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

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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
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. In patients undergoing THA most of the total blood loss can appear postoperatively as “hidden” blood loss. 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. In addition, epinephrine stimulates release of several coagulation factors including fibrinogen, through β-adrenergic receptors. This pro-haemostatic effect of epinephrine lasts up to 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 hydroxethyl 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. 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 Cross formula, with total blood volume estimated using Nadler's equation. All Hb measurements were by venous sampling at the following time-points: 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...
additional subjects receiving a new randomization number, in order to secure a full sample.

**Statistical analyses**

Before analyses, all data were evaluated for normal distribution by histograms and Q-Q plots and by the Kolmogrov-Smirnoff test. The primary and secondary outcomes were analysed by modified intention to treat by group comparison using a two-sided independent samples t-test for continuous outcomes. Continuous data not following the normal distribution were compared using the Mann-Whitney U-test and categorical data were compared by the $\chi^2$ test.

Statistical analyses were performed before breaking the randomization code. Safety data were summarized descriptively and compared between allocation groups. Results are presented as mean (sd) or mean (95% CI) for data following the normal distribution and median with interquartile range (IQR) for skewed data. Data analyses were performed using SPSS software, Version 20.0 (IBM Corp, Troy, NY USA). A two sided $P$-value < 0.05 was considered statistically significant.

**Results**

**Subjects**

Between November 2012 and November 2013 a total of 376 patients were screened for eligibility (Fig. 1). A total of 106 subjects were included, but 5 subjects were excluded (2 in the epinephrine group and 3 in the placebo group) after randomization and assessed for eligibility ($n=376$)

- Not eligible ($n=270$)
  - Did not give consent ($n=62$)
  - Enrolled in other trial ($n=61$)
  - Scheduled for general anaesthesia ($n=31$)
  - Investigator not available ($n=24$)
  - Use of anticoagulants ($n=22$)
  - Revision surgery ($n=17$)
  - Cancer ($n=9$)
  - In fertile age ($n=4$)
  - Refused surgery ($n=2$)
  - Glaucoma ($n=12$)
  - Other comorbidity ($n=9$)
  - Alcohol abuse ($n=2$)
  - Other ($n=15$)

- Randomized: ($n=106$)
  - Epinephrine 0.05 $\mu$g kg$^{-1}$ min$^{-1}$ ($n=52$)
    - Received epinephrine ($n=50$)
    - Did not receive epinephrine:
      - Conversion to GA ($n=2$)
  - Placebo ($n=54$)
    - Received placebo ($n=51$)
    - Did not receive placebo:
      - Conversion to GA ($n=3$)

- Analysed ($n=50$)
  - Excluded from analysis ($n=0$)

- Analysed ($n=50$)
  - Excluded from analysis:
    - Pelvic surgery ($n=1$)

Fig 1 CONSORT flow diagram for screening and inclusion of trial participants.
did not receive the trial drug. One additional subject received the trial drug but was excluded from final analysis as concomitant pelvic surgery was performed (Fig. 1). This resulted in 100 subjects with complete follow-up regarding the primary and secondary outcome. Subject characteristics were comparable between treatment groups (Table 1). Patients had a mean age (range) of 68 (41–87) yr, a BMI of 28 (4) kg m\(^{-2}\) and 47 (47%) were female.

**Intraoperative data**

Duration of surgery was 58 (20) min, spinal bupivacaine dose was 14.6 (1.0) mg and 81 (81%) patients received intraoperative sedation with propofol. A mean volume of 1200 (312) ml crystalloid and median (IQR) 100 (0–300) ml 130/0.4 HAES was administered during surgery. None of the participating subjects received blood transfusion during admission. More subjects in the placebo group received propofol sedation compared with the epinephrine group, while all other intraoperative data were comparable between groups (Table 2).

**Study outcomes**

Perioperative blood loss and the haemoglobin concentration before, 6 h and 24 h after surgery are presented in Table 3. At the end of surgery, intraoperative blood loss (primary outcome) was 343 (95% CI 300–386) ml in the epinephrine group and 383 (353–434) ml in the placebo group, with a mean difference of 40 (95% CI –26 to 107) ml (P = 0.228; Fig. 2). At 24 h after surgery, total blood loss (secondary outcome) was 902 (800–1000) ml in the epinephrine group vs 1082 (946–1220) ml in the placebo group, with a mean difference of 180 (95% CI 10 to 350) ml (P = 0.038).

**Safety**

No subjects experienced serious adverse events (SAE) or drug reactions (SADR), as defined by the ICH-GCP guidelines, during the study period. Of the 11 adverse events (AE) reported, eight were graded as mild, two as moderate and one as severe. All AE’s were considered unrelated to the trial intervention. There was no statistical difference in the number of AE’s reported when compared by allocation group (Table 4).

**Discussion**

The main finding of this trial is that intraoperative blood loss was not different during intraoperative low dose epinephrine infusion compared with placebo. Total 24 h calculated blood loss was reduced significantly by 180 ml compared with placebo, but with little clinical relevance.

### Table 1 Subject characteristics by treatment group. ASA, physical status classification; Hb, Haemoglobin. Data are presented as no. (%) or mean (sd)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Epinephrine (n = 50)</th>
<th>Placebo (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>23 (46%)</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>27 (4)</td>
<td>29 (4)</td>
</tr>
<tr>
<td>ASA Class</td>
<td>I 19 (38%)</td>
<td>I 16 (32%)</td>
</tr>
<tr>
<td></td>
<td>II 27 (54%)</td>
<td>II 26 (52%)</td>
</tr>
<tr>
<td></td>
<td>III 8 (16%)</td>
<td>III 8 (16%)</td>
</tr>
<tr>
<td>Medication</td>
<td>Aspirin 11 (22%)</td>
<td>Aspirin 12 (24%)</td>
</tr>
<tr>
<td></td>
<td>Beta-blocker (metoprolol) 7 (14%)</td>
<td>Beta-blocker (metoprolol) 5 (10%)</td>
</tr>
<tr>
<td></td>
<td>Other antihypertensives 24 (48%)</td>
<td>Other antihypertensives 20 (40%)</td>
</tr>
<tr>
<td></td>
<td>Hb at baseline (g dl(^{-1}))</td>
<td>14.0 (1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.9 (1.3)</td>
</tr>
</tbody>
</table>

### Table 2 Intraoperative data by treatment group. Hydroxyethyl-starch. Data are presented as no. (%), mean (sd) or median (interquartile range). *Significant difference between treatment groups

<table>
<thead>
<tr>
<th>Medication</th>
<th>Epinephrine (n = 50)</th>
<th>Placebo (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol sedation</td>
<td>36 (72%)</td>
<td>45 (90%)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>57 (21)</td>
<td>59 (19)</td>
<td>0.69</td>
</tr>
<tr>
<td>Bupivacaine dose (mg)</td>
<td>14.6 (1.1)</td>
<td>14.6 (0.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Intraoperative fluids (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloids</td>
<td>1170 (310)</td>
<td>1230 (315)</td>
<td>0.37</td>
</tr>
<tr>
<td>HAES 130.4</td>
<td>0 (0–200)</td>
<td>100 (0–203)</td>
<td>0.33</td>
</tr>
<tr>
<td>Total</td>
<td>1370 (393)</td>
<td>1450 (396)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

### Table 3 Perioperative blood loss and haemoglobin concentrations by treatment group. Data are presented as mean (sd). *Significant difference between treatment groups (independent samples t-test)

<table>
<thead>
<tr>
<th>Blood loss (ml)</th>
<th>Epinephrine (n = 50)</th>
<th>Placebo (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative</td>
<td>343 (156)</td>
<td>383 (177)</td>
<td>0.23</td>
</tr>
<tr>
<td>24 h total</td>
<td>902 (368)</td>
<td>1082 (481)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Hb concentration (g dl(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>14.0 (1.2)</td>
<td>13.9 (1.3)</td>
<td>0.89</td>
</tr>
<tr>
<td>End of surgery</td>
<td>11.4 (1.0)</td>
<td>11.3 (1.3)</td>
<td>0.67</td>
</tr>
<tr>
<td>24 h post surgery</td>
<td>11.5 (1.3)</td>
<td>11.3 (1.4)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

**Fig 2 Box-plot of intraoperative- (IOP) and 24 hour (24 h) total blood loss in milliliters (ml) by allocation group. Horizontal line represents median, box represents interquartile range, whiskers represents 10th & 90th percentiles and dots represents 5th and 95th percentiles.**
No previous studies have evaluated the procoagulant effect of low dose epinephrine as an intervention for reducing perioperative blood loss. We administered epinephrine in addition to TXA, which has been demonstrated to reduce intraoperative and postoperative blood loss in major joint arthroplasty,^8,14 and thus our results must be discussed in this context. In a recent meta-analysis including 19 randomized controlled trials in THA, it was concluded that systemic administration of TXA reduced intraoperative and total blood loss by −86 and 305 ml, respectively. However, the majority of these studies used postoperative closed suction drainage that can increase postoperative blood loss. The intraoperative blood loss found in this trial was low (∼350 ml) compared with other published data and was not reduced significantly by intraoperative epinephrine administration, and no patients were transfused during the study period. The low intraoperative blood loss and lack of transfusion in this trial could be explained by the high volume fast-track elective centres with ~500 THA procedures yr−1, a short duration of surgery and a restrictive transfusion trigger. Although splenic platelet release occurs almost instantaneously after epinephrine administration,^6 the peak coagulation factor increase might not be reached until ~20 min after onset of administration. Thus, the relatively short duration of surgery in this trial could have influenced the results regarding intraoperative blood loss. However, in THA, significant blood loss can occur after wound closure,^8,17 and the proportion of this “hidden” blood loss can be as high as 60% of total blood lost perioperatively,^6 as was the case in the present study. The procoagulant effect of epinephrine continues 1-2 h after administration and might have reduced early postoperative oozing, explaining the significant 180 ml (17%) reduction in 24 h total blood loss found in this trial. This suggests that low dose epinephrine infusion combined with TXA can further reduce early postoperative blood loss as a result of oozing. This effect might be augmented by extending the infusion period to the PACU, where sufficient monitoring is in place to allow for such an intervention. However, this approach needs evaluation in future clinical trials. Although 24 h blood loss was reduced with epinephrine administration, this had limited clinical significance in our population and did not translate into differences in transfusion rate. However, future studies may evaluate the effect of low dose epinephrine in procedures with more substantial blood loss and a high overall transfusion rate.

We used the calculated total 24 h blood loss based on changes in Hb concentration using the Gross formula,^12 as opposed to several studies that have used drain output to directly estimate postoperative blood loss. Direct measurement of drains does not account for hidden blood loss and thus can underestimate actual blood loss. Nevertheless, sampling errors or differences in administered fluid volume can influence calculated blood loss by the Gross formula because of dilution, but the fluid administration did not differ between allocation groups, and thus cannot explain the reduction in 24 h blood loss. Changes in intraoperative blood flow as a result of epinephrine administration might also by-itself influence blood loss. However, the low dose used primarily causes β-adrenoreceptor activation, leading to decreased vascular resistance and increased cardiac output. This change is reversed within 5 min of discontinuing epinephrine, thus we consider it unlikely that haemodynamic effects of epinephrine contributed significantly to the observed reduction in blood loss at 24 h after surgery. As a result of ongoing losses, the lowest postoperative Hb concentration might not be reached until day two to four after surgery. We did not follow blood loss for more than 24 h, as we speculated that the majority of postoperative blood loss occurs within this time frame and that no procoagulant effect of epinephrine would remain 24 h after surgery. We did not exclude patients taking β-blocking agents, which could potentially attenuate the increase in coagulation factor activity. Epinephrine induced increase in coagulation factors is abolished by nonselective beta blockade, but not by β1-selective blocking agents, suggesting a β2 mediated effect. Thus, the use of metoprolol by 14% of subjects in the epinephrine group might not have influenced our results.

We found no difference in adverse events between allocation groups. However, any procoagulant intervention to reduce blood loss should be evaluated carefully for the risk of thromboembolic events such as deep venous thrombosis (DVT) and pulmonary embolism (PE). The concerns of such complications have kept some surgical centres from implementing the routine use of TXA. However, several systematic reviews have established the efficacy and safety of TXA in an elective orthopaedic setting. Although we observed no thromboembolic events during the study period, the present trial was not powered to evaluate this. Current evidence regarding the duration of the procoagulant effect after epinephrine administration is sparse and varies with administration protocols,^15 thus emphasizing the need for further studies systematically evaluating this. It is possible that the effect is shorter than that of TXA, which has an elimination half-life of two to three h. Direct measurement of coagulation by TEG was not carried out in this trial because of logistical reasons, and the lack of concomitant coagulation monitoring is thus a limitation of the present study.

In conclusion, this prospective randomized controlled study found no difference in intraoperative blood loss during THA with the administration of epinephrine during surgery compared with placebo, with a small but statistically significant reduction in total 24 h blood loss. Future trials should evaluate the effect of low dose epinephrine in reducing perioperative blood loss in procedures with high risk of bleeding.

**Authors’ contributions**

Study design/planning: ØJ, U.G., H.M., H.K., P.I.J.
Study conduct: U.G., H.M.
Data analysis: ØJ.
Writing paper: ØJ.
Revising paper: all authors
Declaration of interest

P.I.J. is a co-inventor of a patent describing the use of sympathomimetic infusion to improve haemostasis during surgery (WO2009043355 A2). No other authors have conflict of interests regarding this manuscript.

Funding

This work was supported by a grant from The Lundbeck Foundation (Grant Number: R25-A2702).

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