response(s) across patient-participant’s dual existential state (anaesthetized, awake) in order to facilitate research that upholds participants’ contribution and precludes studies borne out of a priori consequentialistic stance.7

Finally, although the editor’s representation of ‘add-on’ study limitations of a study that diligently followed statutory ethical requirements (IRB-approval, informed consent) seems relevant and improves overall understanding, it might be misconstrued as ‘displaced-disclosure’ of the ‘missed’ limitations in the original article and therefore undermine publication ethics.8 Epistemologically, unless appropriate measures are taken to ensure that the readers must go through them in combination, it may sometimes lead to suboptimal gain of the propositional knowledge and inconsistent dissemination, especially when they go exclusively through either the original study or the accompanying editorial.

Declaration of interest

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Antifibrinolytic agents in current anaesthetic practice: use of tranexamic acid in lower limb arthroplasty

Editor—We read with interest the review by Ortmann and colleagues1 on the role of antifibrinolytic agents as a part of a modern blood conservation strategy for patients at risk of haemorrhage in different clinical contexts. They summarized ‘the literature of the past decade with specific relevance to daily anaesthetic practice, to support clinical decision-making and to enhance further discussion of the topic’. Tranexamic acid (TXA), like α-aminocaproic acid, prevents the premature dissolution of the haemostatic clot and reduces the volume of bleeding. Although the effectiveness of the TXA to reduce perioperative bleeding has been demonstrated in many studies, its effect on perioperative thromboembolic events and mortality has not been adequately assessed and remains uncertain.2 In fact, TXA package insert recognized that the frequency of arterial or venous embolism of any localization, and also hypersensitivity reactions including anaphylaxis, is unknown.3 This may be especially relevant for the use of TXA in lower limb arthroplasty, where postoperative hypercoagulability has been demonstrated.4

Owing to the progressive population ageing, an exponential increase in the number of interventions for elective total arthroplasty of hip (THA) and knee (TKA) is expected in the forthcoming years.5 Total lower limb arthroplasty is associated with a significant perioperative blood loss and, even if a transfusion protocol is applied, up to 20–30% of patients receive allogeneic blood transfusion (ABT), with a mean transfusion index of two units.6 The efficacy and very low cost of TXA appear as major drivers of its progressively increased use in TKA and THA, despite orthopaedic surgery is not nominally included within the specific indications of TXA in the revised product package insert.3

A review of published meta-analyses showed that TXA produced a variable reduction of perioperative blood loss and proportion of patients requiring ABT,7 but with significant heterogeneity, which requires careful interpretation of the effect of TXA in this context. Since ABT is also a risk factor of hypercoagulability in TKA and THA patients8 and TXA significantly reduces ABT, a reduced rate of thromboembolic complications could be expected. As this reduction has not been demonstrated,7 it could be hypothesized that TXA administration in TKA and THA would induce an increase in the risk of thromboembolic complications, as observed in hip fracture surgery,9 which could be offset by the benefit conferred by the reduction in exposure to ABT.

Future randomized trials of sufficient power should be designed to examine the safety of TXA. To confirm its safety, it would be necessary to include appropriate numbers of transfused and non-transfused patients, treated or not with this drug. Thromboembolic complications (primary security variable) must be carefully explored, including not only the incidence of deep venous thrombosis and pulmonary embolism but also that of myocardial infarction, cerebral ischaemia, and mortality. Having in mind the low incidence of these complications (<3%), to detect a 1% difference with an 80% power (β-error) and a 95% confidence interval (α-error), data from at least 5000 patients per arm (control and TXA) would be needed.

In the mean time, we should keep in mind that: (i) the available evidence seems to argue for caution, not complacency, regarding the use of TXA in TKA and THA surgery, and (ii) there are other efficacious, safe, and cost-effective alternatives for reducing bleeding, the need for ABT, or both in these...
patients, such as treatment of perioperative anaemia or perioperative autologous blood salvage.10

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**Antifibrinolytics in subarachnoid haemorrhage**

Editor—Dr Ortman and colleagues1 comprehensively review the evidence for antifibrinolytics across a spectrum of anaesthetic specialities. Concluding the section on subarachnoid haemorrhage (SAH), they state ‘there is a place for antifibrinolytic therapy as prophylaxis for early re-bleeding in subarachnoid haemorrhage’. We contend that the situation is more controversial than Ortman and colleagues suggest.

Recent systematic reviews on antifibrinolytics in SAH are equivocal. A recent meta-analysis found evidence of improved functional outcome with short-term use (i.e. <72 h post-ictus);2 but, the most recent Cochrane review found a reduction in re-bleeding was not accompanied by improved mortality or morbidity.2 Recent European guidelines reflect the equivocal evidence base, upholding the decade-old consensus that the benefit of antifibrinolytics in aneurysmal SAH is outweighed by the increased risk of delayed cerebral ischaemia.6 There have been false dawns in SAH management before—notably with supplementary magnesium, which ultimately ended with MASH-25—and enthusiasm for antifibrinolytics in major trauma has been tempered by post hoc analysis showing that administration more than 3 h post-injury is associated with excess mortality.6 This, combined with the increased risk of cerebral ischaemia3 and thromboembolism7 associated with antifibrinolytics in SAH, suggests that further research is needed to clarify their exact role in managing SAH patients, particularly with relation to timing.

Furthermore, the definitive prevention of re-bleeding is aneurysmal coiling or clipping (with an aneurysmal re-bleeding rate under 1% at 6 yr post-intervention).8 Any benefit from antifibrinolytics in SAH is likely to be as a temporary measure until the offending aneurysm is secured. Quality improvement is better coming from greater availability of interventional radiology and prompt coiling than from a drug that is far from risk-free.

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