

Proximal Femoral Fractures and Anticoagulation Therapy – When Is Surgery Safe?

Zlomeniny proximálního femuru a antikoagulační terapie – kdy je operace bezpečná?

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SUMMARY

Patients presenting with proximal femur fractures are at high risk of developing DVT and pulmonary embolism. Many of these patients suffer from additional anticoagulant treatment. Patients on anticoagulation treatment are complex to manage, especially regarding timing of surgery due to implemented quality control recommendations. The present review analyses the present data timing of surgery and perioperative surgical considerations on anticoagulation treatment in this patients group.

Introduction

Proximal femoral fractures are potentially life threatening injuries in the older population group (38), with a one-year mortality rate reported between 11 and 29% (4, 34). However, in this specific patient group up to 62% non-surgical complications have to be expected (35).

An operative delay between time of admission and the operation was found to be one of the most relevant problems in various investigations. Early North American studies showed that an operative delay > 48 h had a significant negative effect on acute complications and one-year mortality (51). The "non-harmful" period was later shortened to 24 hours (23). A current nationwide analysis of 7905 patients with proximal femoral fractures showed a mortality rate after 1-month, 1 year and 2 years of 10%, 26.9% and 36.3%, respectively. Patients treated within 24 hours showed a 6% lower mortality rate compared to patients treated >24h after admission (37).

This organizational problem is increasingly focused in the geriatric literature. Principles of orthogeriatric co-management include recommendations, that the majority of patients benefit from early surgical stabilization to reduce the rate of complications (33).

In an analysis of 242 patients > 64 years (average age 82.5 years), 73.9% were operated within 24h after admission. Surgical complications were increased when operations were performed between 4 pm and 8 am in the on-call duty and night shift times ($p < 0.03$). 21.5% of the patients developed hematomas or seromas. Mortality was influenced by patient age, ASA-classifi-

cation and co-morbidities and not by preoperative delay, whereas early surgery prevented surgical complications and reduced length of stay (36).

Therefore, for medico-legal reasons proximal femoral fractures should be treated as early as possible even in patients with preexisting oral anticoagulation, as the complication rate and the outcome correlated with the time to surgery (28).

Anticoagulative medication

There is a widespread use of additive anticoagulative medication in patients with proximal femoral fractures. 35.7% of patients suffer aspirin and clopidogrel, and 10% are on Marcumar® (Phenprocoumon) medication at the time of injury (35). Others reported an overall incidence of preoperative anticoagulation in 62.3%. 40.9% of patients were treated with acetylsalicylic acid, 16.2% with Phenprocoumon, 2.4% with clopidogrel and further 2.4% had a combination of several anti-coagulants (6).

The effect of anticoagulants in this patient group is of tactical relevance regarding timing of surgery (6):

- the transfusion probability of approximately 50% can be expected in patients with proximal femur fractures,
- patients receiving clopidogrel medication or a combined anticoagulant medication often have surgical delay,
- patients receiving clopidogrel medication or a combined anticoagulant medication showed highest transfusion rates.

General treatment recommendations

Based on a literature review, special recommendations should be considered for previously orally anticoagulated patients with proximal femur fractures (28):

- in contrast to elective procedures, in the acute medical care of hip fractures, preoperative bridging within the first 48 h is not required,
- the bleeding risk is lower in femoral neck fractures compared to pertrochanteric/subtrochanteric fractures,
- the bleeding risk is generally lower after osteosynthesis compared to endoprosthetic replacement,
- osteosynthesis can be safely performed before complete correction of coagulation inhibition,
- coagulation competence should be available prior to endoprosthetic replacement,
- coagulation competence should be present in cases of high risk bleeding situations; the anticoagulation effect should be subsided, but the consequences of venous thrombosis are considered more severe than the consequences of bleeding,
- the anticoagulative effect should be achieved more by a treatment pause than by administration of coagulation factor concentrates as an over-dose increases the risk of thromboembolism,
- in the absence of relevant postoperative bleeding, oral anticoagulation should be re-administered in the pre-existing dosage (approximately starting the 2nd postoperative day); prescribed treatment with vitamin K antagonists (VKA) can be bridged with heparine in a half-therapeutic dose until the target INR (> 2) has been reached; indication, dosage and bridging start is based on the individual risk-stratification.

Aspects of specific anticoagulants

Currently available data and recommendations are presented depend on the frequency of prescribed anticoagulative drugs.

Acetylsalicylic acid

Acetylsalicylic acid causes irreversible inhibition of cyclooxygenase-1. This effect lasts approximately 8 days, corresponding to platelets life. The general risk of bleeding complications is increased by a factor of 1.5, while no increase of mortality has been observed (7, 43). According to the guidelines of the European Society of Cardiology (ESC), acetylsalicylic acid is intended for secondary prevention (recidive prophylaxis of arterial thrombotic complications and re-occlusion prophylaxis after interventional cardiological interventions or bypass systems).

Only in severe perioperative bleeding complications a platelet-transfusion is (rarely) indicated (7, 43). Acetylsalicylic acid can be continued in some planned interventions, but should be preoperatively withdrawn 5–7 days before surgery (42).

Some investigations analyzed the specific group of proximal femur fractures under acetylsalicylic acid medication. The following conclusions can be drawn from these papers:

- data on transfusion requirements are inconsistent reporting increased (6–8%) (27, 29) or comparable transfusion requirements (9, 10),
- acetylsalicylic acid was associated with a clinically non-relevant, slightly increased hemoglobin drop (2.75 g/dl vs. 2.6 g/dl) (27),
- data on influence of mortality are inconsistent with a possible effect on the 1-year mortality (10, 29), whereas in-hospital mortality (10, 19) and 1-month mortality (10) were not adversely affected,
- no influence on wound infection rates were reported (19).

In summary, it can be concluded that treatment with acetylsalicylic acid can be continued and this does not interfere with an operation within the optimal time window (6).

Phenprocoumon (Marcumar)

The main indication for a phenprocoumon therapy is stroke prevention in atrial fibrillation (AF) and biological and/or mechanical heart valves and secondary prophylaxis of venous thromboembolism. Antagonism can be achieved with 1–2 mg oral or intravenous vitamin K or in rare cases with prothrombin concentrate (PPSB) or fresh frozen plasma (FFP) (43, 45). In planned interventions, phenprocoumon treatment should be stopped 5 days before surgery (42, 45).

Bridging, if indicated, is carried out by subcutaneously administered low molecular weight heparine (LMWH) in patients with atrial fibrillation and after venous thromboembolism or by intravenously administered unfractionated heparin (UFH) in patients after mechanical heart valve replacement (20).

The decision for bridging depends on the individual thromboembolism risk. A helpful tool in patients with atrial fibrillation can be the CHA2DS2-VASc Score (45).

Osteosynthesis of proximal femoral fractures and endoprosthetic joint replacement in these fractures are considered as intermediate or high-risk operations under anticoagulation treatment with phenprocoumon (13). As these surgeries should be performed immediately or latest within 48 h after admission, emergent antagonism can be performed with prothrombin concentrate (PPSB) or frozen fresh plasma (FFP). An INR below 1.5 allows even high risk bleeding surgery (20).

In cases of pre-existing oral anticoagulation with vitamin K antagonists (VKA, e.g. phenprocoumon), vitamin K (Konakion®) should be prescribed during the treatment pause (28). Intravenous vitamin K administration is recommended, to achieve a faster effect (45). A Bridging should be considered after a delay of 3–4 days or in cases with an INR < 2.

In general, two possible algorithms are discussed for patients under phenprocoumon medication: an INR-dependent and an INR-independent management protocol (1, 13).

INR-dependent concept

After discontinuation of phenprocoumon, immediate intravenous administration of 1 mg vitamin K for an-

tagonism and 5000 IU deltaparin for additional bridging is recommended. An INR control is then performed after 24 h. If the INR value is < 1.5 , surgery can be performed, whereas if the INR value is > 1.5 , again intravenous 1 mg vitamin K is administered and a further INR control is performed after additional 24 h. At this time, an interdisciplinary consensus (anesthesia, surgery) should be carried out for deciding when and how to perform surgery (1). Similar recommendations are reported from Austria (28). An INR < 1.5 allows early surgery, whereas in patients with an INR ≥ 1.5 , intravenous vitamin K (Konakion®) 10 (5–15) mg/day and aPPT/INR re-evaluation every 12 h is recommended. If no adequate coagulation status is achieved within 48 hours, an interdisciplinary management decision is recommended. It should be decided in these individual cases whether surgery can be performed despite a decreased prothrombin time or an increased INR, whether surgery has to be still postponed or whether preoperative administration of prothrombin complex concentrate (PPSB) has to be considered.

Estimation of the initial PPSB dose can be performed INR-dependent: 25 U/kg with INR < 4 ; 35 U/kg with INR 4–6; 50 U/kg with INR > 6 as 1 U/kg is supposed to increase the FVII and FIX activities by 0.5–1%, and the FII and FX activities by 1–2% (28). Plasma concentrates (fresh plasma, FFP), recombinant factor VIIa (rFVIIa, Novoseven®), tranexamic acid (Cyklokapron®) are not recommended for INR correction.

INR-independent concept

If surgery (osteosynthesis/prosthetic replacement) has to be performed within 24 hours, INR-independent bridging with intravenous vitamin K administration (2–4 mg) and additive FFP is recommended. If surgery can be delayed to 48 hours, FFP administration is not required (13).

German recommendations are based on the prothrombin time. Surgery can be performed after two daily vitamin K administrations (e.g., Konakion® 10 mg) when the prothrombin time increased to $> 50\%$. According to bridging recommendations, a weight- and anti-Xa-dependent low molecular weight heparine treatment is initiated. A postoperative change to new oral anticoagulation medication is recommended only after complete wound healing (6).

Therefore, it can be concluded that bridging should be performed in patients with phenprocoumon medication, but surgery can be performed in an adequate time window (6).

New oral anticoagulants (NOAC)

There are presently insufficient data on NOAC treatment. In Austria it is assumed, that NOAC are already used for long-term anticoagulation in approximately 20% of patients (28).

In cases of preexisting oral anticoagulation with direct thrombin inhibitors (DTI, e.g. Dabigatran, Pradaxa®) or direct FXa inhibitors (DXA, e.g., Rivaroxaban, Xarelto®;

Apixaban, Eliquis®; Edoxaban, Lixiana®), there is no indication for vitamin K administration (28). Methods reducing drug resorption after short-term administration can be considered (activated carbon) (28).

In patients with rivaroxaban medication, renal function dependent recommendations are considered (28):

- creatinine clearance > 30 ml/min: surgery is possible < 48 hours after the last dose,
- creatinine clearance < 15 – 30 ml/min: contraindication for DXA therapy in cases with < 15 ml/min; interdisciplinary decision on surgery despite anticoagulation inhibition, delay of surgery > 48 hours and/or treatment with PPSB (dose estimation 25 U/kg).

Plasma (fresh plasma, FFP), recombinant factor VIIa (rFVIIa, Novoseven®), tranexamic acid (Cyklokapron®) are not recommended for reversion of DXA coagulopathy. Activated PPSB (FVIII bypassing activity, FEIBA) can be considered as a substitute for PPSB.

Particularities with dabigatran (Pradaxa)

Since November 2015 an antidote to reverse the anti-coagulant effects of dabigatran is clinically available: Idarucizumab (Praxbind®). Idarucizumab is a full human monoclonal antibody fragment without Fc-fragment with a 350-fold higher affinity to dabigatran compared to thrombin. It binds with free dabigatran after intravenous administration and with thrombin-fixed dabigatran. It does not bind to other direct thrombin inhibitors or direct FXa inhibitors. Thus, Idarucizumab inactivates the anti-coagulant effect of dabigatran immediately and completely, without a pro- or anticoagulant effect (44, 48).

Although scientific evidence is still missing that Idarucizumab reduces morbidity, mortality and treatment costs in proximal femoral fractures, regarding increased patient safety, its availability in hospitals with trauma/orthopedic departments seems to be justified and necessary (28).

If Idarucizumab is not available, patients with poor renal function (eGFR < 50 ml/min) should be evaluated interdisciplinarily. Interventions such as administration of 25 U/kg prothrombin complex concentrate (PPSB) or hemodialysis should be discussed. In most cases, especially in biological elderly patients with pre-existing coxarthrosis, a waiting period > 48 h seems to be preferable, if medically justified, especially joint replacement is favored.

Reversing the dabigatran effect can be initiated by surgical delay or antidote administration with Idarucizumab. According to the Federal Ministry of Health from Austria some recommendations in relation to renal function were given (28):

- patients with good renal function (eGFR > 80 ml/min) can wait until the dabigatran activity is reduced to adequate levels within 48 h without the administration of Idarucizumab,
- in patients with renal impairment (eGFR 50–80 ml/min) and a normal prothrombin time, surgery can be planned within 48 h – without administration of Idarucizumab,
- alternatively, in patients with normal or impaired renal function, intravenous bolus administration of

- 1–2 × 2.5 g Idarucizumab reverses the dabigatran effects within minutes, thus, surgery can be performed immediately,
- in patients with poor renal function (eGFR < 50 ml/min), dabigatran effects are not fully corrected within 48h; after intravenous bolus administration of 2 × 2.5 g Idarucizumab, surgery can be performed immediately; normal prothrombin time values can confirm the antidote effect.
 - plasma (fresh plasma, FFP), recombinant factor VIIa (rFVIIa, Novoseven®) and/or tranexamic acid (Cyklokapron®) are not recommended for reversal of direct thrombin inhibitors; activated PPSB (FVIII bypassing activity, FEIBA) can be considered as a substitute for PPSB.

Practical aspects dabigatran (Pradaxa) antagonism

- after antagonization, surgery should be performed within 12 h,
- the overall risk of thromboembolism is lower after Idarucizumab compared to "reversing" with (activated) PPSB or recombinant FVIIa,
- there are no interactions with coagulation factor concentrates and haemostyptics,
- if an intraoperative severe bleeding complication occurs, despite antagonization, a second bolus with up to 5 g Idarucizumab may be added; further coagulation tests (e.g., ROTEM) should be initiated,
- there is no interaction between idarucizumab and (dual) antiplatelet therapy.

P2Y₁₂ inhibitors (clopidogrel)

Clopidogrel is an irreversible thrombocyte aggregation inhibitor for prophylaxis of atherothrombotic events. Discontinuation should only be performed in accordance with cardiologists (43). As with acetylsalicylic acid, in elective surgery discontinuation should be initiated 5–7 days preoperatively (42).

There are a large number of studies dealing with additive clopidogrel intake. Essential analyzed parameters included time of surgery, transfusion requirements including hemoglobin drops and overall blood loss, general and bleeding complications as well as early and late mortality.

- Time of surgery: the optimal operation time is either very early (within 24 hours) or very late (after 10 days), since otherwise there is an increased risk for acute coronary syndromes (11); surgical delay was associated with an increase in mortality (31, 50) and an increase in complications (50); Chechik et al. found increases in in-hospital mortality, 1-year mortality and transfusion requirements during surgery after day-7 versus day-1-surgery, while bleeding complications were not observed during further course (0% vs. 3%) and a hemoglobine drop was increased by 0.7g/dl (8).
- Transfusion requirements: Clopidogrel therapy was associated with an increased need for transfusion (10, 12, 16, 25, 49) with an increased transfusion rate of 4–7.5%, especially in patients treated within the first 3 days (11).

- Blood loss: the intraoperative blood loss is slightly increased (< 200 ml) (9).
- Bleeding complications: the rate of postoperative symptomatic hematoma is increased (25, 32).
- In-hospital mortality: no relevant effect was shown, when surgery was performed within 24 hours (10, 19).
- 1-month mortality: a minimal or slight elevation was reported (10, 49).
- 1-year mortality: indifferent results were reported with increased (10) decreased (49) or unrestricted (12, 16) mortality rates; this mortality was supposed to be mainly influenced by underlying diseases.

Overall, it can be concluded, that treatment with clopidogrel does not significantly affect surgery of proximal femur fractures within the optimal time window.

Dual antiplatelet therapy

Dual antiplatelet therapy (DAPT) is the combination of acetylsalicylic acid (AA) and an ADP receptor antagonist (e.g., clopidogrel, prasugrel, ticagrelor), whereas an APT monotherapy is defined as single prescription of either AA or clopidogrel, e.g. in cases of AA intolerance.

In general, the risk of bleeding due to (D)APT has to be compared to the vital risk of stent thrombosis. Patients with coronary artery stents have to be treated life-long with AA and for at least six weeks (patients with uncoated stents, BMS, "bare metal stent") or for at least twelve months (patients with coated stents, DES, "drug-eluting stent") with a P2Y₁₂-Inhibitors (21). DAPT is also indicated for 12 months in patients after acute coronar syndrome.

There is a potential relevant risk of stent thrombosis after in the "dual" phase. The most important risk factor is early discontinuation of DAPT with a 90-fold increased risk (hazard ratio: 89.9) (26, 46).

In case of emergency surgery, there is no possibility of antagonization, thus, focussing on the control of bleeding complications. Usually platelet concentrates have to be administered, possibly in combination with desmopressin (DDAVP) and/or antifibrinolytics (30). Regardless of the stent type, emergency procedures are associated with a relevant higher rate of severe cardiac complications (urgent operations: factor 1.7, emergency operations: factor 3.2 (27, 41)).

If surgery has to be performed within the critical time window, the perioperative continuation of DAPT is recommended (14, 17, 40).

In patients with a combined high risk of bleeding and thromboembolism, the duration of the effective interruption should minimized perioperatively to only few hours.

Postoperatively, P2Y₁₂ inhibitors should be given as soon as possible (5).

Practical aspects (28)

- There is an ongoing coagulopathy and bleeding risk due to APT effects during the first 48 h; the overall duration of anticoagulant effects is 5 days for Clopidogrel and Ticagrelor and 7 days for Prasugrel

- secondary prophylaxis AA as a monotherapy should be continued life-long as it provides vital protection against thrombosis or ischemia
- the risk of acute stent thrombosis is highest in the first few weeks after implantation and then decreases slowly; DAPT can be reduced, in interdisciplinary consensus with the treating cardiologists, early to APT monotherapy in Bare Metal Stents (BMS) and the New drug-eluting stents (DES)
- according to the recommendations of the European Society of Cardiology (ESC) due to the high re-infarction risk, surgery should be performed always in hospitals with a 24 h cardiac catheterization laboratory, if BMS implantation < 1 month ago, DES implantation < 3 months ago, and acute coronary syndrome < 12 months ago
- an interdisciplinary management consensus is recommended, ideally performed by an established special "hip team" consisting of trauma surgeons/orthopedic surgeons, anesthesiologists, internal medicines/cardio-logs and lab technicians, to
- support individualized concepts, decisions and drug prescriptions
- in elective surgery, clopidogrel and ticagrelor should be discontinued 5 days before surgery, Prasugrel 7 days
- AA should always be maintained perioperative with the exception of few cases, where this primary prophylaxis can be discontinued preoperatively
- in the near future, the measurement of platelet function might be helpful to define the earliest possible safe time of surgery
- administration of platelet concentrates can be used to abolish the APT effect considering the potential disadvantages of creating a prothrombotic environment and therefore increasing a risk of a stent-thrombosis; therefore the platelet transfusion should be avoided the first 1–3 months after stent implantation, depending on the stent type
- desmopressin and tranexamic acid can improve the primary hemostasis capacity, but also the thrombosis risk and other specific complications have to be considered
- after operative treatment of the proximal femur fracture a thrombosis prophylaxis has to be initiated
- in the absence of relevant postoperative bleeding oral APT can be individually reestablished on the 1st or 2nd postoperative day in the pre-existing dosage
- bridging with a parenteral thrombocyte function inhibitor is not recommended.

Apixaban (Eliquis®)

Apixaban (Eliquis®) is an oral anticoagulant approved for the prophylaxis of venous thromboembolism (VTE) after elective hip or knee replacement and for prevention of stroke and systemic embolism in non-valvular atrial fibrillation for adults (2).

An operation should be performed, earliest 24 hours after the last dose (15). If such interventions can not be delayed, an increased bleeding risk has to be considered. The risk of bleeding should be weighed against the urgency of the procedure.

- In **patients without additional risk of bleeding**, Apixa-ban should be discontinued at least 24 hours before scheduled surgery or invasive surgery (15, 39). This includes interventions for which any possible bleeding risk is considered minimal, which have an uncritical localization, or which is easy to control.
- In **patients with an additional risk of bleeding**, Apixa-ban should be discontinued at least 48 hours before the planned operation or the invasive procedure (15, 39). This recommendation also is stated to procedures, where a clinically relevant bleeding risk is potentially possible or with an unacceptable bleeding risk (e.g., brain, spinal cord, eye, etc.). Also, elective major procedures such as endoprosthetic replacements and most fracture osteosynthesis around the proximal femur, knee joint etc. are included.

In non-elective interventions or emergency operations (15, 22), the risk of bleeding should be weighed against the urgency of the procedure. It has to be considered, that coagulation tests show variable results with only slight changes of prothrombin time (PT), INR and activated partial thromboplastin time (aPTT) (2, 3).

The degree of anticoagulant activity is determined by anti-FXa activity and therefore is closely related to the plasma concentration of apixaban (2, 47).

Management of active bleeding

If an intra- or perioperative hemorrhage persists, a graduated treatment algorithm is recommended (6):

- use of tranexamic acid (initial bolus of 10–15 mg/kg, then 1–5 mg/kg/h), or administration of thrombocyte concentrates if patient is taking platelet inhibitors,
- desmopressin (0.3 g/kg),
- prothrombin complex concentrates PCC preparations (20–25 IU/kg body weight), especially in detected the blood concentration of apixaban.

Alternatively, PPSB can be infused directly (39). It is important to consider the rapid onset of PPSB (24), resulting in an increased DVT risk.

If there is still a diffuse bleeding without any apparent source, the administration of recombinant Factor VIIa should be considered (15, 47). There is currently no antidote available for Apixaban. Due to the short half-life time of Apixaban of about 12–15 hours (2, 18), the anticoagulant effect of apixaban is significantly reduced after 24–30 hours (2 half-lives). In healthy volunteers, administration of carbon after 2 and 6 hours reduced the half-life of apixaban from 13.4 hours to 5.3 and 4.9 hours respectively. Therefore, the application of activated carbon should be considered preoperatively.

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