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Coagulopathy management of multiple injured patients – a comprehensive literature review of the European guideline 2019

Marcel Niemann[1,2], Ellen Otto[1,2], Christian Eder[1], Yasmin Youssef[3], Lutz Kaufner[4] and Sven Märdian[1]

[1]Charité – Universitätsmedizin Berlin, Center for Musculoskeletal Surgery, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[2]Julius Wolff Institute for Biomechanics and Musculoskeletal Regeneration, Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany
[3]Department of Orthopaedics, Trauma Surgery and Plastic Surgery, University Hospital Leipzig, Leipzig, Germany
[4]Charité – Universitätsmedizin Berlin, Department of Anesthesiology and Intensive Care Medicine, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Correspondence should be addressed to M Niemann
Email
marcel.niemann@charite.de

- The European guideline on the management of trauma-induced major bleeding and coagulopathy summarises the most relevant recommendations for trauma coagulopathy management.
- The management of trauma-induced major bleeding should interdisciplinary follow algorithms which distinguish between life-threatening and non-life-threatening bleeding.
- Point-of-care viscoelastic methods (VEM) assist target-controlled haemostatic treatment. Neither conventional coagulation assays nor VEM should delay treatment in life-threatening trauma-induced bleeding.
- Adjustments may be rational due to local circumstances, including the availability of blood products, pharmaceuticals, and employees.

Keywords
- multiple injury
- coagulopathy
- coagulation management

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Introduction

The European guideline on the management of major bleeding and coagulopathy following trauma is one of the most relevant sources for diagnostic and treatment algorithms in multiple injured patients (1). As trauma-induced coagulopathy is one of the leading causes of mortality among these patients (2), management beyond surgical measures gained further importance (3). Besides the early application of tranexamic acid (TXA) for trauma-induced bleeding patients, physicians became aware of the endothelial, immune system, platelet, and clotting abnormalities, including fibrinogen depletion, inadequate thrombin generation, impaired platelet function, and dysregulated fibrinolysis including hyper- and hypofibrinolysis, as well as fibrinolytic shutdown (4, 5, 6, 7). Since the guideline's most recent update in 2019, evidence of massive trauma-induced coagulopathy management continuously evolved. However, not all aspects of the guideline can be directly transferred into clinical diagnostic and therapeutic routines. Therefore, this narrative review focuses on articles published since 2019, which refer to prospectively conducted studies, and gives particular attention to implementing these recommendations into in-house algorithms.

Results

In this review, we solely focused on literature referring to the first 6 h following trauma. For each recommendation, we summarise existing evidence, introduce newly published data, discuss literature, and display our in-house recommendations derived from the most recent evidence (Fig. 1).

Recommendation 10 (1)

We recommend that *routine practice includes the early and repeated monitoring of haemostasis, using either a combined traditional laboratory determination (prothrombin time (PT), platelet counts, and Clauss fibrinogen level) and/or point-of-care (POC) PT/international normalised ratio (INR) and/or a viscoelastic method (VEM).*

We recommend laboratory screening of patients treated or suspected of being treated with anticoagulant agents.

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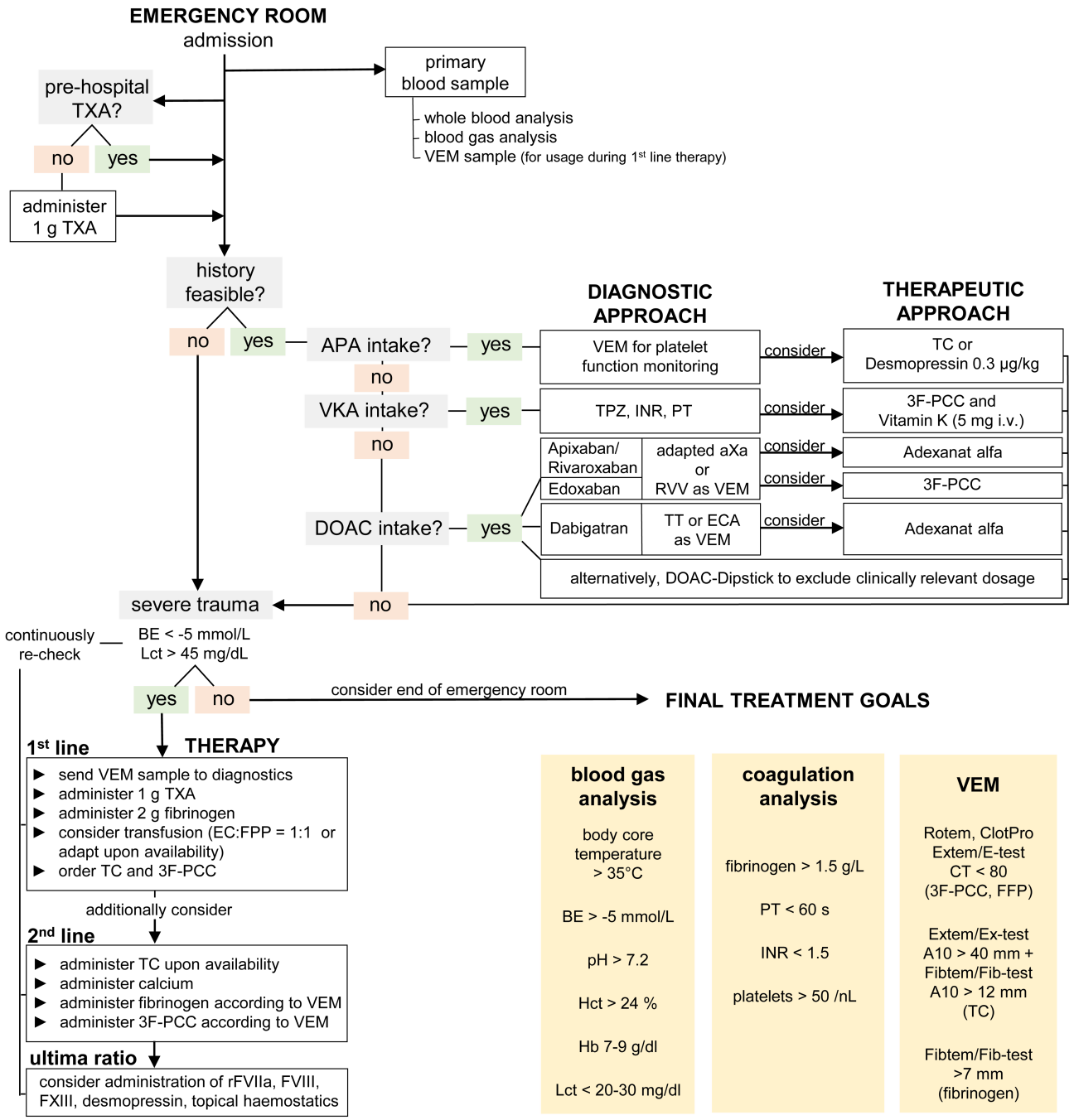

Figure 1

In-house treatment algorithm for managing massive trauma-induced bleeding. 3F-PCC, three-factor prothrombin complex concentrate; APA, antiplatelet agent; aPTT, activated partial thromboplastin time; aXa, anti factor Xa; BE, base excess; Lct, lactate; DOAC, directly acting oral anticoagulants; EC, erythrocyte concentrate; ECA, Ecarin chromogenic assay; FFP, fresh-frozen plasma; FVIII, coagulation factor VIII; FXIII, coagulation factor FXIII; Hb, haemoglobin; Hct, haematocrite; INR, international normalised ratio; PT, prothrombin time; rFVIIa, recombinant-activated coagulation factor VII; RVV, Russell's viper venom; TC, thrombocyte concentrate; TXA, tranexamic acid; VEM, viscoelastic method; VKA, vitamin K antagonists.

Evidence for recommendation

Different POC measures for viscoelastic (e.g. TEG®, ROTEM®, or Clot Pro®) or ultrasound-induced resonance-based (e.g. Quantra®) plasmatic coagulation measurements are available. Until 2015, the evidence for VEM in trauma-induced coagulopathy was scarce (8). Since then, VEM-guided massive transfusion protocols have improved overall survival after trauma compared to

conventional coagulation assays (CCA) (9). In addition, other POC measurements can be even more helpful and cost-efficient in receiving rapid thromboelastography-related values (10).

New data

One randomised controlled trial (RCT) has recently been published (11), investigating viscoelastic haemostatic assay (VHA)-based major haemorrhage protocols (MHPs) compared to conventional coagulation test (CCTs) MHPs to prevent and treat coagulopathy. There were no outcome differences between groups at 24 h and 28 days after trauma.

Discussion

CCAs are essential for baseline measures after hospital admission and guided haemostatic therapy in non-life-threatening coagulopathy, but the turn-around time is too long in life-threatening coagulopathy. VEM allows for the detection of fibrinolytic disorders and pre-trauma use of anticoagulants. However, there is no proof of the superiority of VEM compared to CCA-guided therapy (11). Further, extensive maintenance of VEM systems is needed when used in daily practice. Therefore, in non-life-threatening trauma bleeding, coagulopathy should be excluded, and further therapy should follow standard coagulation assays. Blood should be drawn at hospital admission and before haemostatic therapy. Afterwards, therapy should be initiated according to VEM values or should be monitored using VEM, if therapy initiation cannot be postponed until then.

In-house recommendation

CCA, including PT, activated partial thromboplastin time (aPTT), INR, fibrinogen concentration, blood count, and VEM parameters should be determined at hospital admission. In life-threatening coagulopathy, haemostatic therapy should be initiated following VEM sample preservation.

Recommendation 11 (1)

We suggest the use of POC platelet function devices as an adjunct to standard laboratory and/or POC coagulation monitoring in patients with suspected platelet dysfunction.

Evidence for recommendation

POC platelet function devices are available as whole-blood multiple electrode impedance aggregometry (MEA), platelet reactivity assay, vasodilator-stimulated phosphoprotein, or VEM devices with channels for measuring platelet function. Thus far, methods of published studies are highly heterogeneous and RCT data are entirely missing. Accordingly, there is a gap between monitoring of pharmacologically induced platelet inhibition and platelet dysfunction detection in trauma patients with unknown antiplatelet agent (APA) intake (12). In addition, while preliminary data indicate a correlation between POC-measured platelet function and intracranial haemorrhage (ICH) progression, the use of haemostatic therapy guidance in trauma remains elusive (12).

New data

None.

Discussion

Data concerning trauma-induced platelet function disorders are limited (13). POC platelet function assessments like Multiplate®, TEG® PM, or VerifyNow® should solely be used when APA intake is reasonably suspected. If pre-trauma APA intake is proven, haemostasis should be prioritized and stabilized (e.g. through platelet concentrates). Alternatively, the non-POC Platelet Function Analyser (PFA) 100® can be used for platelet function assessment. However, the maintenance needed for these systems is extensive, and a lab-dependent turn-around time of approximately 2 h needs to be taken into account.

In-house recommendation

In case of suspected pre-trauma APA intake in massive trauma or trauma-induced ICH, platelet function should be determined using POC platelet function measurements and/or non-POC Platelet Function Analyser via whole-blood MEA.

Recommendation 21 (1)

We recommend the use of topical haemostatic agents in combination with other surgical measures or with packing for venous or moderate arterial bleeding associated with parenchymal injuries.

Evidence for recommendation

Few human studies observed an effective use of collagen (14, 15, 16, 17), gelatine (18, 19), cellulose (20, 21), fibrin, synthetic glue, or adhesive (22, 23, 24)-based local haemostatic products for internal and external bleedings. Polysaccharide-based and inorganic substances are only approved for the use of external bleedings (15, 25).

New data

None.

Discussion

Data concerning local haemostatics in trauma-induced bleeding are scarce, as most studies are based on animal models (26, 27, 28). Only few focused on human subjects (12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23), of which most did not cover trauma-related bleeding. Therefore, the use of topical haemostatic agents should solely be considered as an additional measure.

In-house recommendation

Topical haemostatics may be considered following second-line treatment in massive trauma-induced bleeding.

Recommendation 22 (1)

We recommend that TXA be administered to the trauma patient who is bleeding or at risk of significant haemorrhage as soon as possible and within 3 h after injury at a loading dose of 1 g infused over 10 min, followed by an i. v. infusion of 1 g over 8 h.

We recommend that protocols for the management of bleeding patients should consider the administration of the first dose of TXA en route to the hospital.

We recommend that the administration of TXA not await results from a viscoelastic assessment.

Evidence for recommendation

The CRASH-2 trial observed a significantly reduced mortality and a reduced risk of bleeding without increasing thromboembolic complications following TXA administration (29). Evidence for paediatric cohorts is, thus far, minimal.

New data

In the STAAMP trial (30), the early pre-hospital application of TXA was superior to the application beyond 1 h after trauma. The CRASH-3 study confirmed reduced mortality through a preferably early TXA administration (31). Higher concentrations of TXA boluses before hospital admittance were not associated with improved outcomes (32) but with more thromboembolic complications (33).

Discussion

TXA is a broadly accepted agent used when bleeding risk is enhanced, particularly in trauma-induced bleeding. However, TXA bears some risks that need to be weighed up with potential benefits. First, the administration of TXA is associated with reduced concentrations of syndecan-1 and angiopoietin-2, which possibly attenuates a protease-mediated vascular glycocalyx breakdown (34). Further, the application of TXA is strongly associated with an increased risk of fibrinolysis shutdown in trauma patients (35). Fibrinolysis shutdown refers to acute impairment of the physiologic process to break down fibrin clots. In trauma patients, the risk of fibrinolysis shutdown is elevated (36) and associated with increased mortality (36). Last, various adverse events (AE) related to TXA were described (37). In most multicentre studies, thromboembolic events have not been more frequently observed following TXA administration (38, 39). Nonetheless, one must keep in mind that both the CRASH-2 (38) and the WOMAN trial (39) did not focus on trauma-induced bleeding. Despite the adequate study designs and the large cohorts, the findings of these studies may not be unreflectingly transferred to trauma patients.

In-house recommendation

For adults, 1 g of TXA should be administered in case of massive bleeding and/or shock at admission and missing pre-hospital administration, followed by an i. v. infusion of 1 g over 8 h. Further or delayed TXA application should be dependent on proven hyperfibrinolysis in the VEM.

Apart from that, the application of TXA should be made at the scene. An adapted protocol may be used in paediatric patients with expected high bleeding risk.

Recommendation 23 (1)

We recommend that monitoring and measures to support coagulation be initiated immediately upon hospital admission.

Evidence for recommendation

Early algorithm-based coagulation management protocols have reduced transfusion rates and mortality of multiple injured patients (40, 41, 42).

New data

None.

Discussion

A recently published retrospective study observed that early coagulation support was associated with reduced transfusion rates of erythrocyte concentrates (ECs) and shorter length of stay (LOS) (43). An increased plasma usage needs to be accepted, as most fixed transfusion protocols are based on this concept (42). Recently, a sub-analysis of the PROPPR study depicted that time to massive transfusion protocol activation and the initial arrival of blood products was associated with prolonged time to achieve haemostasis and increased mortality (44). Accordingly, goal-directed coagulation management protocols should be implemented as early as possible in the treatment course.

In-house recommendation

Early goal-directed coagulation management should be conducted upon hospital admission.

Recommendation 24 (1)

In the initial management of patients with expected massive haemorrhage, we recommend one of the two following strategies:

- *Fresh-frozen plasma (FFP) or pathogen-inactivated FFP in an FFP:RBC ratio of at least 1:2* as needed.
- *Fibrinogen concentrate and RBC*.

Evidence for recommendation

While the administration of FFP concurrent with ECs was associated with reduced mortality (45), there were no detectable outcome differences regarding mortality between different transfusion ratios (46). The role of fibrinogen will be discussed in recommendation 28.

New data

A *post hoc* analysis of the PAMPer and the COMBAT trials concluded that plasma administration before hospital admittance is associated with reduced mortality if transport to hospital exceeds 20 min (47). However, survival benefits may only be achieved in patients who did not exceed the need for more than ten units of ECs (48). The most significant mortality reduction was observed when pre-hospital plasma and EC transfusion were combined (49). Last, the PROPPR study showed that fixed transfusion ratios might not be rational, as their influence on haemostasis is highly dynamic (50).

Discussion

The new data published mainly focused on the transfusion of blood products before hospital admittance. Accordingly, fixed transfusion ratios may not be comparably beneficial for all patients. When discussing the early administration of blood products, the risk of associated hypocalcaemia and increased mortality needs to be considered (51).

In-house recommendation

Using POC measurement systems, blood products such as FFP, fibrinogen, and PCC products should be administered following the expected extent of trauma-induced coagulopathy and VEM results. In case of life-threatening bleeding, blood products should be administered in an FFP:RBC ratio of at least 1:2 without delay, and VEM results should be reviewed during resuscitation to adapt therapy accordingly. In contrast, in non-life-threatening trauma-induced bleeding, VEM should be checked before administering blood products.

Recommendation 25 (1)

We recommend that resuscitation measures be continued using a goal-directed strategy, guided by standard laboratory coagulation values and/or VEM.

Evidence for recommendation

Several previous studies assessed the use of goal-directed resuscitation strategies guided by POC VEM (52, 53, 54, 55, 56, 57, 58) or CCA (42, 59) in massive trauma-induced bleedings (60, 61, 62, 63). The main advantage of VEM-guided concepts is the gained information about underlying mechanisms of coagulopathy (64, 65). This facilitates a targeted therapy (53, 56, 66), which reduces patients' mortality (9) and outweighs fixed-ratio transfusion protocols (42).

New data

None.

Discussion

Various previously mentioned studies observed outcome improvements when using goal-directed treatment strategies for trauma-induced bleeding. However, observance of such concepts should not delay the treatment of life-threatening bleeding. Further, patients' risk factors need to be considered when planning short- and long-term treatment.

In-house recommendation

Goal-directed strategies should be implemented in trauma-induced bleeding treatment algorithms. However, neither conventional coagulation assays nor VEM should delay treatment in life-threatening trauma-induced bleeding.

Recommendation 26 (1)

If an FFP-based coagulation resuscitation strategy is used, we recommend that further use of FFP be guided by standard laboratory coagulation screening parameters (PT and/or APTT >1.5 times normal and/or viscoelastic evidence of a coagulation factor deficiency).

We recommend that FFP transfusion be avoided in patients without major bleeding.

We recommend that the use of FFP be avoided for the treatment of hypofibrinogenaemia.

Evidence for recommendation

An early administration of plasma and ECs has reduced mortality (46, 67). However, plasma transfusion may lead to vital complications (68, 69, 70, 71) and is an independent risk factor for increased mortality and worse outcomes in some patients (70). Further, FFPs cannot

correct trauma-induced coagulopathy (72, 73) and may lead to haemodilution (74).

New data

None, as we discussed the RCT in recommendation 24 (48).

Discussion

Few findings contribute to the recommendation. Plasma transfusions entail various potential risks but are relevant to consider in the overall concept of trauma coagulopathy treatment. See also the discussion in recommendation 24.

In-house recommendation

In massive trauma-induced haemorrhage, blood products should be administered upon availability, but an FFP-based coagulation resuscitation strategy should be avoided. In non-life-threatening trauma-induced bleeding, different RBC, FFP, and TK should be combined in transfusion algorithms to avoid haemodilution. Further, the additional transfusion of specific coagulation factors may be considered (see recommendation 27).

Recommendation 27 (1)

If a CFC-based strategy is used, we recommend treatment with factor concentrates based on standard laboratory coagulation parameters and/or viscoelastic evidence of a functional coagulation factor deficiency.

Provided that fibrinogen levels are normal, we suggest that PCC is administered to the bleeding patient based on the evidence of delayed coagulation initiation using VEM.

We suggest that monitoring of FXIII be included in coagulation support algorithms and that FXIII be supplemented in bleeding patients with a functional FXIII deficiency.

Evidence for recommendation

Thromboelastometry (TEM) can guide goal-directed therapy based on CFC (75, 76, 77, 78). This leads to improved clinical outcomes and reduces mortality of patients with trauma-induced coagulopathy (79), especially when previously treated with vitamin K antagonists (VKA) (80, 81, 82) (also see recommendation 33). However, prothrombin complex concentrate (PCC) increases the thrombin potential, exposing patients to an enhanced risk of thromboembolic complications (83, 84, 85, 86, 87, 88, 89). In addition, evidence of the administration of coagulation factor XIII (FXIII, which is activated by thrombin and induces fibrin cross-linking) (90) is highly scarce (91). The relevance of the fibrinogen level will be addressed in recommendation 28.

New data

A recently published meta-analysis observed that concurrent administration of PCC and FFP reduces mortality and transfusion rates compared to FFP alone, without enhancing the risk of thromboembolic complications (92). No new data have been published regarding the use of FXIII concentrate.

Discussion

As CFC-based concepts have already been successfully used to treat trauma coagulopathy, further research focused on different PCC products. Four-factor PCC (4F-PCC) seems to normalize INR more effectively in patients with previous VKA treatment than 3F-PCC (93). Further, patients' mortality was lower when using 4F-PCC instead of 3F-PCC (93). However, the potential risk of thromboembolic complications must be considered when administering any PCC product (94).

In-house recommendation

In life-threatening bleeding, blood products should be administered upon availability. A blood sample should be saved for VEM baseline measures before therapy. In non-life-threatening bleeding, treatment should be conducted according to VEM. PCC administration may be rational when EXTEM clotting time (CT) is >80 s. Due to the lower incidence of thromboembolic complications, 4F-PCC should be preferred. Thus far, FXIII does not play an essential role in the primary treatment of trauma-induced coagulopathy but may be relevant in the further course. Therefore, FXIII levels should be regularly monitored.

Recommendation 28 (1)

We recommend treatment with fibrinogen concentrate or cryoprecipitate if major bleeding is accompanied by hypofibrinogenaemia (viscoelastic signs of a functional fibrinogen deficit or a plasma Clauss fibrinogen level ≤ 1.5 g/L).

We suggest an initial fibrinogen supplementation of 3–4 g. This is equivalent to 15–20 single-donor units of cryoprecipitate or 3–4 g fibrinogen concentrate. Repeat doses should be guided by VEM and laboratory assessment of fibrinogen levels.

Evidence for recommendation

As platelet aggregation ligand, fibrinogen is highly relevant for coagulation (95, 96). Accordingly, hypofibrinogenaemia is associated with massive bleeding (97, 98) and increased mortality (99). Thus, an initial administration of 2 g of fibrinogen concentrate has been proposed for early coagulation support before receiving results from VEM and laboratory tests (41). Fibrinogen supplementation can be conducted using FFP, cryoprecipitate, and fibrinogen

concentrate. In FFP, fibrinogen levels are highly variable, which may lead to large amounts of fluid to restore fibrinogen levels, subsequently causing haemodilution worsening of coagulation (43). Furthermore, no clear superiority of either cryoprecipitate or fibrinogen has been shown concerning treatment efficacy (100). Last, there still is no clear evidence that the administration of fibrinogen reduces mortality at all, as most previous studies were only retrospective (101, 102) or of observational character (103).

New data

A recent meta-analysis showed that the administration of fibrinogen did not reduce mortality or the need for transfusion in trauma coagulopathy (104). However, the high risk of bias and the heterogeneity of the included studies may limit the implications of this analysis. In the RETIC RCT, patients with baseline fibrinogen levels beyond 100 mg/dL were successfully treated with a single fibrinogen concentrate dose. In contrast, lower baseline fibrinogen levels were associated with the need for repeated doses (105). Further, fibrinogen administration was observed to shorten LOS, while there was no adverse event attributed to fibrinogen administration (106). Another RCT comparing fibrinogen concentrate, PCC, and plasma transfusion in massive trauma-induced bleeding is still recruiting patients (107).

Discussion

While the administration of fibrinogen may be feasible even before hospital admission (108), evidence of the efficacy of early fibrinogen supplementation in trauma-induced coagulopathy is scarce. In addition, dosing schemes of fibrinogen in trauma coagulopathy are highly heterogeneous, and none of the existing schemes have been proven superior (1, 43, 105, 109). When administering fibrinogen, a greater rise in fibrinogen levels and favourable survival rates were observed for fibrinogen concentrate than cryoprecipitate (43).

In-house recommendation

Based on baseline fibrinogen level and VEM signs of a functional fibrinogen deficit, early fibrinogen concentrate supplementation is recommended. Fibrinogen administration may be rational when FIBTEM A10 is <10 mm. In life-threatening trauma-induced bleeding, 2 g of fibrinogen should be administered as a first-line treatment without prior testing.

Recommendation 29 (1)

We recommend that platelets be administered to maintain a platelet count above 50 × 10^9/L.

We suggest maintenance of a platelet count above 100 × 10^9/L in patients with on going bleeding and/or TBI.

If administered, we suggest an initial dose of four to eight single platelet units or one aphaeresis pack.

Evidence for recommendation

Platelets play an essential role in haemostasis and initial counts can predict patients' outcome (110). While platelet concentrate (PC) transfusions alone may not restore counts (111), mutual transfusion of PCs and ECs reduces mortality in trauma-induced coagulopathy (67, 112). However, a platelet count threshold is not finally defined in trauma patients (113, 114).

New data

Two meta-analyses have recently been published (115, 116), which observed that higher PC:EC transfusion ratios reduce mortality while maintaining thromboembolic complication risks (115). Evidence of efficacy in patients with traumatic brain injury (TBI) is limited (116).

Discussion

The current evidence of PC administration is heterogeneous. Transfusion may improve haemostasis and reduce mortality (46, 117), but the specific role of thrombocyte supplementation remains unclear, as most studies included PC administration in fixed transfusion ratios. Further, target blood concentrations are not finally defined (1, 109) and platelet concentrations highly vary between available products (113, 114).

In-house recommendation

In general, a platelet count above 50 × 10^9/L should be maintained. In patients with on going bleeding, a threshold of 100 × 10^9/L is recommended. When primary haemostasis is compromised (validated via VEM), PC transfusion should be considered.

Recommendation 30 (1)

We recommend that ionized calcium levels be monitored and maintained within the normal range during massive transfusion.

We suggest the administration of calcium chloride to correct hypocalcaemia.

Evidence for recommendation

Calcium is of fundamental relevance for coagulation, as it impacts platelets' functions (118). Hypocalcaemia can directly result from trauma (119), as well as from massive transfusion (120), and is associated with enhanced mortality (121). Calcium chloride is recommended over

calcium gluconate, especially when liver function is impaired (122).

New data

None.

Discussion

There is no evidence that the prevention of hypocalcaemia reduces patients' mortality. However, the monitoring of ionized calcium levels and the avoidance of pathological levels may be recommended.

In-house recommendation

Levels of ionized calcium should be continuously monitored upon hospital admittance and calcium levels should be kept within the reference range (>0.9 mmol/L).

Additional in-house recommendations

Beside normal levels of ionized calcium, hypothermia should be avoided (normothermia or body core temperature above 34°C) and pH levels should be continuously monitored and be kept within the reference range (upon 7.2 avoid acidosis).

Recommendation 31 (1)

We do not recommend the use of recombinant-activated coagulation factor VII (rFVIIa) as first-line treatment.

We suggest that the off-label use of rFVIIa be considered only if major bleeding and traumatic coagulopathy persist despite all other attempts to control bleeding and best-practice use of conventional haemostatic measures.

Evidence for recommendation

RFVIIa plays an essential role in the endogeneous coagulation system. Thus far, few studies have reported beneficial outcomes for patients who were treated with rFVIIa (123, 124, 125).

New data

None.

Discussion

The use of rFVIIa in trauma-induced coagulopathy remains off-label and is associated with an enhanced incidence of thromboembolic complications (126). Accordingly, rFVIIa should be carefully considered as ultima ratio. There is no evidence that the use of rFVIIa improves outcome at all.

In-house recommendation

RFVIIa should solely be considered as ultima ratio in massive trauma-induced bleeding.

Recommendation 33 (1)

In the bleeding trauma patient, we recommend the emergency reversal of vitamin K-dependent oral anticoagulants with the early use of both PCC and 5 mg i.v. phytomenadione (vitamin K1).

Evidence for recommendation

The administration of 4F-PCC facilitates an immediate reversal of VKA through the supplementation of inhibited factors FII, FIX, FVII, and FX (127). Despite various dosing algorithms (127), a standard dose of 25–50 U/kg is most commonly sufficient. Additionally, vitamin K supports VKA antagonisation by supplementing the missing haemostatic protein.

New data

None.

Discussion

The use of 4F-PCC allows the reversal of VKA treatment. Recent studies focused on comparing fixed- and variable-dose protocols in atraumatic bleedings. Overall, weight-dependent variable-dosage protocols were superior to fixed-dosage protocols (128, 129), but door-to-needle time was shorter in fixed-dose protocols (129). When PCC is not available, FFP can be used as an alternative. However, effective volumes are higher, increasing secondary risks associated with high volume supplementation (127, 130).

In-house recommendation

In case of suspected VKA intake in massive trauma-induced bleeding, PCC should be used as an immediate reversal of VKA. If 4F-PCC is not available, 3F-PCC can be used.

Recommendations 34 and 35 (1)

We suggest the measurement of plasma levels of oral direct anti-factor Xa agents such as apixaban, edoxaban, or rivaroxaban in patients treated or suspected of being treated with one of these agents.

We suggest that the measurement of anti-Xa activity be calibrated for the specific agent. If a measurement is not possible or available, we suggest that advice from an expert haematologist be sought.

If bleeding is life-threatening, we suggest the administration of TXA 15 mg/kg (or 1 g) intravenously and that the use of PCC (25–50 U/kg) be considered until specific antidotes are available.

We suggest the measurement of dabigatran plasma levels using diluted thrombin time in patients treated or suspected of being treated with dabigatran.

If measurement is not possible or available, we suggest the measurement of the standard thrombin time to allow a qualitative estimation of the presence of dabigatran.

If bleeding is life-threatening in those receiving dabigatran, we recommend treatment with idarucizumab (5 g intravenously) and suggest treatment with TXA 15 mg/kg (or 1 g) intravenously.

Evidence for recommendation

Besides increased bleeding volume (131), plasma levels of directly acting oral anticoagulants (DOAC) have been shown to affect coagulation assays (132, 133, 134, 135). Therefore, early assessment of coagulation assays and direct measurement of DOAC levels are essential in patients with suspected intake (136). In the presence of life-threatening bleeding following massive trauma and when dabigatran intake is suspected, treatment with idarucizumab should be initiated (137, 138). It is recommended to repeat all coagulation tests after dabigatran neutralisation to demarcate the extent of underlying trauma-induced coagulopathy (139).

New data

None.

Discussion

Despite the rising prevalence of DOAC intake (140), RCT data regarding the detection and therapy following pre-trauma DOAC intake are lacking. Commercially available POC VEM tools for pre-injury DOAC intake are, for example, the viscoelastic ClotPro® clotting time (for apixaban, edoxaban, and rivaroxaban) and Russell's viper venom (RVV) test clotting time (for dabigatran) (141, 142). *In vitro* data showed that idarucizumab reduced plasma concentrations of dabigatran (143) and that andexanet alfa lowered the concentrations of FXa-inhibitors but did not normalize VEM (143). In a porcine trauma model, PCC effectively reduced blood loss, restored haemostasis, and balanced thrombin generation despite previous rivaroxaban intake (144). However, outcome data remain inconclusive. In a retrospective study, pre-injury DOAC intake was not associated with an increased risk of adverse outcomes (145). Further, no outcome differences could be detected between pre-injury DOAC and VKA intake (146, 147). In the AAST trial, DOAC reversal was not independently associated with mortality (148).

In-house recommendation

In case of suspected DOAC intake in massive trauma-induced bleeding or ICH, calibrated aXa-activity, VEM (for apixaban, edoxaban, or rivaroxaban: RVV- test; for dabigatran: ECA-test ClotPro®), or diluted PT (for dabigatran) should be determined. Antidote therapy or 3F-PCC bypassing should be indicated according to DOAC reversal algorithm.

Recommendation 36 (1)

We suggest treatment with platelet concentrates if platelet dysfunction is documented in a patient with continued bleeding who has been treated with APA.

We suggest the administration of platelets in patients with ICH who have been treated with APA and will undergo surgery.

We suggest that the administration of platelets in patients with ICH who have been treated with APA and will not undergo surgical intervention be avoided.

We suggest that the administration of desmopressin (0.3 µg/kg) be considered in patients treated with platelet-inhibiting drugs or von Willebrand disease.

Evidence for recommendation

Pre-trauma APA intake increases mortality, when patients receive surgical treatment for ICH (149, 150). However, there is no proof that PC transfusions can restore platelet function after APA administration. Therefore, PC transfusion in trauma patients with ICH and pre-injury APA intake cannot be recommended unless neurosurgical procedures are planned (151). Besides PC transfusion, rFVIIa, TXA, and desmopressin can be used as direct APA antidotes (152, 153, 154, 155, 156). When using desmopressin, a dose of 0.4 µg/kg is recommended in ICH (151), and it should be combined with an antifibrinolytic agent, such as TXA.

New data

None.

Discussion

In both atraumatic and trauma-related bleeding, the relationship between outcome and pre-existing APA therapy remains controversial (157, 158, 159, 160, 161). Two recently published studies confirmed the efficacy of local (162) and systemic desmopressin administration (163) to reduce bleeding. However, the latter did not observe any functional improvement of the thrombocytes. Other studies observed lower mortality and a reduced haemorrhage volume in patients who received PC following APA therapy (164) and a lower platelet increment when pathogen-inactivated PC was used for transfusion (165). Only in one RCT, a novel pharmacological approach (PB2452) was successfully examined, which directly improved platelet function despite previous APA intake (166).

In-house recommendation

In case of suspected APA intake in massive trauma-induced bleeding or ICH, thrombocyte function should

be assessed through VEM (e.g. Multiplate® analyzer). With VEM guidance, PC transfusion can be evaluated prior to neurosurgical intervention.

Conclusion

The European guideline on the management of trauma-induced major bleeding and coagulopathy represents the gold standard in managing multiple injured patients. However, this guideline needs to be frequently updated to capture the most recent evidence and recommendations can be adapted according to personal and infrastructural resources. Last, the management of massive trauma-induced bleeding should be interdisciplinarily conducted, as coagulopathy entails a high risk of mortality.

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