Supplemental Digital Content

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# Formula used to assess the primary outcome, calculated perioperative blood loss

The method used to calculate perioperative blood loss was based on Hb balance as described previously by Johansson and colleagues.1

The following formulas were used:

Hb loss = (Hbpre – Hbe ) × BV + Hbt

Where Hbpre is the initial preoperative Hb concentration (g/l), Hbe is the Hb concentration (g/l)

on the fifth postoperative day, and Hbt is the total amount of allogeneic transfused Hb (g).

1 unit of red blood cells was considered to contain 52 g of Hb (personal communication from Etablissement Français du Sang, Saint Priest en Jarez, France).

We assumed that the blood volume (BV, ml) was normalized on the fifth postoperative day.

BV was estimated as described previously by Rosencher and colleagues2:

BV (ml) = [body surface area (m2) ] x 2530 (in men)

 Or [ body surface area (m2) ] x 2430 (in women)

body surface area (m2) = 0.0235 x [height (cm) ] 0.42246 x [weight (kg) ] 0.51456

Blood loss (ml) was calculated in relation to the patient’s preoperative Hb value:

blood loss (m) = 1000 × Hb loss / Hbpre

Hemoglobin measurements were obtained as part of a complete blood count by a Coulter counter analyzer.

# Assumptions for sample size calculation

## Studies selected as a basis for blood loss assumptions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Reference | Year | Tranexamic acidregimen | Design |  Patients randomized | Perioperative blood loss, mlMean +/- SD |
|  |  |  |  | Tranexamic acid | Control | Tranexamic acid | Control |
| Randomized trials assessing a single preoperative bolus of tranexamic acid versus placebo or no treatment |
| Duquenne P3 | 1999 | 15 mg/kg before surgery | double- blind | 35 | 35 | 803 +/- 312 | 907 +/- 438 |
| Benoni G4 | 2001 | 10 mg/kg before surgery | double- blind | 18 | 20 | 1028 +/- 333 | 1382 +/- 455 |
| Yamasaki S5 | 2003 | 1 g before surgery | open | 20 | 20 | 1350 +/- 477 | 1667 +/- 401 |
| Johansson T1 | 2004 | 15 mg/kg before surgery | double- blind | 47 | 53 | 969 +/- 434 | 1324 +/- 577 |
| Lemay E6 | 2004 | 10 mg/kg before surgery + 1 mg/kg/h during surgery | double- blind | 20 | 19 | 1308 +/- 462 | 1469 +/- 405 |
| Garneti N7 | 2004 | 10 mg/kg before surgery | double- blind | 25 | 25 | 1443 +/- 809 | 1340 +/- 665 |
| Claeys MA8 | 2007 | 15 mg/kg before surgery | double- blind | 20 | 20 | 801 +/- 244 | 1038 +/- 289 |
| Rajesparan K9 | 2009 | 1 g before surgery | open | 36 | 37 | 1372+/-436 | 1683+/-705 |
| Kazemi SM10 | 2010 | 15 mg/kg before surgery | double- blind | 32 | 32 | n.a. | n.a. |
| McConnell JS11  | 2011 | 10 mg/kg before surgery | open | 22 | 22 | 895+/-99 | 1110 +/- 139 |
| Randomized trials assessing a preoperative bolus and additional perioperative administration of tranexamic acid versus placebo or no treatment |
| Ekbäck G12 | 2000 | 10 mg/kg before surgery + 1 mg/kg/h over 10h + 10 mg/kg 3h after 1st bolus | double- blind | 20 | 20 | 1130 +/- 400 | 1770 +/- 523 |
| Husted H13 | 2003 | 10 mg/kg before surgery + 1 mg/kg/h over 10 h | double- blind | 20 | 20 | 814 +/- 1265 | 1231 +/- 1639 |
| Ido K14 | 2000 | 1 g before surgery + 1 g 3h after surgery | open | 20 | 20 | n.a. | n.a. |
| Niskanen R15 | 2005 | 10 mg/kg before surgery + 10 mg/kg 8h after + 10 mg/kg 16h after | double- blind | 19 | 20 | 792 +/- 349 | 1102 +/- 464 |
| Local retrospective study on the use of a preoperative bolus and additional postoperative administration of tranexamic acid vs no treatment (unpublished) |
| Farissier F | 2012 | 15 mg/kg before surgery + 15 mg/kg 3h after 1st bolus |  | 54 | 17 | Blood loss difference 600 +/- 650 |

## Estimated blood loss reduction with tranexamic acid

* In studies assessing a single preoperative bolus of tranexamic acid versus placebo or no treatment, the mean blood loss reductions ranged from 0 to 350 ml (SD 300-500). The overall mean blood loss reduction was approximately 250 ml (a).
* In studies assessing a preoperative bolus of tranexamic acid and additional perioperative administration versus placebo or no treatment, the mean blood loss reduction ranged from 300 to 640 ml (SD 350-1400). The overall mean blood loss reduction was approximately 500 ml (b).

Indirect comparison favors the administration of an additional perioperative administration of tranexamic acid. The expected gain in blood loss was therefore assumed to be 500 - 250 ml (b-a), which is 250 ml.

## Sample size calculation

Assuming a difference in perioperative blood loss of 250 ml with a standard deviation (SD) of 500 ml, we calculated that a sample size of 84 patients per group would be required to achieve a power of 90% with a two-sided α risk of 0.05.

# Report of the methods used for the meta-analysis following the PRISMA guideline

A meta-analysis of randomized trials was performed to assess the external validity of the PORTO study. The decision to perform this meta-analysis was taken after completion of the PORTO study.

We report here the methods of this meta-analysis as recommended by the PRISMA guidelines for the reporting of systematic reviews.

**Protocol and registration**: There was no review protocol. However, the methods of the analysis and the inclusion criteria were specified in advance.

**Eligibility criteria:**

Type of studies: Randomized clinical trials comparing a single preoperative tranexamic acid bolus with preoperative administration of tranexamic acid followed by perioperative tranexamic acid administration as a bolus or a continuous infusion. No language, publication date, or publication status restrictions were imposed.

Types of participants: Studies had to be performed in adults in primary hip arthroplasty

Type of intervention: Tranexamic acid had to be administered exclusively intravenously

Types of outcome measures: The primary outcome was perioperative blood loss defined as the sum of intraoperative and postoperative blood loss. Perioperative blood loss could be measured or calculated. The secondary outcome was the percentage of patients requiring transfusion of at least 1 unit of allogeneic red blood cells during the perioperative period. There was no restriction for the length of follow up.

**Information sources:** Relevant trials were identified by a computerized search up to June 2016 in MEDLINE (PubMed) and the Cochrane Central Registry of Controlled Trials (Central). In addition, we checked the reference lists of the trials selected. Foreign papers were translated. The authors of the selected trials were contacted to supply missing information or clarifications. If a selected trial was published as an abstract, the author was asked if a full paper of the selected study had been published. Meeting abstracts were nott searched. One reviewer (PJZ) developed and conducted the search.

**Search:** The search strategy in PubMed and Central included the key words “tranexamic acid” and “hip”. In PubMed, the search was limited to randomized controlled trials with use of the article type search filter. In Central, the search was limited to trials with use of the search filter. The search detail in PubMed was:

("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) AND ("hip"[MeSH Terms] OR "hip"[All Fields]) AND Randomized Controlled Trial[ptyp]

**Study selection:** Studies were first screened on the basis of title and/or abstract by one reviewer (PJZ). Assessment for study eligibility and inclusion was performed by two reviewers (CC, PJZ). The study selection process is presented below using the PRISMA flow chart.**Data collection process:** Data were extracted using a data extraction sheet designed for this review in Excel (Microsoft). One review author (PJZ) extracted the data from the studies included and a second author (CC) checked the extracted data. In the event of a discrepancy with regard to either study selection or data extraction, the decision of a third author (SM) was final. We contacted all authors for further information in July 2016. A reminder was sent in August 2016. All but one author answered. One author provided numerical data on the primary outcome that had only been presented graphically in the published paper. One study had also analyzed the data concering the per-protocol population. The author provided numerical data on the primary and secondary outcome for all the available patients. One study had been published in Russian and translated. The author was contacted to provide additional data on study characteristics and methodology. This author provided another Russian article that had not been identified by the electronic search. The analysis in the latter study had been performed on the per-protocol population. The author provided the results of the analysis on the intention-to-treat population and confirmed the accuracy of the information included in the review. This author is also an author of this manuscript (DB).

**Data items:** “Information was extracted from each trial included with respect to: (1) the characteristics of trial participants (including age, weight, type of anesthesia, surgery and thromboprophylaxis implemented); (2) regimen of tranexamic acid used (dose, type of administration (bolus or infusion), duration or number of administrations); (3) type of outcome measure (including perioperative blood loss and the method used to measure this outcome, and the proportion of patients transfused with allogeneic red blood cells); (4) the number of patients randomized and the number of patients available for analyses.

**Risk of bias in individual studies:** Studies were classified by consensual agreement of two authors (CC and PZ) as having a low risk of bias, an unclear risk of bias, or a high risk of bias, based on the Cochrane tool.16 The Cochrane tool takes into account random sequence generation, concealment of the allocation sequence, blinding of participants and study personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.

Summary measures: Data concerning the primary continuous outcome, perioperative blood loss, were pooled using the ratio of the means method.17 Data concerning the binary outcome, transfusion of at least 1 unit of allogeneic red blood cells, were pooled using the Mantel-Haenszel odds ratio method without corrections.18

**Planned methods of analysis:** In trials with more than two intervention groups, it was planned to combine results for groups that received similar but non-identical interventions (as long as the group fulfilled the criteria for eligibility, as defined above) and it was planned not to include an intervention group if it did not match our inclusion criteria. Heterogeneity was explored by visual inspection of the forest plot, calculation of the Cochran Q heterogeneity statistic and calculation of the I2 statistic. A fixed-effect model was planned in the absence of heterogeneity, defined by a p value > 0.10 for the Cochran Q heterogeneity statistic and an I2 value < 25%. The random-effects model approach is also presented.

**Risk of bias across studies:** The risk of publication bias was checked using the funnel plot technique for the primary outcome.

**Additional analyses:** A sensitivity analysis was performed by restricting the meta-analysis to studies considered at low risk of bias (data not shown).

**Software:** The meta-analysis was performed using R software (meta package, version 2.15.1; downloaded from [www.r-project.org](http://www.r-project.org)). Computation was performed by one review author (CC).

# Flow chart of the study selection process



Five studies were included in addition to the current trial. Two were identified in CENTRAL,19,20 one in MEDLINE,21 one in MEDLINE and CENTRAL 22 and one was provided by a study investigator.23

# Summarized results of individual studies included in the meta-analysis

\*One patient did not undergo surgery; %one patient withdrew his consent and refused participation.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reference | Year | Number of patients available for analysis/ Number of patients randomized | Perioperativeblood loss (ml)Mean (SD) | Number of patients transfused with allogeneic red blood cell |
|  |  | Perioperative group | Preoperative group | Perioperative group | Preoperative group | Perioperative group | Preoperative group |
|  |  |  |  |  |  |  |  |
| Borisov19  | 2011 | 30/30 | 30/30 | 1235 (605) | 994 (318) | 1 | 0 |
| Borisov23  | 2011 | 35/35 | 35/35 | 1035 (332) | 1034 (320) | 0 | 0 |
| Imai20  | 2012 | 26/26 | 25/25 | 852 (261) | 914 (248) | 0 | 0 |
| Hourlier22  | 2014 | 79/79 | 85/85 | 1047 (442) | 1107 (508) | 0 | 0 |
| Barrachina21\*  | 2016 | 37/38 | 35/35 | 1276 (660) | 1377 (689) | 4 | 8 |
| Current trial% | 2017 | 84/84 | 83/84 | 919 (338) | 888 (366) | 3 | 3 |

# Meta-analysis forest plot for red blood cell transfusion



# References

1. Johansson T, Pettersson L-G, Lisander B: Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. Acta Orthop 2005; 76:314–9

2. Rosencher N, Kerkkamp HEM, Macheras G, L. M. Munuera, Menichella G, Barton DM, Cremers S, Abraham IL, OSTHEO Investigation: Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. Transfusion 2003; 43:459–69

3. Duquenne P, Lhoehst L, Henkes W, De Sart F: Tranexamic acid reduces postoperative blood losses associated with elective total hip replacement. J Bone Joint Surg Br 1999; 81(suppl 2):233

4. Benoni G, Fredin H, Knebel R, Nilsson P: Blood conservation with tranexamic acid in total hip arthroplasty: a randomized, double-blind study in 40 primary operations. Acta Orthop Scand 2001; 72:442–8

5. Yamasaki S, Masuhara K, Fuji T: Tranexamic acid reduces blood loss after cementless total hip arthroplasty-prospective randomized study in 40 cases. Int Orthop 2004; 28:69–73

6. Lemay E, Guay J, Côté C, Roy A: Tranexamic acid reduces the need for allogenic red blood cell transfusions in patients undergoing total hip replacement. Can J Anaesth 2004; 51:31–7

7. Garneti N, Field J: Bone bleeding during total hip arthroplasty after administration of tranexamic acid. J Arthroplasty 2004; 19:488–92

8. Claeys MA, Vermeersch N, Haentjens P: Reduction of blood loss with tranexamic acid in primary total hip replacement surgery. Acta Chir Belg 2007; 107:397–401

9. Rajesparan K, Biant LC, Ahmad M, Field RE: The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. J Bone Joint Surg Br 2009; 91:776–83

10. Kazemi SM, Mosaffa F, Eajazi A, Kaffashi M, Daftari Besheli L, Bigdeli MR, Zanganeh RF: The effect of tranexamic acid on reducing blood loss in cementless total hip arthroplasty under epidural anesthesia. Orthopedics 2010; 33:17

11. McConnell JS, Shewale S, Munro NA, Shah K, Deakin AH, Kinninmonth AWG: Reduction of blood loss in primary hip arthroplasty with tranexamic acid or fibrin spray. Acta Orthop 2011; 82:660–3

12. Ekbäck G, Axelsson K, Ryttberg L, Edlund B, Kjellberg J, Weckström J, Carlsson O, Schött U: Tranexamic acid reduces blood loss in total hip replacement surgery. Anesth Analg 2000; 91:1124–30

13. Husted H, Blønd L, Sonne-Holm S, Holm G, Jacobsen TW, Gebuhr P: Tranexamic acid reduces blood loss and blood transfusions in primary total hip arthroplasty: a prospective randomized double-blind study in 40 patients. Acta Orthop Scand 2003; 74:665–9

14. Ido K, Neo M, Asada Y, Kondo K, Morita T, Sakamoto T, Hayashi R, Kuriyama S: Reduction of blood loss using tranexamic acid in total knee and hip arthroplasties. Arch Orthop Trauma Surg 2000; 120:518–20

15. Niskanen RO, Korkala OL: Tranexamic acid reduces blood loss in cemented hip arthroplasty: a randomized, double-blind study of 39 patients with osteoarthritis. Acta Orthop 2005; 76:829–32

16. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC, Cochrane Bias Methods Group, Cochrane Statistical Methods Group: The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011; 343:d5928

17. Friedrich JO, Adhikari NKJ, Beyene J: The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study. BMC Med Res Methodol 2008; 8:32

18. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A: Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007; 26:53–77

19. Borisov DB, Yudin SV, Krylov OV, Markov BB, Istomina NA: Reduction of perioperative blood loss during endoprosthetic replacement of large joints. Gen Reanimatol 2011; 7:34–7

20. Imai N, Dohmae Y, Suda K, Miyasaka D, Ito T, Endo N: Tranexamic acid for reduction of blood loss during total hip arthroplasty. J Arthroplasty 2012; 27:1838–43

21. Barrachina B, Lopez-Picado A, Remon M, Fondarella A, Iriarte I, Bastida R, Rodríguez-Gascón A, Achaerandio MA, Iturricastillo MC, Aizpuru F, Valero CA, Tobalina R, Hernanz R: Tranexamic acid compared with placebo for reducing total blood loss in hip replacement surgery: a randomized clinical trial. Anesth Analg 2016; 122:986–95

22. Hourlier H, Fennema P: Single tranexamic acid dose to reduce perioperative morbidity in primary total hip replacement: a randomised clinical trial. Hip Int 2014; 24:63–8

23. Borisov DB, Yudin SV, Lebedev LA, Vardanashvili VK, Istomina NA: Choice of a tranexamic acid dose regimen during endoprosthetic replacement of joints. Messenger Anesthesiol Resusc 2011; 8:41–4