

Blood Management in Total Knee Arthroplasty: State-of-the-Art Review

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Key Words:

Knee
Arthroplasty
Total Joint Replacement
Blood Management
Blood Transfusion

Word Count: 4699

41 ABSTRACT:

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43 Total blood loss from primary total knee arthroplasty (TKA) may exceed two litres with greater blood loss
44 during revision procedures. Blood loss and allogeneic transfusion are strongly associated with adverse
45 outcomes from surgery including postoperative mortality, thromboembolic events, and infection. Strategies
46 to reduce blood loss and transfusion rates improve patient outcomes and reduce healthcare costs.
47 Interventions are employed preoperatively, intraoperatively, and postoperatively. The strongest predictor
48 for allogeneic blood transfusion is preoperative anaemia. Over 35% of patients are anaemic when scheduled
49 for primary and revision knee arthroplasty, defined as haemoglobin <130g/L for males and females, and the
50 majority of cases are secondary to iron deficiency. Early identification and treatment of anaemia can reduce
51 postoperative transfusions and complications. Anti-coagulation must be carefully managed perioperatively
52 to balance the risk of thromboembolic event versus the risk of haemorrhage. Intraoperatively, tranexamic
53 acid reduces blood loss and is recommended for all knee arthroplasty surgery; however, the optimal route,
54 dose, or timing of administration remains uncertain. Cell salvage is a valuable adjunct to surgery with
55 significant expected blood loss, such as revision knee arthroplasty. Autologous blood donation is not
56 recommended in routine care, sealants may be beneficial in select cases but further evidence of benefit is
57 required, and the use of a tourniquet remains at the discretion of the surgeon. Postoperatively, restrictive
58 transfusion protocols should be followed with a transfusion threshold haemoglobin of 70g/L, except in the
59 presence of acute coronary syndrome. Recent studies report no allogeneic transfusions after primary knee
60 arthroplasty surgery after employing blood conservation strategies. The current challenge is to select and
61 integrate different blood conserving interventions to deliver an optimal patient pathway with a multi-
62 disciplinary approach.

63 INTRODUCTION:

64

65 The number of primary and revision knee arthroplasty procedures continues to increase,¹ and blood
66 management strategies form a key intervention to improve outcomes and reduce costs.² The primary goal is
67 to reduce the severity of postoperative anaemia through preoperative optimisation and minimising
68 intraoperative and postoperative blood loss through patient-specific approaches. Strategies to reduce blood
69 loss may have secondary benefits to improve postoperative pain and functional outcomes.³

70

71 Total knee arthroplasty (TKA) represents major surgery that is performed on an aging population. Over 35%
72 of patients undergoing lower limb arthroplasty are anaemic preoperatively^{4,5} and over 85% are anaemic
73 after knee arthroplasty surgery, defined by the World Health Organisation (WHO) as a haemoglobin (Hb)
74 concentration below 120g/L for females and 130g/L for males.^{6,7} The strongest risk factor for transfusion is
75 preoperative anaemia and preoperative patient optimisation is essential.^{8,9}

76

77 Studies report a large variation in blood loss during knee arthroplasty surgery, in part due to heterogeneous
78 patient cohorts, surgical and anaesthetic techniques, and methods of calculating the volume of blood loss.⁶ A
79 study of 4769 patients who underwent primary TKA had a calculated mean total blood loss of 2181ml
80 (standard deviation [SD] 931) with a mean postoperative drop in Hb concentration of 3.0g/L (SD 1.2) and
81 14.6% of patients received a allogeneic blood transfusion.⁵ Blood loss is higher for revision procedures, albeit
82 difficult to quantify due to the heterogeneity of these procedures.

83

84 This review article discusses preoperative, intraoperative, and postoperative measures than can be utilised
85 to deliver optimal blood management and improved patient outcomes after knee arthroplasty.

86

87 TEXT BOX:

88

89 MEASURING BLOOD LOSS:

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91 Research in this field is frequently limited by different measures of blood loss, making it difficult to interpret and compare studies. A
92 key distinction is between visible and hidden blood loss.¹⁰ Visible blood loss is that from the operative field and in drains, whereas
93 hidden loss includes blood lost through extravasation into tissues and residual haemarthrosis. Hidden blood loss may account for
94 49% of calculated total blood loss.¹⁰ Total blood loss is the sum of visible and hidden losses and is calculated using a number of
95 available formulas.¹¹ Many formulas require calculation of the total blood volume, typically estimated using Moore's or Nadler's
96 formula.

97

98 BLOOD LOSS OUTCOME MEASURES:

99

100 Change in Hb Concentration
101 Estimated Intraoperative Loss
102 Drain Output
103 Transfusion Rate
104 Number of Units Transfused
105 Calculated Total Blood Loss

106

107 CALCULATED TOTAL BLOOD LOSS:

108

109 Many different formulas have been proposed for calculating total blood loss and those described by Gross and Mercuriali are used
110 most frequently.¹¹ Formulas to calculate total blood loss require an estimate of circulating blood volume using either the Moore or
111 Nadler formulas.¹¹

112

113 GROSS FORMULA:

114

115 Estimated Total Blood Loss (ml) = Estimated Blood Volume x (Hct₀ – Hct₁)/Hct_{Av}

116

117 Hct₀ preoperative haematocrit
118 Hct₁ postoperative haematocrit
119 Hct_{Av} average of preoperative and postoperative haematocrit

120

121 MERCURIALI FORMULA:

122

123 Estimated Total Blood Loss (mls of RBC) = Estimated Blood Volume x (Hct₀ – Hct₅) + ml transfused RBC

124

125 Hct₀ preoperative haematocrit
126 Hct₅ haematocrit postoperative day five

127

128 PREOPERATIVE:

129

130 Preoperative Anaemia:

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132 The strongest risk factor for allogeneic blood transfusion after primary and revision TKA is preoperative
133 anaemia.^{4,6} The WHO defines anaemia as a Hb concentration below 120g/L in females and 130g/L in males.
134 However, a recent consensus statement outlines key limitations of sex specific thresholds when optimising
135 patients for surgery. The same surgical procedure will result in comparable blood loss for both sexes, and
136 therefore a higher blood loss in females relative to their circulating volume may result in higher transfusion
137 rates.^{6,9} The recommended target preoperative Hb is therefore 130g/L for both sexes.⁹

138

139 Preoperative anaemia is prevalent amongst orthopaedic patients but varies between patient population and
140 depends on the Hb threshold used to define anaemia. Adopting a threshold of 130g/L, Jans et al report an
141 anaemia prevalence of 31% of patients undergoing primary TKA in Denmark,¹² and the same prevalence has
142 been reported in Spain.¹³ Anaemia is more prevalent in patients undergoing revision surgery in association
143 with increasing age and co-morbidities. Adopting the WHO thresholds for anaemia, the prevalence of
144 anaemia has been reported as 13%¹⁴ and 19%¹⁵ for primary TKA compared with 42%⁴ for revision TKA.

145

146 *Iron-Deficiency Anaemia:*

147

148 The most frequent aetiology of preoperative anaemia is iron deficiency,⁹ which can be classified as absolute
149 or functional. Absolute iron deficiency describes reduced or absent total body iron stores, whereas
150 functional iron deficiency usually describes a reduced ability to mobilise iron from these stores due to
151 chronic inflammation.⁹ A large number of protocols have been proposed to treat preoperative iron
152 deficiency, which typically consist of oral iron supplementation for absolute deficiency, and intravenous iron
153 for functional iron deficiency or where oral iron proves ineffective.⁹ Lower oral iron doses can increase
154 efficacy and reduce gastrointestinal side effects.¹⁶ Patients diagnosed with iron deficiency anaemia must also
155 be screened for gastrointestinal malignancy and other causes of chronic blood loss.

156

157 The diagnosis and treatment of iron deficiency anaemia increases Hb concentrations, reduces transfusion
158 rates and improves outcomes from surgery. Evidence is limited to cohort studies, but the introduction of a
159 preoperative anaemia algorithm reduces rates of hospital readmission and admission to critical care, length
160 of stay^{2,17} and possibly infection.¹⁸ Increased Hb concentrations also prevent transfusion related
161 complications.¹⁹ Health economic analysis reveals significant savings from preoperative anaemia screening

162 and management.² The benefits of treating anaemia may not purely reflect increased Hb concentrations, as
163 iron plays a role in erythropoiesis, and is important in cellular processes such as oxygen transport and
164 cellular immunity.²⁰

165

166 *Other Causes of Anaemia:*

167

168 When anaemia is not secondary to iron deficiency, alternative causes must be sought and addressed.
169 Vitamin B12 and folate deficiency account for 15% of preoperative anaemia,²¹ while anaemia may also result
170 from renal, haematological, and endocrine disorders. Anaemia management may therefore require input
171 from multiple medical specialties to address the underlying cause. Besides iron supplementation, additional
172 strategies to increase Hb concentration include administration of recombinant human erythropoietin to
173 stimulate haematopoiesis. Erythropoietin increases preoperative and postoperative Hb in TKA patients,²² but
174 it is expensive and may not be approved for patient use. Erythropoietin is only recommended in specific
175 circumstances, including anaemia secondary to chronic renal failure or when blood products are not
176 available or acceptable to patients.²³

177

178 *Preoperative Autologous Blood Donation:*

179

180 Preoperative autologous blood donation, where blood is donated and stored preoperatively and then
181 administered if required postoperatively, was used widely prior to elective surgery, particularly in the United
182 States. However, disadvantages include the potential exacerbation of preoperative anaemia and risks
183 associated with interval reinfusion. There is also significant cost and wastage, since less than half of the
184 preoperative blood collected is utilised.²⁴ The technique is now rarely used, but may be indicated in select
185 cases, such as patients with multiple red cell antibodies where compatible donor blood may not be available.

186

187 *Optimising Patients for Surgery:*

188

189 Preoperative optimisation of anaemia requires early identification and treatment. A full (complete) blood
190 count should be requested at the time patients are scheduled for knee arthroplasty, with renal function and
191 group and save (type and screen) if the patient is anaemic.²⁵ Iron studies and markers of inflammation, such
192 as C-reactive protein (CRP), should also be included if Hb measurements are below 130g/L in both males and
193 females. If iron studies are normal, preoperative anaemia requires further investigation, and interventions to
194 optimise anaemia should commence at diagnosis. Significant increases in Hb can be obtained within four
195 weeks, and there is no required minimum time between commencing iron or other therapy and surgery.¹⁸

196

197 An additional scenario to consider is when patients have adequate iron stores to support erythropoiesis and
198 are therefore not anaemic preoperatively but have low iron stores that restrict the ability to restore Hb
199 concentration after surgical blood losses. Patients with low iron stores may therefore benefit from iron
200 supplementation prior to surgery in the absence of anaemia, and iron studies may be appropriate for all
201 preoperative patients.⁹

202

203 There is no agreed Hb threshold to proceed with surgery and decisions must take into account the clinical
204 urgency of a procedure, particularly in the case of peri-prosthetic fractures or infection. The lower the
205 preoperative Hb, the higher the risk of perioperative transfusion.⁸ The goal is to correct reversible causes of
206 anaemia prior to elective surgery, acknowledging that it may not be possible to achieve a preoperative Hb
207 greater than 130g/L in all patients. Correcting anaemia with preoperative transfusion is not recommended
208 and can be detrimental to outcomes.⁹

209

210

211 TEXT BOX:

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213 CLASSIFICATION OF PREOPERATIVE ANAEMIA:⁸

214

215 Ferritin < 30mcg/L

Absolute Iron Deficiency

216 Ferritin > 30mcg/L and CRP > 5mg/L

Iron Deficiency in Presence of Inflammation

217 Ferritin > 30mcg/L and CRP ≤ 5mg/L and Transferrin Saturation ≥20% Restricted Iron Stores for Expected Significant Blood Loss

218 Ferritin > 30mcg/L and CRP ≤ 5mg/L and Transferrin Saturation <20% Probable Iron Deficiency

219 Ferritin > 100mcg/L and CRP ≤ 5mg/L Non-Iron Deficiency Anaemia

220

221 Management algorithm for preoperative anaemia should be agreed locally with engagement of multidisciplinary team

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229 Preoperative Management of Anti-Platelet Agents and Anti-Coagulants:

230

231 A significant proportion of patients who undergo knee arthroplasty may take anti-platelet agents to modify
232 cardiovascular and cerebrovascular risk, and anticoagulant agents to modify thromboembolic risk where
233 indications include atrial fibrillation, previous thromboembolic events, and prosthetic heart valves.
234 Perioperative management of these agents is patient specific and must balance the risk of haemorrhage with
235 the risk of thromboembolic events. Management decisions may require input from the patient, surgeon,
236 physician, and anaesthetist.

237

238 *Anti-Platelet Agents:*

239

240 Anti-platelet agents inhibit platelet aggregation and thrombus formation. Most agents irreversibly bind
241 platelet receptors, which means their action lasts the lifetime of a platelet, typically up to ten days. It
242 therefore takes approximately seven days after drug cessation before platelet function is restored.

243

244 Aspirin withdrawal precedes up to 10% of acute cardiovascular events,²⁶ and stopping aspirin seven days
245 prior to surgery in patients with high cardiovascular risk significantly increases the 30 day risk of major
246 cardiovascular event from 1.8% to 9%.²⁷ Individual studies have not identified differences in the rate of
247 thromboembolic or bleeding events when comparing preoperative aspirin cessation or continuation.²⁸
248 However, a meta-analysis concluded that continuing aspirin results in a 1.5 times increase in the risk of
249 bleeding complications, but does not increase the number of bleeding complications that require medical
250 intervention.²⁶ Consensus guidelines recommend continuing aspirin monotherapy for knee arthroplasty
251 surgery,^{29,30} and this strategy still allows for the use of neuroaxial anaesthesia.³¹ There is currently
252 insufficient evidence to guide management of adenosine diphosphate (ADP) receptor antagonist
253 monotherapy, such as clopidogrel.²⁹

254

255 An increasing number of patients are prescribed dual antiplatelet therapy after a cardiac event or coronary
256 revascularisation. Dual antiplatelet therapy consists of aspirin and an ADP receptor antagonist. Current
257 guidance is to stop the ADP receptor antagonist seven days preoperatively and to continue aspirin
258 monotherapy.^{29,30}

259

260 *Warfarin:*

261

262 Warfarin inhibits the synthesis of vitamin K dependent procoagulation factors and has a half-life of
263 approximately 36 hours. In the acute setting, warfarin can be reversed with intravenous phytonadione or
264 prothrombin complex, and in the elective setting, warfarin must be stopped five days before surgery to
265 normalise laboratory tests of coagulation.²⁹ Treatment options include stopping warfarin five days prior to
266 surgery with or without treatment dose bridging heparin, or potentially continuing warfarin throughout
267 surgery.

268

269 Evidence to support bridging therapy with heparin is limited and studies reveal a similar risk of
270 thromboembolic events but an increased risk of bleeding when using bridging heparin compared with no
271 anticoagulation.³² Bridging anticoagulation is no longer indicated in most patients receiving warfarin for
272 atrial fibrillation.³³ However, it may be appropriate in patients at particularly high risk of thromboembolic
273 events such as those who experienced a venous thromboembolic event or stroke within the past three
274 months, or patients with a mechanical heart valve.²⁹ It is best practice to measure the international
275 normalized ratio (INR) on the day preceding surgery to ensure there is no residual anticoagulation.²⁹

276

277 Small studies report no difference in complication or transfusion rates between individuals continuing
278 therapeutic warfarin dose throughout surgery compared with individuals that stop warfarin and commence
279 bridging low-molecular weight heparin for primary and revision knee arthroplasty.^{34,35} Further evidence is
280 required before recommending this practice, which prevents the use of neuroaxial anaesthesia.

281

282 Complications after TKA are more frequent in patients taking warfarin preoperatively compared with
283 patients not taking anticoagulants, including prolonged wound discharge, superficial and deep infection, and
284 further surgery.³⁶ However, this may reflect comorbidity rather than the anticoagulation itself.

285

286 *Direct Oral Anti-Coagulants (DOACs)*

287

288 Direct oral anticoagulants either inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban,
289 edoxaban). They have several advantages over warfarin, including more predictable pharmacokinetics
290 resulting in no requirement to monitor laboratory tests of coagulation. When it is desirable to monitor
291 laboratory tests, patients require an assay of thrombin time for dabigatran and factor Xa for rivaroxaban,
292 apixaban, and edoxaban. Normal prothrombin time and activated partial thromboplastin times do not
293 exclude residual action of DOACs. A disadvantage of DOACs over warfarin is the lack of reversal agents,
294 however, these are under development. Idarucizumab is now available as a reversal agent for dabigatran,
295 although this is usually only used in emergency settings.

296

297 The shorter half-life of DOACs compared with warfarin means they can be stopped closer to the date of
298 surgery, leaving patients non-anticoagulated for a shorter period of time. In the presence of normal renal
299 and hepatic function, guidelines recommend stopping DOACs 48 hours prior to surgery.^{29,30} Stopping
300 dabigatran 48 hours prior to surgery does not result in any significant difference in perioperative bleeding
301 events compared with stopping warfarin five days previously.³⁷ As with warfarin, the role of bridging
302 anticoagulation is debated and a study has shown higher rates of major bleeding and no difference in the
303 rate of thromboembolic events when comparing no anticoagulation with bridging anticoagulation in patients
304 with atrial fibrillation.³⁸

305

306

307 INTRAOPERATIVE:

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309 Surgical Technique:

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311 Surgical technique varies significantly between surgeons and may influence blood loss. An alternative to the
312 traditional medial parapatellar surgical approach for TKA is the midvastus or subvastus approach, which can
313 be used as part of a minimally invasive procedure. These techniques may improve early pain and range of
314 movement, but do not reduce blood loss.^{39,40} A computer-navigated midvastus approach may even increase
315 blood loss compared with a computer-navigated medial parapatellar approach, potentially secondary to
316 increased operating times.⁴¹ Retrospective cohort studies demonstrate that increased operative time is
317 associated with increased rates of allogeneic transfusion, however, confounding factors including the
318 indication for surgery may contribute to this observation. Computer-navigation may reduce total blood loss
319 during surgery by negating the need for entering the intramedullary canal, however, gains may be offset by
320 increased operating times.⁴² The same advantage may therefore prove valid for patient-specific knee
321 prostheses. Retrospective studies demonstrate that unicompartmental knee arthroplasty results in less
322 blood loss than total knee arthroplasty,⁴³ and that there is less blood loss with a cruciate retaining implant
323 than a posterior stabilised implant.⁴⁴ Implant selection may therefore affect expected blood loss from
324 arthroplasty procedures.

325

326 Anaesthesia:

327

328 Anaesthetic factors to reduce intraoperative blood loss include maintaining patient normothermia and
329 reducing blood pressure. Spinal anaesthesia produces a blockage of preganglionic sympathetic nerves that
330 reduces peripheral vascular resistance and blood pressure. During total hip arthroplasty, regional
331 anaesthesia results in lower blood loss than general anaesthesia, however, this finding is not reliably
332 reproduced for knee surgery, perhaps due to the use of tourniquets.^{5,45} The choice of anaesthetic modality
333 should be driven by other factors such as lumbar spine pathology and recent anticoagulation.

334

335 Normovolemic haemodilution is a technique where blood is collected in the immediate preoperative period
336 with fluid replacement to reduce the haematocrit of blood lost during surgery. Surgery is followed by
337 autologous reinfusion of the preoperative collected blood, however, the benefits remain uncertain. ²²

338

339 Tourniquet:

340

Tourniquet application is used by most surgeons during knee arthroplasty procedures with the goal of reducing blood loss and creating a bloodless field to improve visualisation of tissues. Proposed potential benefits also include improving cement integration with bone, which has not been supported by recent imaging studies.⁴⁶ Patients also experience increased pain with compromised quadriceps function^{47,48} and a higher incidence of thrombotic events⁴⁹ with the use of a tourniquet.

Studies report conflicting outcomes with respect to the effect of tourniquet use on blood loss. Meta-analyses suggest that while a tourniquet decreases intraoperative blood loss, there is no difference in total blood loss.^{49,50} Tourniquet use may even increase total blood loss through the release of inflammatory mediators secondary to limb ischaemia.⁵¹ Surgeons may elect to have the tourniquet inflated for different portions of the procedure, and overall, the effects on blood loss do not appear to be clinically significant.⁵² The decision of whether to use a tourniquet may be guided by factors other than blood management.

Tranexamic Acid:

Tranexamic acid is a synthetic lysine analogue that competitively inhibits plasminogen activation to provide anti-fibrinolytic action and clot stabilisation. It is recommended for all TKA surgery in the United Kingdom,²³ but it is not approved by the Food and Drug Administration (FDA) for this purpose. Tranexamic acid has been shown to reduce the need for transfusion by 69%⁵³ without increased risk of thromboembolic complications.⁵⁴ A vast number of studies investigate the efficacy of tranexamic acid, and while they invariably demonstrate that tranexamic acid reduces blood loss and the need for transfusion, the optimal route, dose, and timing of administration remains undetermined. A further uncertainty is whether the risk of thromboembolic events has been adequately addressed in high risk subgroups.

Tranexamic acid administration can be intravenous, intra-articular or oral, or in combination. Combined intra-articular and intravenous delivery has been shown to result in a greater reduction in blood loss than intravenous delivery alone for primary TKA,⁵⁵ or intra-articular delivery alone for revision TKA.⁵⁶ Intra-articular delivery alone may be as efficacious as intra-venous⁵⁷ or combined intra-articular and intravenous delivery⁵⁸ for primary TKA, however, the use of different tranexamic doses between studies limits the interpretation. No differences in rate of thromboembolic complications have been observed with different routes of administration.^{55,58} There is emerging evidence that tranexamic acid reduces postoperative swelling, and improves range of movement and patient-reported outcomes after TKA.^{48,59}

374 Current evidence supports the use of topical tranexamic acid with or without intravenous delivery. Oral
375 tranexamic acid also reduces blood loss after primary TKA and requires further exploration due to lower
376 costs.⁶⁰ Potential advantages of intra-articular delivery are that it may overcome systemic contraindications
377 such as renal insufficiency due to lower plasma levels.⁶¹ Concerns over tranexamic acid chondrotoxicity may
378 prevent topical use in unicompartmental knee arthroplasty, but studies investigating the effect on
379 chondrocytes are limited to in-vitro experiments.⁶²

380

381 A limitation to comparing routes of delivery is that different doses and timing of delivery are used in each
382 study, and determining the optimal regimen is a research priority. Some studies suggest reduced blood loss
383 with higher doses of tranexamic acid (>25mg/kg) with combined routes of administration⁶³ or as a single
384 preoperative dose.⁶⁴ There are conflicting studies as to whether multiple doses of intravenous tranexamic
385 acid confer a greater reduction in blood loss or allogeneic transfusion rates.^{65,66} Continuous intravenous
386 infusions of tranexamic do not appear superior to a single bolus.⁶⁷ Standardisation of tranexamic acid
387 regimens would greatly aid future clinical practice in this field.

388

389 Haemostasis after TKA may be enhanced when topical tranexamic acid is supplemented with topical
390 adrenaline.⁶⁸ An alternative anti-fibrinolytic agent to tranexamic acid is ε-aminocaproic acid and has
391 demonstrated equivalent efficacy to tranexamic acid at lower cost.⁶⁹ In the USA, the approximate cost per
392 surgery for ε-aminocaproic acid is \$2, compared with \$40 for tranexamic acid.⁶⁹

393

394 Fibrin Sealant:

395

396 Topical application of fibrin sealants (fibrinogen and thrombin) to bleeding tissues is another haemostatic
397 strategy that can be used during TKA. Meta-analyses offer contradictory conclusions as to whether fibrin
398 sealant reduces total blood loss, however, there may be a reduction in drain output and transfusion rate
399 without an increased risk of complications.⁷⁰ Fibrin sealant is not as effective as tranexamic acid at reducing
400 blood loss⁷¹ and given the high additional cost, the role of fibrin sealant in a multimodal blood management
401 algorithm is uncertain.

402

403 Diathermy:

404

405 Monopolar radiofrequency electrocautery is a valuable tool to achieve intraoperative haemostasis. An
406 alternative is a bipolar sealer system that works at lower temperatures to denature collagen and seal blood
407 vessels, which is thought to cause less damage to adjacent healthy tissues.^{72,73} It is challenging to quantify

the effects of cautery due to variation in technique amongst surgeons. At present, there is insufficient evidence to recommend routine use of bipolar sealer systems to reduce blood loss, which carry a significant cost. Bipolar sealer systems do not appear to confer benefits in the presence or absence of tranexamic acid for primary TKA,⁷² or in the absence of a tourniquet during revision TKA.⁷³

Cell Salvage and Drains:

Cell salvage describes the recovery of blood from the surgical field, and it is recommended for major orthopaedic procedures where blood loss exceeds 20% of estimated blood volume.^{23,74} Cell salvage reduces the risk of exposure to allogeneic blood by 54%^{75,76} and can be performed intraoperatively by collecting blood through a suction system or postoperatively using an autologous reinfusion drain that is inserted at the time of surgery. Collected blood is anticoagulated and filtered (40 micron or leucocyte depletion filter) and can then be reinfused directly, or the red blood cells can be washed and resuspended in normal saline prior to reinfusion. Blood from intraoperative cell salvage is typically washed, whereas blood from reinfusion drains is typically unwashed, but either technique can be used in each setting. Concerns over unwashed blood include low Hb concentration, and the presence of anticoagulant and inflammatory mediators in the reinfused blood. Both washed and unwashed blood results in a hypocoagulable state, albeit less so with washed blood⁷⁷, but no difference in clinical outcomes has been identified.⁷⁵

Intraoperative cell salvage is less widely used than postoperative drain collection during knee arthroplasty surgery due to the frequent use of a tourniquet. In the absence of a tourniquet, cell salvage may be a valuable adjunct to blood conservation, particularly during revision surgery where there is greater blood loss.²³ Previous contraindications to cell salvage have included bacterial infection and malignancy; however, these guidelines are now debated.⁷⁸ When a leucocyte depletion filter is used and the collected blood is washed, there is a 99% reduction in bacterial contamination.⁷⁹ Thus, while there is a theoretical increased risk of adverse events with reinfusion of blood with bacterial contamination, there is a definite risk of bacterial contamination from allogeneic blood transfusion. No association has been identified between the use of cell salvage and development of metastases in cancer surgery.⁷⁸

Conventional suction drains were widely adopted with the aim of reducing haemarthrosis and may reduce the need for dressing reinforcement, but can increase postoperative blood loss.⁸⁰ Temporary clamping of conventional suction drains postoperatively only serves to reduce drain output and not total blood loss.⁸¹ Drains have not been shown to increase infection rates, despite concerns over leaving a tract into the joint,

441 but may interfere with mobilisation after surgery, and the optimal time of for drain removal has not been
442 established.

443

444 Autologous reinfusion drains can half the proportion of patients requiring allogeneic blood compared with
445 conventional suction drains.^{82,83} However, this is not true in more recent studies with restrictive transfusion
446 thresholds (Hb \leq 80g/L).⁸³ In addition, autologous reinfusion drains result in a smaller reduction in allogeneic
447 transfusion rates when compared with no conventional suction drain.⁸³ It therefore remains unclear whether
448 autologous reinfusion drains provide clinical benefit or cost-effectiveness when used alongside other blood
449 conservation strategies and restrictive transfusion triggers.⁸⁴

450

451

452 POSTOPERATIVE:

453

454 Cryotherapy:

455

456 A number of compression dressings and cryotherapy strategies have been adopted to reduce blood loss,
457 however, their role in routine clinical practice remains uncertain.⁸⁵ Most studies do not demonstrate a
458 reduction in blood loss using cryotherapy devices for knee arthroplasty.⁸⁶ Assessment of new devices should
459 take into account combined benefits in terms of blood loss, pain, and functional outcomes.

460

461 Transfusion:

462

463 There is a large variation in transfusion rates after TKA. A study of arthroplasty surgeons in the United States
464 revealed transfusion rates ranging from 3.8% to 63.8% for primary TKA,⁸⁷ rising to 84% for bilateral TKA.⁸⁸
465 Studies in the United Kingdom reported transfusion rates of 2.7% for primary TKA² and 29.1% for revision
466 TKA.⁴

467

468 Transfusions rates are dictated by a number of factors, including the adoption of blood conservation
469 strategies and different patient cohorts. Transfusion triggers also play a role. A number of studies compared
470 outcomes after restrictive transfusion regimens (transfusion threshold Hb 70g/L and post transfusion target
471 70-90g/L) and liberal transfusion regimens (transfusion threshold Hb 80g/L and post transfusion target 80-
472 100g/L) for non-cardiac surgery.⁸⁹ In the absence of cardiovascular disease, there is no difference between
473 liberal regimens and restrictive in terms of functional recovery, mortality or medical complications.⁸⁹ The
474 exception is patients with ischaemic heart disease, where the risk of acute coronary syndrome may be
475 increased with restrictive regimens.⁸⁹ Recent guidelines recommend lowering the threshold for transfusion
476 from 80g/L to 70g/L in all patients excepts those with acute coronary syndrome.^{23,74,90}

477

478 Restrictive transfusion regimens reduce the use of allogenic blood, and if all liberal regimens were replaced
479 by restrictive regimens, patient exposure to blood transfusion would decrease by 43%.⁹⁰ Adoption of a
480 restrictive transfusion regimen reduces overall infection rates after orthopaedic surgery.⁹¹ In the United
481 States, allogeneic blood transfusions after arthroplasty surgery increased over a 19 year period, although
482 this may be secondary to reduced rates of autologous blood transfusion.⁹² A recent study evaluating blood
483 conserving protocols in 376 patients undergoing primary TKA reported no autologous or allogeneic blood
484 transfusions.⁵⁸ Such low transfusion rates question whether a preoperative group and save (type and screen)

485 is required, particularly for unicompartmental knee arthroplasty where blood loss is lower than TKA.⁴³ Given
486 the variation in transfusion rates, such decisions should be made after local departmental audits.

487

488 Allogeneic blood transfusion carries a number of risks, including haemolytic and allergic reactions,
489 transfusion-related acute lung injury and circulatory overload, graft-versus-host disease, and transmission of
490 blood borne infection.¹⁹ Transfusion is an independent predictor of in-hospital mortality.⁹² There are
491 concerns that transfusion may increase the risk of venous thromboembolism,⁹³ and immunomodulation also
492 increases susceptibility to postoperative infection including of the lower respiratory tract, urinary tract, and
493 surgical site.⁷⁴ Increased infection rates are observed with allogeneic but not autologous blood¹⁹ and
494 leucocyte depletion decreases postoperative infection rates.⁹⁴ Leucodepletion of all blood products was
495 introduced in the United Kingdom in 1998 but is not utilised globally. Whether transfusion specifically
496 increases the risk of bone and joint infection after arthroplasty surgery remains uncertain.⁹⁵

497

498 Postoperative Management of Anti-Platelet Agents and Anti-Coagulants:

499

500 Patients that regularly take anti-platelet agents and anti-coagulant medication prior to surgery require these
501 postoperatively. In addition, it is recommended that physical and chemical measures are utilised to prevent
502 venous thromboembolic events during the postoperative period.⁹⁶ The drug, time of initiation and duration
503 of administration, and dose of thromboprophylactic agents may influence postoperative bleeding.

504

505 When recommencing anticoagulation, the long half-life of warfarin means it can be restarted within 24 hours
506 of surgery²⁹ with a mean time to reach therapeutic levels in eight days.²⁶ Dosing warfarin can prove
507 challenging after surgery due to the metabolic response to surgery, and an interesting development is
508 genotype-guided dosing after hip or knee arthroplasty to reduce the risk of bleeding, venous
509 thromboembolism, and death.⁹⁷ When bridging anticoagulation is indicated, the last dose of LMWH should
510 be given 24 hours prior to the procedure and restarted 48 hours after the procedure.³³ Anti-platelet agents
511 and DOACs should be restarted once haemostasis is achieved and typically reaching full dose 48-72 hours
512 after surgery.⁹⁸

513

514 The optimal agent for chemical venous thromboprophylaxis after knee surgery is a source of great
515 controversy, and there is significant regional variation in practice. In the United Kingdom, low-molecular
516 weight heparin (LWMH) is most widely employed, although aspirin and prophylactic dose DOACs are
517 recommended alternatives.⁹⁶ In the United States warfarin and aspirin are widely used. Prophylactic dose
518 DOACs are also increasingly used for thromboprophylaxis.

519

520 The choice of agent for venous thromboprophylaxis and timing of administration may significantly influence
521 blood loss. In the United Kingdom, thromboprophylaxis LMWH is typically commenced between 6 and 12
522 hours after surgery,⁹⁶ whereas in the United States, it is typically commenced between 12 and 48 hours after
523 surgery.⁹⁹ In elective hip surgery, the administration of LMWH within four hours of surgery increased the risk
524 of major bleeding to 6.3% compared with 2.5% when administered between 12 and 48 hours after surgery,
525 but with a possible decrease in risk of venous thromboembolic event.⁹⁹

526

527

528 FUTURE DEVELOPMENTS:

529

530 A large number of interventions demonstrate the potential to reduce blood loss during knee arthroplasty
531 surgery. The current challenge is to determine how to combine these interventions to deliver an optimal
532 patient pathway. Heterogeneity of studies to date with respect to interventions and outcome measures
533 severely limits the ability to compare the efficacy of different interventions. A consensus agreement to
534 develop a core set of outcome measures and to recommend standardised treatments in future studies may
535 facilitate progress. Collaborative trials may also overcome the small patient numbers observed in most
536 studies published in this field, allowing adequate power to assess outcomes in patient subgroups, such as
537 those at high cardiovascular risk. The most effective strategies to date are optimisation of anaemia,
538 tranexamic acid delivery, and restrictive transfusion strategies. It may be that further gains from additional
539 blood conservation strategies are not clinically important or cost-effective. Nevertheless, strategies must be
540 patient specific, and small gains may become clinically significant in select groups, such as patients with
541 haemophilia or Jehovah witnesses. In addition, different algorithms will be needed for successful and cost-
542 effective blood conservation strategies for unicompartmental knee arthroplasty, and primary and revision
543 TKA.

544

545

546 CONCLUSIONS:

547

548 Implementing strategies to reduce blood loss can improve patient outcomes and reduce healthcare costs.
549 Such interventions in patients undergoing knee arthroplasty are employed preoperatively, intraoperatively,
550 and postoperatively. The strongest predictor for allogeneic blood transfusion is preoperative anaemia, and
551 early identification and treatment reduces the rates of transfusion and complications. Intraoperatively,
552 tranexamic acid reduces blood loss. The optimal route, dose, or timing of administration remains uncertain.
553 Postoperatively, cell salvage is a valuable adjunct for cases with significant expected blood loss. Autologous
554 blood donation is not recommended, sealants require further evidence of benefit but may play a role in
555 select cases, and the use of a tourniquet remains at the discretion of the surgeon. Restrictive transfusion
556 protocols should be followed, and more current studies report no allogeneic transfusions after primary knee
557 arthroplasty surgery.

558

559

560

561 TEXT BOX:

562

563 TIPS AND TRICKS

564

565 Obtain laboratory tests for full (complete) blood count and renal function at the time patients are scheduled for surgery

566

567 Investigate the aetiology of preoperative anaemia and commence treatment at the earliest opportunity (target Hb > 130g/L)

568 Use topical, intravenous, oral, or combined routes of tranexamic acid administration for all knee arthroplasty procedures

569

570 Do not use conventional suction drains. Consider cell salvage for revision knee arthroplasty when significant blood loss is expected

571

572 Follow postoperative restrictive transfusion regimen with Hb threshold <70g/L except in patients with acute coronary syndrome

573

574 MAJOR PITFALLS

575

576 Late diagnosis and treatment of preoperative anaemia

577

578 Failure to discuss blood conservation strategies with the anaesthetic team

579

580 Transfusion of allogeneic blood with no clinical indication

581

582

583

584 TEXT BOX:

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586

587 TEN KEY PUBLICATIONS:

588

589 Jans Ø, Jørgensen C, Kehlet H, Johansson PI. Role of preoperative anemia for risk of transfusion and
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621

622 DECLARATIONS:

623

624 No author declares a conflict of interest relevant to the submitted work. Outside of the submitted work, AFC
625 received grant funding from the Orthopaedic Research and Education Foundation, consultancy fees from
626 Heraeus, Zimmer, 3M, Convatec, Irrisept, Haylard, Pfizer, DJO, ACI, bOne, and Stryker, royalties from SLACK
627 publishing, holds equity in Joint Purification Systems, and sits on the advisory board for Recro. AJP receives
628 grant funding from Arthritis Research UK and the National Institute for Health Research, and personal fees
629 from Zimmer Biomet, DePuy, and Smith and Nephew.

630

631 AUTHOR CONTRIBUTIONS:

632

633 AJRP drafted the initial manuscript. All authors performed critical revision and approved the final
634 manuscript.

635

636

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