Characteristics of studies

Cvetanovich 2018

Methods	
Participants	**Procedure performed:** Primary anatomic and reverse total shoulder arthroplasty **Indication for primary arthroplasty:** Not reported **Mean age per study arm:** intervention: 70.3 (SD 9.3) years, placebo: 71.3 (SD 7.9) years **Males (%) per study arm:** **BMI per study arm:** **Preoperative Hemoglobin (g/dL):** **Exclusion criteria:** allergy to TXA, acquired disturbances of color vision, preoperative use of anticoagulant therapy within 5 days of surgery, history of arterial or venous thromboembolic disease (including deep venous thrombosis, pulmonary embolism, stroke, transient ischemic attack), ongoing pregnancy or breast-feeding, recent myocardial infarction (within 6 months before surgery), cardiac stent placement, renal impairment, hemophilia, refusal of blood products, revision TSA, TSA performed for the indications of acute proximal humeral fracture, or prior open shoulder surgery, including failed open reduction and internal fixation of proximal humeral fractures..
Interventions	**Tranexamic acid** **Dose:** 1 g of IV TXA diluted in 10 mL normal saline (X-Gen Pharmaceuticals, Inc., Horseheads, NY, USA). This dose of TXA was chosen because it is standard practice at their institution to administer 1 g IV TXA 10 minutes before the incision for total hip and knee arthroplasty. **Route of administration:** Topical **Control:** 10 mL of IV normal saline placebo
Outcomes	**Primary outcome:** • postoperative blood loss based on a formula accounting for initial patient hemoglobin, the lowest postoperative hemoglobin, and patient blood volume approximated based on patient sex, height, and weigh **Secondary outcomes:** • transfusion rates • weight of hemoglobin loss • intraoperative estimated blood loss • hospital length of stay • complications (postoperative complications, including thromboembolic events, were noted for a 90-day postoperative period. Complications were noted on routine postoperative follow-up examinations)

	Transfusion protocol: underwent transfusion if their postoperative hemoglobin dropped below 7.0 g/dL or for higher hemoglobin values only for specific medical indications specified by the consulting hospitalist attending.
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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number algorithm was used for the randomization process
Allocation concealment (selection bias)	Low risk	Pharmacy controlled unlabeled syringes for allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Participants and surgeons were blinded to the allocation
Blinding of outcome assessment (detection bias)	Low risk	Data acquisition was performed by a research assistant blinded to patient study group allocation.
Incomplete outcome data (attrition bias)	Low risk	There were no losses to follow-up. The 110 participants initially randomized were not all included. Two patients were excluded, one in each group for no postoperative complete blood count. This is a reasonable attrition and not expected to affect results.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No other important bias detected

Gillespie 2015

Methods	Trial duration October 2012 and June 2014 118 randomized. 111 analyzed. Setting: Multi-center trial. USA
Participants	**Procedure performed:** Primary anatomic and reverse total shoulder arthroplasty **Indication for primary arthroplasty:** degenerative joint disease of the shoulder, with the decision for TSA or RTSA based on the integrity of the rotator cuff at the time of the initial preoperative evaluation **Mean age per study arm:** intervention: 66.4 years, placebo: 67.9 years **Males (%) per study arm:** intervention: 41.1%, placebo: 47.2% All patients discontinued the use of aspirin and nonsteroidal anti-inflammatory medications 7 days before surgery **Exclusion criteria:** revision surgery, history of cardiac disease, liver disease, renal disease, preoperative hemoglobin level <11.5 g/dL or hematocrit <35%, severe joint deformity, history of joint infection, history of bleeding or metabolic disorder, history of peripheral vascular disease, history of prior deep venous thrombosis (DVT) or pulmonary embolism (PE), any patient unwilling to accept a blood transfusion, and any patient with a documented allergy to TXA.
Interventions	**Tranexamic acid** **Dose:** 100 mL of normal saline infused with 2 g of TXA poured into the surgical wound and left in place for 5 minutes **Route of administration:** Topical **Control:** placebo. The control group had 100 mL of normal saline poured into the wound and left in place for the same duration.
Outcomes	**Primary outcome:** • Postoperative blood loss as measured by cumulative drain output (mL) at 24 hours **Secondary outcome:** • Change in hemoglobin (g/dL) level at 24 hours • Rate of transfusions • Other complications. The protocol for blood transfusions called for these to be administered only for a hemoglobin level <7.0 g/dL or a hemoglobin level of >7.1 but <9.0 g/dL with accompanying signs and symptoms of acute blood loss anemia, as demonstrated by tachycardia (heart rate >100 beats/min), hypotension (systolic blood pressure <100 mm Hg), or subjective complaints of light-headedness or dizziness that did not resolve after administration of intravenous fluids.

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized using block randomization to reflect a randomization of 1:1 TXA to placebo in blocks of 6
Allocation concealment (selection bias)	Low risk	Pharmacy controlled and sealed envelope.
Blinding of participants and personnel (performance bias)	Low risk	Participants and surgeons were blinded to the allocation
Blinding of outcome assessment (detection bias)	Unclear risk	While these are objective outcomes with a low risk of detection bias (transfusion, thromboembolic events and laboratory blood results), the study did not describe who did the acquisition of the data and if was blinded to the allocation of the patients.
Incomplete outcome data (attrition bias)	Low risk	There were no losses to follow-up. The 118 participants initially randomized were not all included. Seven were excluded. Two patients in the placebo group and 3 patients in the treatment group ultimately had their operations canceled for medical reasons. Two patients in the treatment group were also excluded from the analysis because of intraoperative findings of major glenoid deformity. This is a reasonable attrition and not expected to affect results.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No other important bias detected

Pauzenberger 2017

Methods	Trial duration July to December 2015 56 randomized. 54 analyzed. Setting: Single-center trial. Austria
Participants	**Procedure performed:** Primary anatomic and reverse total shoulder arthroplasty **Indication for primary arthroplasty:** Not reported **Mean age per study arm:** intervention: 70.3 (SD 9.3) years, placebo: 71.3 (SD 7.9) years **Males (%) per study arm:** intervention: 67%, placebo: 74% **BMI per study arm:** intervention: 31.1 (SD 7.5), placebo: 30.8 (SD 5.4) **Preoperative Hemoglobin (g/dL):** intervention: 13.7, SD 1.2, placebo: 13.6, SD 1.5. **Exclusion criteria:** refusal to participate in the study, revision surgery, indication for hemiarthroplasty, known allergy to TXA, anticoagulative medication, severe comorbidities, history of arterial or venous thromboembolic events, coagulopathy, hematological disorders, retinopathy, refusal to receive blood transfusion, pregnancy, or breastfeeding. Administration of acetylsalicylic acid, antiplatelet agents, or cyclooxygenase inhibitors was not a reason for exclusion.
Interventions	**Tranexamic acid** **Dose:** 1 g TXA in 100 ml saline within 30 minutes prior to skin incision, and a second dose of 1 g of TXA in 100 ml saline was administered during wound closure. **Route of administration:** Intravenous Control: placebo
Outcomes	**Primary outcome:** • Post-operative drain blood loss (mL) at 24 hours **Secondary outcomes:** • Total blood loss was calculated according to Nadler's formula and modified Gross' formula • number of transfusions necessary during the study period was documented Protocol of transfusion: Blood transfusion was planned for patients with a Hb level < 8.0 g/dL, patients with a Hb level of 8 g/dL to 10 g/dL with on-going blood loss or patients who showed symptoms related to anemia.
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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized random number sequence generation.
Allocation concealment (selection bias)	Unclear risk	One investigator communicated the patient's group allocation to the anesthetist. There were no explicit methods to conceal the allocation sequence for that investigator. There were no pharmacy central control of the allocation sequence or sealed envelopes mentioned. While allocations could have been foreseen before or during enrollment, that investigator was not involved in the surgery or collection of the data, and we do not consider this bias may alter the results seriously.
Blinding of participants and personnel (performance bias)	Low risk	Surgeons, patients, and all personnel involved in either treatment or evaluation of study participants were blinded to the group allocation
Blinding of outcome assessment (detection bias)	Low risk	Clinical parameters were documented by a staff physician unaware of group allocation.
Incomplete outcome data (attrition bias)	Low risk	There were no losses to follow-up. The 56 participants initially randomized were not all included; two were excluded (arthroplasty system, no post-op drain). This is a reasonable attrition and not expected to affect results. Adequate sample size of 23 per group was achieved
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No other important bias detected

Vara 2017

Methods	Trial duration September 2013 to December 2015 116 randomized. 102 analyzed. Setting: Single-center trial. USA
Participants	**Procedure performed:** Primary reverse total shoulder arthroplasty (RTSA) **Indication for primary RTSA:** massive cuff deficiency, with or without glenohumeral arthrosis. **Mean age per study arm:** intervention: 66, (SD 9) years, placebo: 67, (SD 9) years. **Males (%) per study arm:** intervention: 49%, placebo: 38% Preoperative Hemoglobin (g/dL): intervention: 13.7, SD 1.2, placebo: 13.6, SD 1.5. The exclusion criteria were: acute proximal humeral fracture, concomitant procedures (e.g., latissimus dorsi tendon transfer), known allergy to TXA, preoperative anemia (Hb <11 g/dL in women, Hb <12 g/dL in men), refusal of blood products, coagulopathy (thrombophilia, platelet count <150,000 mm3, international normalized ratio >1.4, partial thromboplastin time >1.4 times normal), history of thromboembolic event, major comorbidities (severe pulmonary disease, coronary artery disease, previous myocardial infarction, renal failure), or refusal to give written consent.
Interventions	Intervention group Tranexamic acid Dose: One 10 mg/kg dose was given within 60 minutes before surgery, and a second 10 mg/kg dose was given at wound closure. Route of administration: Intravenous Control: placebo
Outcomes	Primary outcomes: Total Blood Loss as calculated according to method as described by Good et al. Total Blood Loss (mL) = 1000 X Hb(loss)/Hb(initial) [Time Frame: Preoperative through Postoperative Days 1 and 2] Total hemoglobin loss estimated using the formula for total blood volume described by Nadler et al Hb(loss) = blood volume (L) x [Hb(initial)(g/L) - Hb(final)(g/L)] + Hb(transfused) Total Drain Output as measured postoperatively 0-48 hours Secondary outcomes: The occurrence of DVT, pulmonary embolism, myocardial infarction, hematoma and surgical site infection within 6 weeks of surgery will be recorded. Data will be obtained from EMR and from patient at standard of care 2 week and 6-week follow-up appointment.

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Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random allocation sequence was generated
Allocation concealment (selection bias)	Low risk	Pharmacy controlled unlabeled syringes for allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Surgeon, surgical staff members, all health care providers, and the patient were blinded to the allocation
Blinding of outcome assessment (detection bias)	Unclear risk	While these are objective outcomes with a low risk of detection bias (transfusion, thromboembolic events and laboratory blood results), the study did not describe who did the acquisition of the data and whether was blinded to the allocation of the patients.
Incomplete outcome data (attrition bias)	Low risk	There were two losses to follow-up (one for each group) patients. There was a higher than 10% attrition rate because 9 patients in the placebo group and 5 patients in the TXA group were excluded in the beginning of the study. However, we did not cosider a high risk of bias because those were ineligible patients mistakenly randomised into the trial and the authors demonstrated that there was no an imbalance of the groups after those exclusions.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No other important bias detected