BJA

British Journal of Anaesthesia, 2016, 1–6

doi: 10.1093/bja/aev408
Circulation

A randomized trial of the effect of low dose epinephrine infusion in addition to tranexamic acid on blood loss during total hip arthroplasty

Ø. Jans[1,4,*], U. Grevstad[2], H. Mandøe[3], H. Kehlet[1,4] and P. I. Johansson[4,5]

[1]Section of Surgical Pathophysiology, Rigshospitalet, Copenhagen, Denmark, [2]Department of Anaesthesia, Gentofte Hospital, Copenhagen, Denmark, [3]Department of Anaesthesia, Vejle Hospital, Vejle, Denmark, [4]Lundbeck Foundation Centre for Fast-track Hip and Knee Arthroplasty, Copenhagen, Denmark, and [5]Section for Transfusion Medicine, Rigshospitalet, Copenhagen, Denmark

*Corresponding author. E-mail: oeivind.jans@regionh.dk

Abstract

Background: Total hip arthroplasty (THA) is associated with both intraoperative and postoperative blood loss resulting in anaemia and, in some patients, transfusion of red blood cells. Epinephrine enhances coagulation by several mechanisms. We evaluated the effect of intraoperative low dose infusion of epinephrine on intraoperative and early postoperative blood loss.

Methods: After consent, 106 subjects undergoing THA under spinal anaesthesia were randomly assigned to receive an i.v. infusion of either epinephrine 0.05 μg kg^{-1} min^{-1} or placebo (saline 0.9%) during the entire surgical procedure. Intraoperative tranexamic acid (TXA) was administered to all subjects. The primary outcome was intraoperative blood loss directly measured by drains and weighing swabs. Secondary outcome was total blood loss at 24 h postoperatively calculated using the Gross formula.

Results: Of 106 subjects randomized, 6 were excluded, leaving 100 subjects for analyses. Mean duration of surgery was 58 (21) min. Intraoperative blood loss was 343 (95% CI 300–386) ml in the epinephrine group compared with 385 (353–434) ml in the placebo group, $P = 0.228$. 24 h blood loss was 902 (800–1004) ml in the epinephrine group compared with 1080 (946–1220) ml in the placebo group, $P = 0.038$.

Conclusion: In subjects also receiving TXA, intraoperative low dose epinephrine infusion did not reduce intraoperative blood loss in THA but calculated 24 h blood loss was reduced by 180 ml compared with placebo. Further studies on low dose epinephrine in patients at high risk of significant bleeding are warranted.

Clinical trial registration: NCT 01708642.

Key words: arthroplasty; blood loss; epinephrine; hip replacement, total

Measures to reduce perioperative blood loss are an integral part of patient blood management strategies.[1] Blood loss in patients undergoing total hip arthroplasty (THA) causes postoperative anaemia and risk of receiving allogeneic blood transfusions.[2] Although interventions such as systemic or topical tranexamic acid (TXA) administration can reduce perioperative blood loss in THA,[3 4] THA patients receive blood transfusion during or after surgery, but with a large variation between countries and

Accepted: September 22, 2015

Editor's key points

- The efficacy of low dose epinephrine in reducing blood loss during hip surgery performed with spinal anaesthesia was evaluated in a randomized study of 100 subjects.
- Intraoperative i.v. epinephrine combined with tranexamic acid did not reduce intraoperative blood loss; total blood loss was significantly reduced but by a clinically insignificant amount.
- Further evaluation of epinephrine to reduce blood loss in procedures with higher blood loss is warranted.

surgical centres.[5–7] In patients undergoing THA most of the total blood loss can appear postoperatively as "hidden" blood loss.[8] Thus additional measures to decrease both intraoperative and postoperative blood loss in THA are warranted.

The administration of low doses of epinephrine could act as a procoagulant by increasing platelet aggregation and decreasing platelet transit time in the spleen, through α-adrenergic activation, resulting in an instant 20–30% increase in platelet count.[9 10] In addition, epinephrine stimulates release of several coagulation factors including fibrinogen, through β-adrenergic receptors.[10] This pro-haemostatic effect of epinephrine lasts up 90 min after administration. We hypothesized that epinephrine administration could reduce perioperative blood loss and aimed to evaluate the effect of intraoperative i.v. administration of low dose epinephrine, on intraoperative and early postoperative blood loss in patients undergoing elective fast-track THA.

Methods

Trial design and oversight

This randomized, double-blind, parallel group, placebo controlled trial was conducted in two Danish surgical centers from 2012 to 2013, in patients undergoing elective fast-track hip arthroplasty (THA). The trial was conducted in accordance with the declaration of Helsinki and was approved by the Danish Health and Medicines Authority (EudraCT 2012-002889-12) and the Regional Ethics Committee of The Capital Region of Denmark (H-2-2012-087). The trial was approved by the Danish Data Protection Agency, monitored by the Agency for Good Clinical Practice at the University of Copenhagen and registered on ClinicalTrials.Gov (NCT01708642).

Participants

Patients ≥ 18 years of age undergoing elective unilateral THA under spinal anaesthesia and able to give informed consent were screened for inclusion. Exclusion criteria were general anaesthesia, acute coronary syndrome < 6 months, glaucoma, pheochromocytoma, thyrotoxicosis, digoxin intoxication, serum K+ < 3.0 mmol l^{-1}, alcohol abuse, premenopausal women, enrolment in other interventional trials < 30 days or current treatment with ADP receptor antagonists, Factor Xa or thrombin inhibitors, heparin (excluding LMWH for perioperative thromboprophylaxis), tricyclic antidepressants, or MAO or COMT inhibitors.

Randomization, blinding and trial intervention

Before surgery subjects were randomly allocated to receive an infusion of either epinephrine (Adrenalin "DAK", Nycomed Denmark ApS) at a weight-adjusted rate of 0.05 μg kg^{-1} min^{-1} or placebo (0.9% saline) from placement of spinal anaesthesia to end of surgery (last suture).

A computer generated randomization list (www.randomization.org) was generated by a researcher outside the author group using permuted blocks (block size 10, allocation ratio 1:1). Subjects were enrolled in the trial by a dedicated study nurse and assigned a unique randomization number based on sequentially numbered, sealed, opaque envelopes in which allocation was concealed. Just before surgery the envelope was opened by the anaesthesia nurse, who also prepared the study drug (epinephrine or placebo). All other care providers, subjects, trial investigators and the surgical nurse assessing outcomes were blinded to the allocation group.

Anaesthesia and surgery

Subjects underwent spinal anaesthesia with bupivacaine (5 mg ml^{-1}) according the standard operating procedure at the participating hospital. Intraoperative sedation with propofol 1–5 mg kg^{-1} h^{-1} was administered at the discretion of the attending anaesthetist. All subjects received 1 g of (TXA) i.v. before the start of surgery. Intraoperative fluid therapy was standardized to 0.9% saline 12 ml kg^{-1} the first hour during surgery, followed by 6 ml kg^{-1} h^{-1} until end of surgery. Blood loss was replaced 1:1 by hydroxyethyl starch (HAES 130/0.4; Voluven, Fresenius Kabi A/B, Sweden) and transfusion of blood products followed guidelines issued by the Danish National Board of Health.[11] In the post-anaesthesia care unit (PACU), subjects were allowed to drink freely and further i.v. fluid administration was at the discretion of the attending physician. All subjects were operated using the standard postero-lateral approach and monitored using noninvasive bp, continuous standard 3-lead ECG and pulse oximetry. No postoperative drains were used.

Outcome measures

The primary outcome measure was intraoperative blood loss as assessed by a surgical nurse by measuring suction drain content and weighing swabs at the end of surgery. The secondary outcome measure was blood loss at 24 h after surgery, calculated by haemoglobin differences using the Gross formula,[12] with total blood volume estimated using Nadler's equation.[13] All Hb measurements were by venous sampling at the following timepoints: preoperatively on the day of surgery, immediately after surgery and 24 h after end of surgery (last suture). Hb analyses were performed by the clinical biochemical department at the participating hospitals.

Sample size calculations

The trial was conducted as a superiority trial. Based on previous data from the participating centres that showed a mean (SD) intraoperative blood loss of 461 (317) ml and assuming a two-sided alpha level of 5% and a power of 80%, it was calculated that a total of 94 subjects had to be included in order to detect a 40% (184 ml) difference in the primary outcome (intraoperative blood loss) between treatment groups. Regarding the secondary outcome (24 h blood loss), it was calculated that a total of 70 subjects were needed to detect a reduction of 330 ml based on previous data, showing a 24 h calculated blood loss of 1230 (488) ml. Thus, we planned to include 100 subjects in the trial. Included patients that terminated the trial prematurely were replaced by