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Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS). Comment on *Br J Anaesth* 2021; 126: 163–71

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Keywords: anaemia; mortality; perioperative bleeding; risk assessment; transfusion

Editor—We wish to congratulate Roshanov and colleagues[1] for their important study on Bleeding Independently associated with Mortality after noncardiac Surgery (BIMS). The authors identified three diagnostic bleeding criteria that were independently associated with postoperative 30 day mortality after noncardiac surgery: postoperative haemoglobin <70 g L^{-1}, transfusion of ≥1 unit of red blood cells, or bleeding judged to be the cause of death, requiring at least one of the aforementioned diagnostic criteria for BIMS.[1] We believe there is additional information that will help address some concerns and better put their findings into clinical perspective.

First, the authors studied candidate criteria in a subgroup of patients (Supplementary Fig. S1)[1] that was enrolled in the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) prospective international cohort study.[2] The population used for selecting variables, including threshold to predict BIMS, overlaps with the population used afterwards for estimating the prognostic importance of BIMS. This approach might lead to a performance bias caused by overfitting, which could be reduced using a standard internal validation approach such as bootstrapping, split sample, or cross-validation for model derivation and validation.[3]

Second, the list of adjustment variables and candidate diagnostic criteria for BIMS (Supplementary Table S1)[1] requires 31 degrees of freedom in total. A total of 167 events (30 day mortality) were observed in the cohort for deriving the BIMS definition, leading to a total of 5.4 events per predictor parameter (EPP), again raising concern regarding overfitting.[4,5]

Lastly, we recognise the selection and ranking of the candidate criteria with consideration of their pragmatic value by the authors. Nonetheless, haemoglobin itself or haemoglobin-derived parameters are overrepresented (Supplementary Table S1) and limit the power to test their associations with mortality, as discussed by the authors.[1] We are concerned that multicollinearity was not assessed. Multicollinearity might lead to inflated standard errors and therefore coefficients wrongly determined to be non-statistically significant. Moreover, collinear coefficients cannot be interpreted independently.[6] The authors should provide the variation inflation factor for each variable of the multivariable prediction model used for deriving the BIMS definition.

Prospective diagnostic studies of patients undergoing noncardiac surgery have proven to be an important source for evaluating and identifying risk factors for perioperative mortality.[2,7–9] Approaches such as the ones undertaken by Roshanov and colleagues[1] are critical to reducing perioperative morbidity and mortality.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Ringer's acetate solution-induced precipitation of remimazolam

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Editor—Certain drug-solvent combinations can result in precipitation. We report formation of a precipitate in an i.v. line induced by combined use of remimazolam and Ringer's acetate solution. In a patient undergoing oral surgery under general anaesthesia, i.v. fluid infusion was started with Ringer's acetate solution containing glucose 1% (Physio140, Otsuka Pharmaceutical, Tokushima, Japan), and general anaesthesia was initiated with administration of remifentanil (0.2 μg kg^{-1} min^{-1}) and fentanyl (0.1 mg) i.v. After 1 min, a bolus of remimazolam (0.2 mg kg^{-1}) was administered, and continuous infusion (1 mg kg^{-1} h^{-1}) was started to maintain anaesthesia, and after administration of rocuronium (40 mg), nasotracheal intubation was carried out uneventfully. I.V. infusion of Ringer's acetate solution was then set to 150 ml h^{-1}. At 20 min after the start of the continuous infusion of remimazolam, the i.v. drip rate was gradually decreased, and finally ceased. We identified a white precipitate that clogged the i.v. line at the joint of the i.v. catheter and drip needle (Fig. 1a), and fluid in the i.v. line had a white turbidity (Fig. 1b). Infusion of remimazolam and surgery was immediately stopped, and a new peripheral i.v. catheter was placed. Desflurane was used as an alternative for maintenance of anaesthesia, and the operation was completed uneventfully. The postoperative course was uneventful.

We tested remimazolam precipitation in our laboratory, examining whether remimazolam concentration, infusion rate of Ringer's acetate solution, or both contribute to the precipitates. We tested formation of the precipitates with three different concentrations of remimazolam (1, 2.5, or 5 mg ml^{-1} dissolved in saline; 13 ml h^{-1}) and three different infusion rates of Ringer's acetate solution (100, 150, or 300 ml h^{-1}). With remimazolam 2.5 and 5 mg ml^{-1} we observed precipitation in the i.v. catheter at slower infusion rates (100 and 150 ml h^{-1}) of Ringer's acetate solution (Fig. 1c). The precipitates began to form ~2 min after the start of remimazolam infusion, and the precipitates gradually increased in the i.v. catheter. At a higher infusion rate of Ringer's acetate solution (300 ml h^{-1}) with continuous infusion of remimazolam (5 mg ml^{-1}), precipitate was not observed in the i.v. line, but was observed around the three-way stopcock. In contrast, a lower concentration of remimazolam (1 mg ml^{-1}) did not produce precipitation in the i.v. catheter at any infusion rate of Ringer's acetate solution.

We conducted experiments to investigate whether the formation of precipitate differs depending on the type of Ringer's solution. When Ringer's lactate solution was infused at slower infusion rates (100 and 150 ml h^{-1}), continuous infusion of the higher concentration of remimazolam (5 mg ml^{-1}; 13 ml h^{-1}) also formed precipitates, which began to form ~5 min after the start of remimazolam infusion (Fig. 1d). The rate of precipitate formation in Ringer's lactate solution was slower than in Ringer's acetate solution. In contrast, lower concentrations of remimazolam (1 and 2.5 mg ml^{-1}) did not form precipitates at any infusion rate of Ringer's lactate solution.

Remimazolam (Anerem® in Japan; ByFavo™ in the USA; Aptimyda™ in the EU) is a novel benzodiazepine that was first approved in Japan as a general anaesthetic.[1,2] Remimazolam is distributed as remimazolam besylate, which is a hydrophilic white powder.[3,4] It is plausible that the white precipitates were formed by the combined use of remimazolam and Ringer's acetate solution. According to the package insert of remimazolam: (i) pH of the remimazolam solution is 2.9–3.9 when one vial (Anerem® 50 mg, ByFavo™ 20 mg) of remimazolam is dissolved into 10 ml of normal saline,[3,4] (ii) remimazolam