Blood Management for Elective Orthopedic Surgery

Introduction

The number of surgical procedures performed globally continues to rise(1, 2). **Orthopedic** procedures can result in significant blood loss **from both the surgical field and drains (visible blood loss), and from extravasation into tissues (hidden blood loss)(3). When considering visible and hidden loss, surgeons can expect total blood loss of approximately one liter during the perioperative period for primary hip and knee arthroplast~~y~~ies(4). Blood loss is significantly greater for revision procedures(5). Modern blood management strategies, which recognize the importance of reducing blood loss and blood transfusions, ~~and~~ improve patient outcomes(6-9) and should represent routine clinical care(10, 11). Preoperative anemia is independently associated with 30-day postoperative morbidity (OR 1.41 95%:CI:1.30-1.40) and mortality (OR 1.42 95%CI:1.31-1.54)(12, 13). Postoperative anemia may increase the risk of myocardial infarction and impede recovery after joint replacement(14, 15). Allogeneic transfusion is also ~~an independent predictor of~~associated with postoperative complications including surgical site infection(16, 17) and mortality(18). Blood conservation strategies improve perioperative outcomes and reduce costs(19).** This review **discusses** pre-, intra- and post-operative surgical and **anesthetic** blood management strategies**(Figure 1).**

Pre-operative optimization

Hemoglobin Assessment

The World Health Organisation (WHO) defines anemia as a hemoglobin concentration **(Hb)** of <12g/dL in women and <13 g/dL in men(20), **however, consensus guidelines recommend~~suggest~~ a target preoperative Hb concentration >13g/dL for both sexes(21). Prior to primary hip and knee arthroplasty, over 10% patients are anemic according to WHO criteria and over 25% have a Hb <13g/dL(22).** The etiology of anemia varies greatly

and the prevalence increases with age. Within the general population, the prevalence of anemia according to WHO thresholds is 10%, but exceeds 20% in those aged 85 years(23). In orthopedic patients, preoperative anemia is secondary to iron-deficiency in approximately 40% cases(22, 24) and treatment improves patient outcomes(19).

The 2018 Frankfurt Consensus **made a strong recommendation for the detection and management of preoperative anemia prior to major elective surgery**(11). Screening **is traditionally** performed **by blood sampling** and laboratory analysis, **but invasive and non-invasive point-of-care testing is now available~~or alternatively by invasive and more recently, non-invasive point of care testing~~(25).**

Recommendations:

1) **Define anemia as a Hb concentration less than 13g/dL.**
2) **Screen for anemia when patient is listed for major surgery**

Risk of transfusion

Preoperative Hb and transfusion threshold are the strongest predictors of allogeneic blood transfusion(26). A retrospective study of 1132 arthroplasties with an overall transfusion rate of 1.06% found that allogeneic transfusion was only required in patients with a Hb≤13.0g/dL(27). Other studies propose a preoperative Hb threshold of 12.4g/dL for total knee arthroplasty, above which it is suggested that a type and screen (T&S) is not indicated. Setting a transfusion threshold of 8g/dL, 0.6% of their patients without T&S required allogeneic blood(28). Institutional data for specific procedures and surgical techniques, accounting for preoperative Hb, may allow selective preoperative T&S if the risk of transfusion is deemed acceptably low. In addition to preoperative Hb, patient demographics and comorbidity are important predictors of perioperative blood transfusion(27, 28). T&S is necessary for patients with known antibodies.

Recommendation:

1) **The decision to T&S may be based on the planned surgical procedure, preoperative Hb, patient comorbidities and transfusion history.**

Delaying surgery

Anemia should be diagnosed, investigated, and treated prior to proceeding with elective orthopedic surgery. Surgery should be delayed until anemia has been optimised given the increased risk of adverse events associated with anemia and allogenic blood transfusion. This practice is supported by multiple national and international guidelines(21, 29, 30).

It is not possible to correct anemia in all patients, however, reversible causes should be addressed. Mild iron-deficiency anemia should correct with oral iron supplementation within 4-6 weeks, but in the absence of a response intravenous iron supplementation may be indicated(21). It is important to exclude gastrointestinal malignancy as a cause for iron-deficiency anemia(31). It remains unclear whether patients without anemia but with iron deficiency benefit from iron supplementation(11, 21).

Erythopoetin, may be indicated in combination with iron supplementation to treat patients with anemia who are undergoing major elective surgery(11, 21). However, its cost effectiveness is unclear, and it may increase the risk of thrombotic or adverse events(32). Investigating the value of EPO has been identified as a research priority(11).

Recommendation:

1) **Investigate and treat reversible causes of anemia prior to elective orthopedic surgery.**

Coagulation *assessment:*

Asymptomatic hereditary **coagulative** disorders are rare (1/40,000)(33). The ability to detect **coagulative** disorders by routine tests of hemostatic function such as PTT and INR is limited(34-36). Various organizations recommend against routine preoperative tests of **coagulation** function(37-39). **Obtaining a** careful bleeding history **that includes questions relating to previous excessive surgical bleeding, family history of bleeding disorders, and the use of antiplatelet and anticoagulants is important (Table 1)(40)**. The HEMESTOP and the Condensed MCMDM1-VWD Bleeding Questionnaire may be useful **supplementary** tools(41) **(Table 2)**.

Thromboelastometry (TEM) and Thromboelastography (TEG) are methods of analysing the viscoelastic properties of clot formation and dissolution. These can help determine which components of clot formation are deficient and **guide the administration of blood products during the perioperative period(42).**

Recommendation:

1) **Do not routinely perform laboratory tests for coagulation dysfunction unless screening questions indicate a patient is at elevated bleeding-risk .**

Optimization of pre-operative ***anticoagulants*** *to reduce bleeding risk* ***(Table 2).***

An increasing number of patients are taking antiplatelet and anticoagulant medication. Clinicians must balance the risk of thrombotic events against ensuring adequate hemostasis during the perioperative period in a patient-specific manner.

There is conflicting evidence as to whether acetylsalicylic acid (ASA) should be stopped perioperatively. **In patients already taking ASA,** ~~T~~the POISE-2 trial **did not demonstrate a difference in death or myocardial infarction or major bleeding events if ASA was continued as opposed to withheld**(43). Other antiplatelet agents such as clopidogrel**, (as well as other P2Y12 inhibitors)** may have more marked effects on platelet function and perioperative bleeding(44). A 2018 Cochrane database systematic review found **evidence of** moderate-certainty that either continuation or discontinuation of antiplatelet therapy before non-cardiac surgery makes little or no difference to bleeding requiring transfusion, and evidence of **low-certainty of** little or no difference to mortality, bleeding requiring surgical intervention, or ischemic events(45). **Acknowledging the controversy, most consensus statements recommend continuation of ASA peri-operatively for orthopedic procedures, whereas clopidogrel should be stopped seven days prior to surgery(46)**. **In** patients with **prior** cardiovascular events or revascularization procedures**, and patients taking glycoprotein IIb/IIIa inhibitors, discussion with** an anesthesiologist and/or a cardiologist or other specialist **is** indicated(47).

The perioperative management of warfarin depend**s** on the indication for the therapy. Although bridging with **low molecular weight heparin (LMWH)** is no longer recommended for most patients with atrial fibrillation(48), there are indications where bridging may be appropriate including mechanical prosthetic mitral valves, older generation mechanical aortic valves, arterial or venous thromboembolism **within past three months(49), in which case referral** to a hematologist is **indicated**(50). **P**atients using direct oral anticoagulants (DOACs) for atrial fibrillation can be safely managed with no bridging **therapy**(51). **If renal and hepatic function are normal, DOACs should be stopped 48 hours prior to surgery**(46, 51).

Non-steroidal anti-inflammatory drugs (NSAIDs) act on the cyclooxygenase (COX)-1 and COX-2 enzymes. While the COX-2 inhibition is responsible for the anti-inflammatory effect which is desirable for analgesia, the COX-1 inhibition blocks thromboxane A2 production causing platelet dysfunction(52). The only COX-2 selective NSAID that remains on market is Celecoxib. COX-2 selective NSAIDs have **not been shown to increase perioperative bleeding(53), but** should be administered at the lowest effective dose and for the shortest course necessary due to a potential association with cardiovascular events(54). **Continuation of ASA and NSAIDs is not a contraindication to neuroaxial anesthesia(50).**

Recommendation*:

1) **Consider continuation of ASA monotherapy per-operatively**
2) **Stop clopidogrel seven days prior to surgery**
3) **Stop warfarin five days prior to surgery**
4) **Stop DOACs two days prior to surgery if normal renal function**

*** (in the absence of recent cardiovascular or thrombotic event or prior revascularization procedure. Otherwise the case should be discussed with an anesthesiologist and/or cardiologist)**

Intra-operative optimization (Table 3)

Anesthesia

Choice of anesthetic technique

A 2019 consensus recommendation from the International Consensus on Anaesthesia-Related Outcomes after Surgery group (ICAROS) recommends spinal anesthetics for primary hip and knee arthroplasties(55); spinal **anesthesia was considered to be** associated with less

blood loss than general **anesthesia**. This is **contrary** to a 2018 meta-analysis that included **few high-quality studies**(56). **I**ndividual patient factors such as specific comorbidities **and** patient preference may determine type of anesthetic**, and both general anesthesia and neuraxial techniques have roles within multimodal anesthesia regimes**(57). Ventilation strategies may **influence** bleeding due to increased venous pressures created by positive pressure ventilation and positive end expiratory pressure**. However, there is insufficient evidence to support specific ventilation strategies(58).**

Recommendation:

1) **General and neuraxial anesthesia both have roles within multimodal anesthesia regimes**

Hypotensive anesthesia

A 2007 meta-analysis showed that hypotensive anesthesia results in a significant reduction in blood loss**, although the included studies were** small and of variable quality(59). Controlled hypotension may be best achieved with epidural anesthesia(60). There is no clear evidence that controlled hypotension with neuraxial anesthesia is associated with post-operative cerebrovascular accidents, delirium, renal dysfunction, or cardiac complications(61). However**,** concerns remain that hypotension is associated with poor post-operative outcomes(62-65). There is ongoing research into intraoperative optimal blood pressure targets to prevent cardiac injury(66).

Recommendation:

1) **Hypotensive anesthesia should only be used in carefully selected patients whilst ensuring adequate organ perfusion.**

Temperature management

Both general and neuraxial anesthesia may lead to hypothermia due to vasodilation and impaired thermoregulation. This can be compounded by the room temperature, degree of patient exposure, the **surgical** wound, and use of room temperature fluids. **Hypothermia adversely affects platelet function and enzymes within the coagulation cascade, increasing** blood loss by 16%(4%-26%) and the relative risk of transfusion by approximately 22%(3%-37%)(67, 68). **Hypothermia is also associated with surgical site infection(69) and cardiovascular events(70).**

Interventions to reduce the incidence of hypothermia include pre**- and intra-operative** warming, use of reflective blankets, and warm intravenous fluids. Pre-operative and intra-operative warming can be achieved by both forced air and air-free warming ~~**(resistive polymer or fluid filled)**~~ devices(71). Reflective blankets may be as effective as forced air warmers(72). Although warm intraoperative fluids can be used, the impact depends on fluid volume administered(73). The impact of operating room temperature is less clear(74).

Recommendation:

1) **Adopt interventions to prevent hypothermia**

Transfusion thresholds

Guidelines from the American Association of Blood Banks (AABB) suggest that a restrictive RBC transfusion threshold of 8g/dL is recommended for patients undergoing **orthopedic** surgery(75). A threshold of **7g/dL** is recommended in the UK**(76)**. This is supported by a more recent systematic review and meta-analysis which determined that there is "moderate-strength evidence that restrictive transfusion practices reduce utilization of transfusions and may decrease infections without increasing adverse outcomes in major **orthopedic** surgery"(77-79). The threshold of **8g/dL** applies to patients with a history of

cardiovascular disease, but there is insufficient evidence for those experiencing acute cardiac ischemia(75, 76). Given there may be a dose-response relationship between the number of blood units transfused and adverse outcomes, each unit transfused must be clinically justified following recommended transfusion thresholds(16, 75, 76).

Recommendation:

1) **Adopt restrictive transfusion thresholds of 7-8g/dL**

Surgery

Surgical Technique

An increasing number of **orthopedic** procedures are performed arthroscopically or with robot assistance. Blood loss has been shown to be lower for arthroscopic procedures, compared to open procedures(80). Computer-navigation **and robot-assistance** for arthroplasty procedures may reduce blood loss as they avoid the need to instrument the intramedullary canal, although evidence is limited (81). It should not be assumed that minimally invasive approaches reduce blood loss as the operative times may be increased(82).

Recommendation:

1) **Surgical technique should be based on multiple outcome measures that may include blood loss**

Diathermy

Intraoperative **hemostasis** is aided by monopolar or bipolar radiofrequency electrocautery. Newer developments such as bipolar sealer systems and plasma scalpels have not demonstrated benefit over conventional monopolar electrocautery and they incur significant additional cost(83, 84). It is challenging to compare electrosurgery devices as performance is heavily influenced by surgical technique.

Recommendation:

1) **There is insufficient evidence to support the use of bipolar sealer systems and plasma scalpels over standard electrocautery**

Tourniquet

Tourniquets are frequently used during limb surgery with the aim of reducing blood loss and producing a bloodless surgical field. Meta-analyses suggest that tourniquets reduce intraoperative blood loss but may increase total blood loss due to production of inflammatory mediators secondary to tissue ischemia(85, 86). Tourniquets also increase postoperative pain, slow functional recovery, and increase the risk of complications including venous thrombotic events(87). **However, a recent randomised controlled trial found tourniquets reduced blood loss and did not adversely affect postoperative outcomes following knee arthroplasty(88).**

Recommendation:

1) **Tourniquet use should be at the discretion of the surgeon**

Antifibrinolytics

Antifibrinolytics include tranexamic acid and epsilon-aminocaproic acid, which are synthetic lysine analogues. They competitively inhibit plasminogen activation to provide anti-fibrinolytic action and clot stabilisation. Tranexamic acid may decrease allogeneic transfusion rates by 69% for primary arthroplasties(89-91). There **is no evidence for an** increased risk of thromboembolic events in patients undergoing **orthopedic** procedures(92), but there is uncertainty whether this risk has been adequately explored in high risk **patients**(93). There is

no clinically relevant difference in the efficacy of tranexamic acid or epsilon-aminocaproic acid(4, 94).

The optimal timing, dose, and route of antifibrinolytic administration remains unknown(95). Antifibrinolytics can be administered intravenously, topically, orally, or in combination. All methods of administration are superior to placebo at reducing blood loss and the need for allogeneic blood transfusion(93) and there is no benefit from multiple doses(90, 91). Topical tranexamic overcomes systemic contraindications such as renal insufficiency(96), but there are concerns over possible chondrotoxicity(97). A consideration with oral administrations is that it should be given two hours prior to surgery(93).

Most studies of antifibrinolytics focus on arthroplasty given these procedures account for 77% of all allogeneic blood transfusions in **orthopedic** surgery(98). There is evidence to support the value of anti-fibrinolytics in shoulder arthroplasty(99), spinal surgery in both adults(100) and children(101), and all procedures where blood loss is anticipated to exceed 500ml(76).

Recommendation:

1) **Administer antifibrinolytics when anticipated blood loss exceeds 500ml**

Cell salvage

Cell salvage describes the recovery of blood from the surgical field during the intraoperative or postoperative period.

Salvaged blood is collected and anticoagulated. It is then filtered and reinfused directly without washing, or alternatively the salvaged red blood cells are washed and resuspended in saline prior to reinfusion. Blood salvaged intraoperatively is usually washed, whereas blood salvaged postoperatively from reinfusion drains is usually unwashed.

Cell salvage can reduce exposure to allogeneic blood by 54% with a reduction in the number of allogeneic blood units transfused of 0.81 units per patient after **orthopedic** procedures(102), however, there is significant heterogeneity between studies(102, 103). Approximately 500ml of **intraoperative** blood loss is required to produce a clinically valuable volume of blood for reinfusion(104). When it is not possible to anticipate whether there will be sufficient blood loss to warrant salvage, equipment can be used in a collect-only mode and only processed for reinfusion once more than 500ml is collected(104). Cell salvage is therefore of greatest value for revision hip surgery, bilateral hip and knee arthroplasty, and major spinal procedures(105). Further research is required to establish its cost-effectiveness (104).

Bacterial infection and malignancy were previously considered absolute contraindications to cell salvage, but this is no longer the case with the use of a leucocyte depletion filter(106). A leucocyte **reduction** filter leads to a 99% reduction in bacterial contamination(107). The potential risk of bacterial contamination must be considered against the known association between adverse events and allogeneic blood transfusion(16).

Recommendation:

1) **Consider using cell salvage when anticipated intraoperative blood loss exceeds 500ml**

Drains

Conventional suction drains are often used to reduce hemarthrosis and haematoma incidence, but can increase perioperative blood loss(108). There is no established relationship between surgical site infection and the use of postoperative drains(108-110), but they may interfere with postoperative mobility.

Autologous reinfusion drains (cell salvage) reduce allogeneic blood requirements compared with conventional suction drains and warrant consideration when drain insertion is

indicated(111). Drains have not been shown to improve patient outcomes and may not be cost-effective when used in combination with other blood conservation strategies and restrictive transfusion triggers(112).

Recommendation:

1) **Routine use of conventional suction drains is not recommended**

Topical agents

The value of topical agents including fibrin sealants (fibrinogen and thrombin), gelatine–thrombin matrices and oxidized cellulose for facilitating **hemostasis** has been investigated in a wide range of surgical procedures(113, 114). Meta-analyses provide contradictory evidence and it is unclear whether topical agents reduce blood loss or improve clinical outcomes(115-117). Fibrin sealants are less effective than tranexamic acid in reducing blood loss(118) nor is there an additive effect(119).

Recommendation:

1) **Routine use of topical hemostatic agents is not recommended**

Desmopressin and Procoagulants

Desmopressin is a synthetic analogue of the antidiuretic hormone vasopressin, it leads to a transient increase in plasma levels of factor VIII and von Willebrand factor (120).. Desmopressin may reduce total blood loss but not allogeneic blood transfusions; potentially at the expense of clinically important hypotension(120). Concerns also persist over an increased risk of arterial or venous thrombosis and evidence to support the use of desmopressin is very limited except in cases of platelet dysfunction(121).

Fibrinogen depletion occurs before deficiencies in coagulation factors during **hemorrhage** and is the primary reason for dilutional coagulopathy during **orthopedic**

surgery(122). Fibrinogen is available as concentrate or within cryoprecipitate and administration may reduce perioperative blood loss(123). Evidence to support the use of fibrinogen and other procoagulants remains very limited, but there are a number of ongoing trials in this field(124).

Recommendation:

1) **There is currently insufficient evidence to recommend routine use of desmopressin or procoagulants.**

Post-operative Optimization

Recommencing anti-platelet and anticoagulation agents:

Consensus statements provide guidance for recommencing preoperative medication as there is limited evidence to support practice(46, 125). Anti-platelet agents ~~that were~~ stopped prior to surgery can be recommenced once hemostasis is~~has been~~ achieved and usually within 24 hours of surgery. Warfarin can also be restarted at the preoperative dosing regimen within 24 hours of surgery (46). ~~Suggested regimens for restarting other anticoagulants including t~~It is safe to restart t~~T~~herapeutic bridging LMWH and DOACs ~~typically reach full dose~~ 48-72 hours after surgery(51, 126).

Recommendation:

1) **Recommence antiplatelet and anticoagulant medication within 48-72 hours of surgery**

Thromboprophylactic pharmacological agents

Mechanical and pharmacological measures are recommended to prevent postoperative venous thromboembolism after lower limb procedures associated with

reduced mobility or anesthesia time exceeding 90 minutes(127, 128). Pharmaceutical agents **used for thromboprophylaxis** include **ASA**, low-molecular weight heparin (LMWH), direct oral anticoagulants (DOAC), or a combination of agents. The selected thromboprophylaxis regimen influences blood loss and must therefore take **specific** patient and surgical **risk** factors **for bleeding and thrombosis into account**(127). After elective hip arthroplasty, LMWH administration within four hours of surgery increases the risk of major bleeding to 6.3% compared with 2.5% when administered 12-48 hours postoperatively, but decreases the incidence of venous thromboembolic events(129). **ASA (commenced five days after procedure) was found to be non-inferior to rivaroxaban for preventing symptomatic venous thromboembolism after hip and knee arthroplasty, with no difference in clinically important bleeding between groups(130). Whether ASA is non-inferior to LMWH is currently under investigation(131).** The American Society of Hematology**(ASH)** Guidelines **recommend ASA or DOACs over LMWH for thromboprophylaxis after orthopedic surgery(128), whereas NICE Guidelines recommend LMWH as an alternative to ASA and DOACs, which should be commenced within 6-12 hours or surgery, or once hemostasis is achieved(127).**

Recommendation:

1) **Use mechanical and chemical thromboprophylaxis after lower limb arthroplasty**
2) **ASA, DOAC, and LMWH are all acceptable chemical agents as per local guidelines**
3) **Commence thromboprophylaxis 6-12 hours after surgery if there is hemostasis**

*When/Where should post-operative **hemoglobin** be part of routine assessments?*

Consensus guidelines recommend that all patients undergoing major surgery with blood loss exceeding 500mls should be considered for postoperative anemia screening, especially for patients with preoperative anemia(132). **Institutional data for specific procedures and surgical techniques, taking into account preoperative anemia, risk factors for bleeding, and operative findings may allow more selective postoperative Hb measurement. M**easurements during the **immediate** perioperative period may be confounded by plasma volumes derangements, most frequently resulting in an overdiagnosis of anemia secondary to **hemodilution**(133).

Recommendation:

1) **Measure Hb the day following surgery when intraoperative blood loss exceeds 500ml or patients are anemic pre-operatively**

*When does **hemoglobin** return to pre-operative values following **orthopedic** surgery?*

Over 90% of patients are anemic when discharged following arthroplasty surgery(134, 135). **Postoperative anemia may increase the risk of adverse events, including myocardial infarction(15), acute kidney injury(136), and functional recovery(14).** The prevalence and severity of postoperative anemia will increase with more widespread adoption of restrictive transfusion triggers(137). After unilateral primary hip arthroplasty, two thirds of patients have restored their preoperative **Hb** within 28 days of surgery(138). The rate of recovery from postoperative anemia depends on the volume of blood loss and patient erythropoiesis, which is blunted by postoperative inflammation and nutritional deficiencies such as iron, vitamin B12, and folic acid(132).**Further research is required to guide the management of postoperative anemia.**

Overview

Strategies to reduce blood loss and exposure to allogeneic blood transfusions **can** improve patient outcomes, lower risk of perioperative complications, and reduce healthcare costs. Interventions should be considered preoperatively, intraoperatively, and postoperatively(Table 4). The development of a patient-specific blood management plan often requires input from multiple specialties and delivery by a multidisciplinary team.

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Figure Legends:

Figure 1: The three-pillar, nine-field matrix of perioperative patient blood management for orthopedic patients.