) is seldom achieved. This lack of randomisation to treatment will render causal inferences impossible – because you cannot determine whether

the difference in outcome is due to the treatment received, or due to other factors which favoured allocation to that particular treatment.

One option to address this problem is propensity score matching. This is an increasingly popular method used to improve causal inferences when analysing observational data in retrospective studies. For example, propensity score matching was used in two recent retrospective studies published in *Anaesthesia*, one looking at the effect of prolonged propofol infusion [13] and one investigating potentially modifiable risk factors for atrial fibrillation [14].

The propensity score matching method will assign a 'propensity score' (also known as 'predicted probabilities') to each patient in the dataset using a model similar to logistic regression (the dependent variable here being treatment received, the independent variables being confounding variables or covariates which the investigator deems to be relevant in the analysis, such as age, sex, education level). Once the propensity score is obtained, patients are matched (one to one, or one to many) from each treatment group, according to their propensity scores and the data are then analysed in these two matched groups. We should, however, be wary of results obtained after propensity score matching in retrospective studies, because no matter how well the propensity scores match in the two groups, there will always be some unmeasured, and therefore, unaccounted for, variables which may be confounders which have not been fitted into the propensity score model. In addition, there is a lack of consensus as to which variables should be included in the propensity score model [15], and so there must exist investigator 'degrees of freedom', and bias.

Returning to the paper from Stein et al, the key point is, can the authors' practice be translated into other settings with the same benefits? To UK anaesthetists, some details look unfamiliar. The mean arterial pressure chosen for permissive hypotension (55-60 mmHg in the absence of brain injury), although part of the European Trauma guidelines, is rather high by UK standards [16] and the patients received colloids rather than crystalloids (starch in the first cohort, gelatin in the second), both of which affect coagulation in the volumes used. The use of ROTEM in elective surgery (where it has most commonly been studied) is supported by reasonable evidence [17] but it is not clear how widely it is used in the UK during trauma management, for instance [18].

The general message seems to be that introducing standardised routines of care leads to improvement in outcomes. As with many 'bundles' of processes, the effects of the individual components may or may not have been tested, but the composite effect often remains unquantified. In this case, by demonstrating what is possible, and by sharing the means by

which it was achieved, Stein et al have done us a service. The retrospective design simply means that we must be more circumspect about the exact size of the effect.

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