Effect of consent rituals on mortality in emergency care research

Clinical trials are important in improving the safety and effectiveness of emergency care. Many such trials seek to assess the effects of time-critical treatments for life-threatening disorders such as traumatic brain injury, severe haemorrhage, or respiratory distress. In general, before patients can be enrolled in such trials, current regulations require that they or their legal representatives provide written informed consent.[1,2] Although the requirement for written informed consent can sometimes be waived[3]—eg, if the patient is unconscious, treatment is urgent, and no relative is available—written consent is usually required in emergency-care research, despite the delays to treatment that this will usually entail.

Analysis of data from the Medical Research Council (MRC) CRASH Trial,[4] a multicentre randomised controlled trial of corticosteroid administration in acute severe head injury, provides an estimate of the delay associated with the requirement for written consent. On average, compared with hospitals that waived the need for consent, initiation of treatment was delayed by 1·2 h (95% CI 0·7–1·8) in hospitals where written consent from relatives was required.[5] This delay would not occur if the treatment was given (or withheld) outside the context of a clinical trial, in normal clinical practice.

The delay can be life threatening. The CRASH-2 trial[6] showed that giving tranexamic acid to trauma patients with bleeds results in a significant and clinically important reduction in overall mortality (relative risk 0·91, 95% CI 0·85–0·97), as well as in mortality specifically ascribed to bleeding (0·85, 0·76–0·96). Further analyses have shown that these beneficial effects depend importantly on the promptness with which treatment with tranexamic acid is started. Taking account of the average delay (1·2 h) associated with the need to obtain written consent in the MRC CRASH trial, we used CRASH-2 data to provide an estimate of the consequences for survival of a (more conservative) 1-h delay resulting from the requirement to obtain written consent.

We used a logistic regression model, with mortality due to bleeding as the outcome variable and "treatment group", "time to treatment", and an interaction term as explanatory variables. The interaction term from this model estimates how the effect of treatment (odds ratio) changes with time to treatment. We then calculated the risk of death for patients by treatment group, according to time to treatment.

The results are shown in the figure. The green and blue lines in the bottom part of the figure give the risk of death in treated and untreated patients, respectively. The effect of a treatment delay in treated patients was estimated by applying the odds ratio corresponding to a 1-h treatment delay to the risk of death in the untreated group. The red line gives the estimated risk of death in patients in whom treatment is delayed. The point at which the green and red lines intersect the blue line gives the time when the trial treatment no longer provides patient benefit. Using these data and data from the CRASH-2 trial on the proportion of patients who arrive at hospital within a given time since injury, we estimate that a 1-h treatment delay reduces the proportion of patients who benefit from the trial treatment from 63% to 49%. Whereas the relative risk of death from bleeding with tranexamic acid was estimated in the CRASH-2 trial as 0·85 (95% CI 0·76–0·96), the corresponding relative risk in the presence of a 1-h delay is 0·96 (0·86–1·08).

The delay from consent rituals in emergency situations has important consequences. First, it results in avoidable mortality and probably morbidity in participants in the trial. Indeed, far from protecting the interests of patients participating in research, requirements for written informed consent and the resultant delay in starting treatment could be lethal. Second, the delay in starting treatment can obscure a real treatment benefit from the administration of a time-critical treatment. In the CRASH-2 trial, the requirement for written informed consent probably means that the trial has underestimated the beneficial effect of tranexamic acid in trauma patients with bleeds, which would be given without delay in normal clinical practice.

In the context of research involving people who are incapable of giving informed consent, the Declaration of Helsinki[7] states that, if no patient representative is available and the

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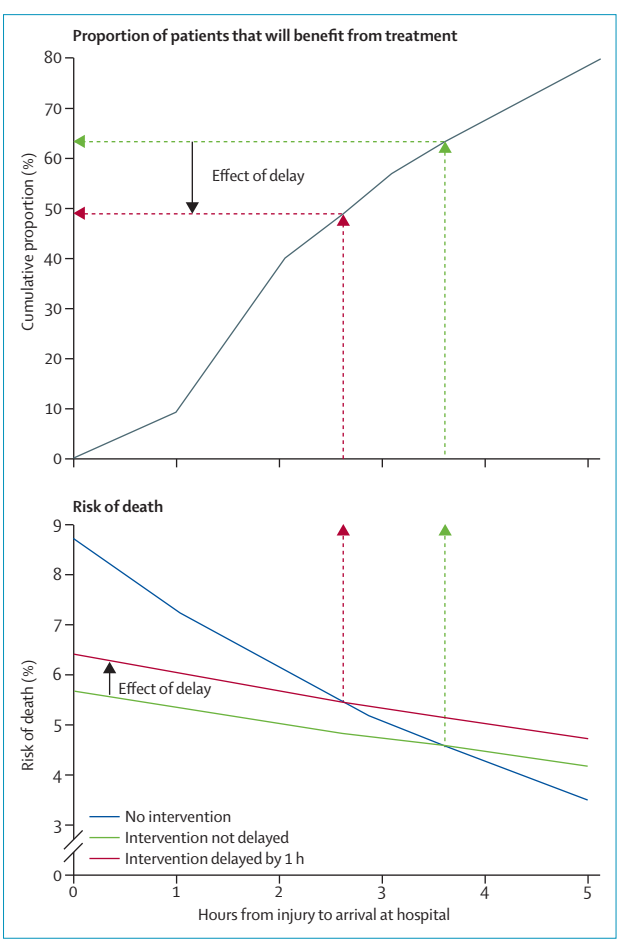

Figure: **Effect of 1-h delay in start of treatment with tranexamic acid on proportion of patients who will benefit and on risk of death**

research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a disorder that renders them unable to give informed consent have been stated in the research protocol and that the study has been approved by a research ethics committee.

We argue that the need for an urgent trial treatment, even in patients who are conscious and whose relatives are available, by itself excludes the possibility of fully informed consent. If consent rituals delay the start of a trial treatment such that the treatment effect could be reduced or obscured, we maintain that seeking consent is actually unethical. There might be other treatments whose benefits have been missed or underestimated as a result of insistence on the rituals of informed consent, against the precepts of the Declaration of Helsinki, with resultant avoidable harm to patients. There is little evidence that widely promoted forms of research regulation do more good than harm.[8] Informed consent procedures, like other well-intentioned public health interventions, should be assessed rigorously. The lethal effects we have shown might have been found decades ago had the research ethics community accepted a responsibility to provide robust evidence that its prescriptions are likely to do more good than harm.

We declare that we have no conflicts of interest.

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Risk assessment for recurrent venous thrombosis

In the Review entitled "Risk assessment for recurrent venous thrombosis" (Dec 11, p 2032),[1] Paul Kyrle and colleagues report that women who continued hormone intake after a first event of venous thromboembolism (VTE) were at high risk of recurrent VTE. However, findings from a French cohort of postmenopausal women emphasise that the risk of recurrent VTE in users of hormone therapy depended on the route of oestrogen administration.

Consistent with previous data,[2] women using oral oestrogens after a first thrombotic event were at high risk of recurrent VTE (adjusted hazard ratio 6·4, 95% CI 1·5–27·3). By contrast, transdermal oestrogens were not associated with an increased risk of recurrent VTE compared with non-use (1·0, 0·4–2·4).[3] These data provide evidence to support the safety of the transdermal route of oestrogen administration with respect to the risk of VTE recurrence and add to the current epidemiological evidence that transdermal oestrogens have no effect on thrombotic risk in postmenopausal women.[4,5]

In light of these data, the evidence for the implication of continuous oestrogen use in the increased risk of recurrent venous thrombosis should be modulated according to the route of oestrogen administration in postmenopausal women.

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Paul Kyrle and colleagues[1] suggest that patients with D-dimer concentrations of more than 250 µg/L are at risk of recurrence of idiopathic venous thrombosis and thus candidates for resuming anticoagulation therapy. Although a meta-analysis of seven randomised controlled trials showed that a positive D-dimer result after stopping anticoagulation therapy was associated with a 2·5-fold increase