might reduce the risk of fluid overload compared with FFP.[902–904]

Two RCTs involving patients with PPH, a mean estimated blood loss of 900 to 1500 ml and normofibrinogenaemia, found no benefit of early pre-emptive treatment with 2 or 3 g of fibrinogen concentrate compared with placebo.[891–893,895,905] An RCT of targeted FIBTEM-guided fibrinogen substitution during PPH increasing the FIBTEM A5 level above 15 mm (to the normal level of pregnancy) found no clinical benefit or side-effects.[891] No SAEs were reported with fibrinogen concentrate in the obstetric setting.[891,892,895,906,907]

Guiding therapy in obstetric bleeding

What are the indications for the use of antifibrinolytic therapies (tranexamic acid) in obstetrics?

Fibrinolysis is decreased during pregnancy;[908] however, abnormally increased fibrinolysis is associated with complications such as placental abruption with antepartum bleeding.[909] Antifibrinolytic therapy used when postpartum bleeding evolves seems to reduce mortality due to bleeding and the need for acute laparotomies.[910,911]

Treatment with TXA 1 g i.v. should be given as soon as possible within 3 h to women with significant PPH (blood loss of >500 ml after vaginal birth/1000 ml after caesarean section/any blood loss sufficient to compromise haemodynamic stability) together with additional first-line treatment.[911,912]

Antifibrinolytic therapy, used prophylactically for vaginal[913,914] or caesarean delivery[915,916] might reduce blood loss and the need for additional treatment, but the clinical impact and relevance needs to be established together with the identification of relevant high-risk groups.[917] TXA might be given before or after cord clamping or delivery, but neonatal aspects are not clarified yet.[918] Oral and intramuscular administration of TXA is being investigated as an alternative route.[919]

Treatment with TXA as treatment or prophylaxis in parturients is not associated with increased risk of thrombosis.[911,914,916] Intravenous treatment with TXA is associated with nausea and vomiting.[914,916,920] Prolonged infusion and high-dose treatment with TXA might increase the risk of postpartum cortical necrosis and renal impairment in cases of severe PPH.[921]

What are the indications for other coagulation factor concentrates?

In two cases of amniotic fluid embolism, sufficient haemostasis was achieved by thrombo-elastometric-guided coagulation therapy constituting TXA, fibrinogen concentrate, platelets and PCC, as well as RBC and FFP in a 1 : 1 ratio, and rFVIIa.[922] Use of PCC might reduce the need for FFP in PPH,[923,924] but further evaluation is needed.

What are the indications for the use of rVIIa?

rFVIIa can be considered as second-line haemostatic therapy alongside intra-uterine tamponade, uterine compression sutures, pelvic vessel ligation and interventional radiology.[925,926] Case reports[927–931] and retrospective studies[926,932–936] support off-label use of rFVIIa for severe obstetric coagulopathic bleeding. Additional observational studies report increased risk of thrombosis.[937,938]

An open-label unblinded RCT of 84 patients showed reduced need for interventional second-line therapies (mainly arterial embolisation) following early administration of 60 μg rFVIIa compared with standard treatment for severe PPH (>1500 ml/24 h after delivery and unresponsive to uterotonics). No reduction in hysterectomies or arterial ligation was found. The intervention was not successful in over half of the patients. Furthermore, the risk of thromboembolism was increased (1 in 21 patients).[939] This trial was performed before TXA, and coagulation monitoring were established as standard (trial data collection period 2007 to 2010), so only 33 to 42% of patients received an initial TXA dose before rFVIIa. An extrapolation of these results and significant risk of thrombosis to present day scenarios remains to be evaluated.

2.7 Patients undergoing neurosurgical bleeding

Recommendation 13

For reversal of VKA-associated nontraumatic intracranial bleeding, PCC is recommended. 1B

For reversal of VKA-associated nontraumatic intracranial bleeding, we recommend against plasma transfusion. 1B

Intracranial surgery can be safely performed in the presence of low-dose aspirin. 2C

For reversal of APAs-associated nontraumatic intracranial bleeding, we suggest platelet transfusion or DDAVP. 2C

TXA intravenously as bolus with or without infusion, beginning from induction of anaesthesia until end of surgery, is recommended prophylactically for reducing peri-operative blood loss in elective intracranial surgery and elective spine surgery. 1B

Evidence summary

Intracranial surgery

Ten studies reported on intracranial tumour surgery.[940–949] A retrospective observational study including 8924 patients reported an RBC transfusion rate of 7% with an increased morbidity and mortality.[950] Other studies demonstrated an incidence of peri-operative bleeding resulting in RBC transfusion between 2.4 and 7%.[950,951]

Although Dasenbrock *et al.*[941] identified different levels of thrombocytopenia in a huge, retrospective cohort study ($n = 14\,852$) as risk factors for peri-operative