# Tranexamic Acid

## *What Is Known and Unknown, and Where Do We Go From Here?*

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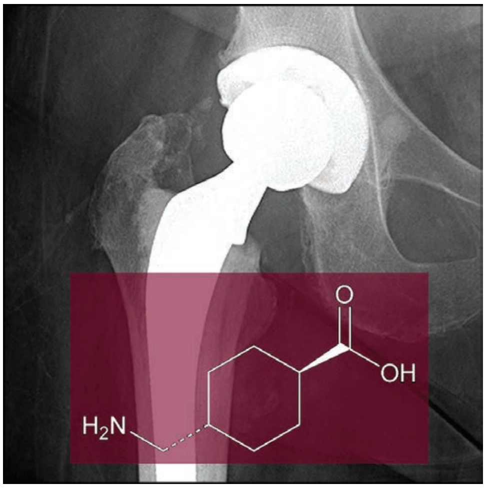
CME

This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

Anesthesiologists are experts at drug dosing, and we likely have more experience doing so than any other specialty in medicine. With anesthetic drugs such as fentanyl or propofol, we often dose by titrating to effect, which is sometimes more an art than a science. So what about drugs that are not titrated? Why do we give 2 g of cefazolin to virtually all adult patients, whether they are 40 or 120 kg? In fact, we give many such nontitratable drugs, tranexamic acid being one of them, for which the optimal dosing regimens have yet to be determined. Perhaps one dose does not fit all.

Although tranexamic acid was first discovered more than 50 yr ago, its clinical utility to reduce blood loss and transfusion requirements has only been popularized in the past decade. A synthetic lysine analog that competitively inhibits the conversion of plasminogen to plasmin,[1] tranexamic acid reduces the proteolytic action of plasmin on fibrin clots, resulting in inhibition of fibrinolysis. The mechanism of action is to stabilize existing clots rather than promoting new clot formation. Although the Food and Drug Administration–approved indications are limited to reducing bleeding in hemophiliacs having tooth extraction and in women with menorrhagia, the off-label use to reduce blood loss and transfusion requirements has increased dramatically. In fact, the evidence supporting tranexamic acid is so extensive that in 2011 the World Health Organization included tranexamic acid on their list of 350 essential medicines.[2] There is ongoing debate, however, around optimal perioperative tranexamic acid dosing, which varies widely, by up to tenfold, in recent studies.[3–5]




***"There is ongoing debate, however, around optimal perioperative tranexamic acid dosing, which varies widely, by up to tenfold..."***

In this issue of Anesthesiology, Zufferey *et al.*[6] report a double-blind prospective randomized trial on tranexamic acid dosing regimens in total hip orthroplasty. The authors enrolled about 80 patients in each of two groups: one group receiving a single 1-g bolus of tranexamic acid preincision and the other receiving the same bolus, followed by 1 g infused during 8 h. The primary outcome, calculated blood loss based on hemoglobin change over a 5-day period, was no difference between groups. The secondary outcomes—blood loss from surgical drains, percentage of patients transfused, and postoperative thrombotic events—were also similar between groups. The authors conclude that supplementary tranexamic acid as a perioperative infusion did not add benefit to a single preincision bolus dose and that blood loss, transfusion rates, and thrombotic event rates were all very low. The authors also include a small meta-analysis (six studies, 611 patients), showing that additional tranexamic acid did not further reduce blood loss in hip replacement surgery, when compared to a single bolus dose.

Overall, the study was well designed and conducted and adds to the growing body of evidence supporting the efficacy and safety, as well as optimal dosing regimens for tranexamic acid. There are, however, some limitations that should be recognized. The doses were not weight-based, and according to recent pharmacokinetic studies,[7] the postoperative infusion may have been subtherapeutic. In addition, a placebo

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Corresponding article on page 413.

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group was not used; therefore, we cannot comment on efficacy or safety compared to no treatment.

It is useful to summarize what is known and unknown regarding perioperative tranexamic acid. We know that tranexamic acid is being called a game changer at national orthopedic and blood management meetings, and transfusion rates for hip and knee arthroplasties are now under 5% in many centers. When summarizing a large number of studies comparing tranexamic acid to placebo, overall blood loss and transfusion requirements are both reduced by ≈30%.[4,5,8] We also know that the worldwide popularity of tranexamic acid was greatly enhanced after the CRASH-2 Trial in trauma, published in 2011,[9] and may be further enhanced by the much anticipated WOMAN Trial in postpartum hemorrhage published in 2017.[10] In these trials, a 1-g loading dose was given, followed by an infusion of 1 g during 8 h (in CRASH-2) or the option for a second 1-g bolus for continued bleeding (in WOMAN). In both these large trials (each more than 20,000 patients), mortality was significantly reduced with tranexamic acid, while thrombotic events were not increased. Both studies also revealed the importance of early tranexamic acid administration within 3 h of the injury or the childbirth. Of interest, the dosing regimen for CRASH-2 was identical to the bolus-plus-infusion group in the Zufferey study. Other known facts are that tranexamic acid is tenfold more expensive than ε-aminocaproic acid for an equipotent dose; however, whether tranexamic acid has advantages over ε-aminocaproic acid is unclear given the lack of head-to-head randomized trials. The cost per case for the tranexamic acid dose advocated by the Zufferey study (1 g) is only $36 given current U.S. pricing.

There is plenty, however, that we do not know. The optimal plasma concentration to inhibit fibrinolysis has been reported between 10 and 20 μg/ml in older *in vitro* studies, and as high as 150 μg/ml in more recent studies.[7] To date, the minimal effective plasma concentration to inhibit fibrinolysis based on the *in vivo* dose–response relationship has not been determined. Furthermore, the pharmacokinetic profile of tranexamic acid is just now starting to be elucidated. Sophisticated pharmacokinetic modeling studies report that steady-state concentrations of 20 μg/ml are obtained by a 10 mg/kg loading dose, followed by a 5 mg/kg/h infusion,[7] an infusion dose about three times greater than used in the Zufferey study, perhaps explaining why their infusion did not add benefit. Another reason may be that for a 1-h surgery, tranexamic acid simply does not need to be redosed or infused given its 2- to 3-h half-life. However, given that orthopedic patients continue to bleed postoperatively, the rationale for assessing the impact of an 8-h infusion after the bolus makes sense. Regarding venous thromboembolism (VTE) risk, we know that tranexamic acid is a clot stabilizer, and multiple sources report the thromboembolic risk to be negligible. We do not, however, know the safety profile in patients at higher VTE risk since most studies are either underpowered or exclude such high-risk patients. We also do not know the true contraindications for using tranexamic acid. Even in the Zufferey study, they changed one contraindication midstudy, from any history of VTE to acute, ongoing VTE. The package insert says any seizure history is a contraindication, but is this really necessary? Seizures have been mostly reported with high-dose regimen in high-risk patients. And what about renal insufficiency? Should a creatinine clearance less than 15 ml/min be a contraindication, or can we simply reduce the dose according to renal function?

In summary, the study in this issue of Anesthesiology supports the efficacy and safety of tranexamic acid in hip arthroplasty and shows that in short-duration orthopedic procedures, a single bolus of tranexamic acid is adequate, with no additional benefit of a continuous infusion. Further studies, however, need to determine the ideal therapeutic plasma level to reduce bleeding and transfusion while avoiding adverse effects. In addition, for longer surgeries, pharmacokinetic studies are needed to identify the optimum bolus dose and infusion rates to achieve the desired steady-state plasma concentrations. Ongoing well designed tranexamic acid trials including the CRASH-3 trial (head injury) and ClinicalTrials.gov NCT01813058 (scoliosis surgery) will provide answers to these questions. Zufferey *et al.* should be congratulated for adding to our knowledge base for perioperative tranexamic acid use which will benefit our patients by reducing allogeneic transfusions and their associated risks and costs, thus adding value to the care we deliver.

## Competing Interests

Dr. Frank has received consulting fees from Haemonetics (Braintree, Massachusetts), Medtronic (Minneapolis, Minnesota), and Zimmer/Biomet (Warsaw, Indiana). Dr. Goobie declares no competing interests.

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## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

# New Orthoform for Old Freud: Insoluble Numbing for Sigmund's Insoluble Cancer


Sculptor Robert Toth captured Sigmund Freud (1856 to 1939, *left*) in one of those rare moments when the "Father of Psychoanalysis" was not puffing on one of his 20 cigars daily. That heavy smoking habit led to an oral cancer, which ulcerated the area where all of those cigar butts had rested at the back right of Freud's mouth. As the cancer recurred and was surgically carved away, a painful nonhealing crater developed. To ease Freud's suffering, one consultant, Dr. Joseph Weinmann, directed that New Orthoform (*right*) be dusted liberally onto the gaping hole at the back of Freud's mouth before a massive oral prosthesis was inserted. That white dusting powder was a highly insoluble hydroxyaminobenzoic ester which had been synthesized by Alfred Einhorn (1856 to 1917) and manufactured by Hoechst, as had its predecessor, Orthoform. By interchanging "Old" Orthoform's hydroxy and amino groups, New Orthoform had proven to be not only a cheaper local anesthetic to manufacture but also one which could double as a bactericidal desiccant. How ironic that Freud's academic career had opened with his professional (and personal) use of one local anesthetic, cocaine, and would close with his terminal use of another, New Orthoform! (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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# Intravenous Tranexamic Acid Bolus plus Infusion Is Not More Effective than a Single Bolus in Primary Hip Arthroplasty

## *A Randomized Controlled Trial*

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CME

This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

## ABSTRACT

**Background:** Preoperative administration of the antifibrinolytic agent tranexamic acid reduces bleeding in patients undergoing hip arthroplasty. Increased fibrinolytic activity is maintained throughout the first day postoperation. The objective of the study was to determine whether additional perioperative administration of tranexamic acid would further reduce blood loss.

**Methods:** This prospective, double-blind, parallel-arm, randomized, superiority study was conducted in 168 patients undergoing unilateral primary hip arthroplasty. Patients received a preoperative intravenous bolus of 1 g of tranexamic acid followed by a continuous infusion of either tranexamic acid 1 g (bolus-plus-infusion group) or placebo (bolus group) for 8 h. The primary outcome was calculated perioperative blood loss up to day 5. Erythrocyte transfusion was implemented according to a restrictive transfusion trigger strategy.

**Results:** The mean perioperative blood loss was 919 ± 338 ml in the bolus-plus-infusion group (84 patients analyzed) and 888 ± 366 ml in the bolus group (83 patients analyzed); mean difference, 30 ml (95% CI, −77 to 137; $P = 0.58$). Within 6 weeks postsurgery, three patients in each group (3.6%) underwent erythrocyte transfusion and two patients in the bolus group experienced distal deep-vein thrombosis. A meta-analysis combining data from this study with those of five other trials showed no incremental efficacy of additional perioperative administration of tranexamic acid.

**Conclusions:** A preoperative bolus of tranexamic acid, associated with a restrictive transfusion trigger strategy, resulted in low erythrocyte transfusion rates in patients undergoing hip arthroplasty. Supplementary perioperative administration of tranexamic acid did not achieve any further reduction in blood loss. (Anesthesiology 2017; 127:413-22)

Tranexamic acid has been shown to be effective in reducing blood loss and transfusion in surgical patients.[1] The basis for tranexamic acid efficacy is thought to be inhibition of tissue fibrinolysis and consequent clot stabilization.[2] In total hip arthroplasty, fibrinolytic activation in the operated limb begins just after the start of surgery and is maintained postoperatively up to 18 h.[3,4] To maximize efficacy in hip arthroplasty, tranexamic acid should be initiated preoperatively.[5] Yet the optimal duration of intravenous tranexamic acid administration in hip arthroplasty is unknown. A single preoperative bolus may not be the best choice given that about the same amount of bleeding occurs after surgery as during surgery[6] and given the duration of increased postoperative fibrinolytic activity and the 2-h half-life of tranexamic acid.[7] Furthermore, results concerning

### What We Already Know about This Topic

- The half-life of tranexamic acid is about 2 h
- Preoperative tranexamic acid reduces blood loss after hip arthroplasty
- It remains unknown whether adding an intraoperative infusion to an initial bolus further reduces blood loss

### What This Article Tells Us That Is New

- In a randomized, blinded trial comparing an initial bolus of tranexamic acid with an initial bolus followed by an infusion, blood loss was comparable in each group
- Combining current results with five previous trials in a meta-analysis also shows no benefit of adding an infusion of tranexamic acid to an initial bolus

Corresponding article on page 405. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).







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the impact of tranexamic acid use on erythrocyte transfusion in major orthopedic surgery seem to favor administration of more than just a single bolus limited to the intraoperative period.[8]

We therefore performed a double-blind, randomized, controlled trial in patients undergoing hip arthroplasty to evaluate the effect of a supplementary 8-h perioperative infusion of tranexamic acid on blood loss in patients having received a preoperative loading dose of tranexamic acid.

## Materials and Methods

The PeriOpeRative Tranexamic acid in hip arthrOplasty (PORTO) study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, Good Clinical Practice, and relevant French regulations regarding ethics and data protection. The protocol and amendments were approved by the central independent ethics committee (Committee for the Protection of Personal Data South-Est I, Saint-Etienne, France; reference 2013-20). Written informed consent was obtained from all patients before randomization in this prospective, double-blind, parallel-arm, randomized, superiority clinical trial. The PORTO trial was a single-site study conducted at the university hospital of Saint-Etienne, France. This study is registered at EudraCT (2013-000791-15, principle investigator P.J.Z., registered August 8, 2013) and at www.ClinicalTrials.gov (NCT02252497, principle investigator P.J.Z., registered September 26, 2014).

### *Patients*

Consecutive patients aged 18 yr or older undergoing primary unilateral total hip arthroplasty through a posterior approach were eligible for inclusion between April 2014 and December 2015. Exclusion criteria were pregnancy or breastfeeding, hip fracture less than 3 months previously, contraindication for venous thromboprophylaxis with apixaban, chronic anticoagulation therapy, absence of French social security health insurance coverage, and contraindication for tranexamic acid treatment (previous or acute arterial or venous thrombosis, creatinine clearance less than 15 ml/min, or previous seizure). Exclusion criteria for patients with arterial or venous thrombosis were amended in June 2014 (2 months after study initiation, by which time six patients had been enrolled) to exclude only those with acute thrombosis, after modification of the French national agency for medicines and health products summary of product characteristics for tranexamic acid. Potential study participants were identified at the preoperative anesthesia consultation and were approached by study staff during their preadmission clinic visit before the day of surgery.

### *Randomization and Interventions*

Patients were randomized in a 1:1 ratio to one of the two study groups by means of a central telephone system ensuring concealed allocation. Randomization was performed using a computer-generated randomization sequence with randomly permuted blocks of 4 or 6. After initiation of anesthesia, patients in both study groups received an unblinded intravenous bolus of 1 g of tranexamic acid (Exacyl 0.1 g/ml; Sanofi-Aventis, France). They were then allocated to receive immediately either an intravenous infusion of 1 g of tranexamic acid for 8 h (bolus-plus-infusion group) or a matching placebo (0.9% saline; bolus group). The intravenous solutions were prepared outside the orthopedic department by a nurse and directly sent to the anesthetist in charge in the operating room. Masking was ensured by the use of apparently identical 50-ml syringes. Patient caregivers and investigators collecting the data remained unaware of study-group assignments.

Patient blood management included various individualized strategies. In accordance with the French guidelines for erythrocyte transfusion, a restrictive transfusion trigger strategy was used. The transfusion trigger was a hemoglobin level of 7 g/dl, increased to 8 to 9 g/dl in patients with a history of cardiovascular disease and to 10 g/dl in patients with severe symptoms (*e.g.*, persistent hypotension despite adequate volume replacement, syncope, transient ischemic attack, stroke, acute respiratory failure, or acute coronary syndrome). During surgery, blood losses were replaced by Ringer's lactate solution in a 3:1 ratio. Each patient received 1 l of rehydration fluid (sodium 40 mM, potassium 20 mM, glucose 250 mM) for the first 12 h after surgery. Perioperative hemoglobin was measured before starting surgery (day 1), in the postanesthetic care unit, on days 2 and 5, and after each postoperative transfusion. Patients received an oral iron supplement of 200 mg/day during the postoperative period. Venous thromboprophylaxis included 2.5 mg of apixaban two times daily, initiated 24 h after the end of surgery and continued for 5 weeks. Use of desmopressin, recombinant factor VIIa, topical tranexamic acid, or a cell-salvage device was not allowed. Preoperative anemia was assessed 3 to 4 weeks before surgery without further investigation of the cause. The use of preoperative iron supplementation, the administration of erythropoiesis-stimulating agents, and the perioperative management of antiplatelet therapy were left to the discretion of the anesthetist. No preoperative autologous blood donation was implemented.

The choice of anesthesia and postoperative analgesia was left to the discretion of the anesthetists. All patients received cefazolin (2 g) before surgery and were operated in a lateral position

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through a posterior approach. The implants chosen combined a cementless femoral stem with a cementless dual-mobility cup. A single intraarticular low-vacuum drain was used for postoperative wound drainage, remaining in place for at least 24 h.

### Outcome Measures

The primary efficacy outcome was calculated: perioperative blood loss based on hemoglobin balance (using preoperative and day 5 hemoglobin values), on the assumption that blood volume on day 5 was the same as before surgery (see formula used to calculate blood loss in the Supplemental Digital Content, http://links.lww.com/ALN/B521). Secondary efficacy outcomes included measured blood loss *via* the drain during the first 24 h and the percentage of patients requiring transfusion of at least 1 unit of allogeneic erythrocytes from surgery up to week 6. The safety outcome was the incidence of vascular events and death up to 6 weeks. Vascular events were defined as the composite of any confirmed symptomatic deep venous thrombosis, pulmonary embolism, stroke, myocardial infarction, and limb ischemia. Blood samples were collected to perform a pharmacokinetic study of tranexamic acid, which is not reported here.

### Statistical Analysis and Sample Size Calculation

Sample size calculation was based on data from previous studies assessing a single preoperative tranexamic acid injection with or without additional perioperative tranexamic acid administration (see assumptions for sample size calculation in the Supplemental Digital Content, http://links.lww.com/ALN/B521). Assuming a difference in perioperative blood loss of 250 ml with a 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 $\alpha$ risk of 0.05.

All analyses were performed on a modified intention-to-treat population, defined as all randomized patients except those who withdrew their consent and refused participation (French legislation precludes any reporting of data from these patients). Categorical data were described as frequencies and proportions and were analyzed using Fisher's exact test. The Shapiro–Wilk test was used to examine the normality of distribution of continuous outcomes, including the primary outcome, calculated perioperative blood loss. Normally distributed continuous variables were described as the mean ± SD and were analyzed using Student's *t* test. Continuous data that were not normally distributed were presented as median, first, and third quartiles. They were analyzed using the Mann-Whitney U test. No stratification variables were used in the analyses. No subgroup analyses were planned in the protocol, and none were performed. The analyses were performed using SAS software, version 9.4 (SAS Institute, USA).

A meta-analysis of randomized trials was performed to assess the external validity of our study. A report of the methods used for this meta-analysis, following the PRISMA guidelines, is presented in the Supplemental Digital Content (http://links.lww.com/ALN/B521). Briefly, the studies included had to compare 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. Studies had to be performed in primary hip arthroplasty and tranexamic acid had to be administered intravenously. Relevant trials were identified by a computerized search up to June 2016 in Medline and the Cochrane Central Registry of Controlled Trials. The Cochrane Collaboration risk-of-bias tool for randomized controlled trials was used for quality assessment. In this meta-analysis, the experimental group corresponded to both pre- and perioperative tranexamic acid administration, and the control group corresponded to single preoperative tranexamic acid bolus administration alone. The ratio of mean perioperative blood loss values between the experimental and control groups was calculated for each study.

Data concerning the continuous outcome, perioperative blood loss, were pooled using the ratio of the means method.[9] Data concerning the binary outcome, transfusion of at least 1 unit of allogeneic erythrocytes, were pooled using the Mantel–Haenszel odds ratio method without corrections.[10] Both fixed-effect and random-effects models were implemented. The risk of publication bias was checked using the funnel plot technique. The meta-analysis was performed using R software (meta package, version 2.15.1; downloaded from https://CRAN.R-project.org/package=meta; accessed September 12, 2013).

## Results

Between April 2014 and December 2015, 279 patients were screened for participation in the study, of whom 168 were included and randomized. One patient withdrew his consent after randomization but before administration of the study drug. A total of 84 patients were analyzed in the bolus-plus-infusion group, and 83 were analyzed in the bolus group (fig. 1). Both patient characteristics and surgical characteristics were similar in the two groups (table 1).

The mean perioperative blood loss was 919 ± 338 ml in the bolus-plus-infusion group and 888 ± 366 in the bolus group (table 2). The difference in mean perioperative blood loss between the groups, namely 30 ml (95% CI: −77 to 137 ml), was not statistically significant ($P$ = 0.58). The hemoglobin values used to calculate perioperative blood loss are presented in table 2. Median blood loss *via* the drain during the first 24 h was similar in the two groups (fig. 2).

Three patients (3.6%) in each group required transfusion of at least 1 unit of erythrocytes up to day 45 ($P$ > 0.99) (table 2). Two patients experienced symptomatic bilateral distal venous thrombosis up to day 45, both in the bolus group. No other venous or arterial vascular event occurred, and no patient died.

### Meta-analysis

Literature search identified five studies in addition to the current trial, yielding a total of 611 patients (see flow chart of the study selection process in the Supplemental

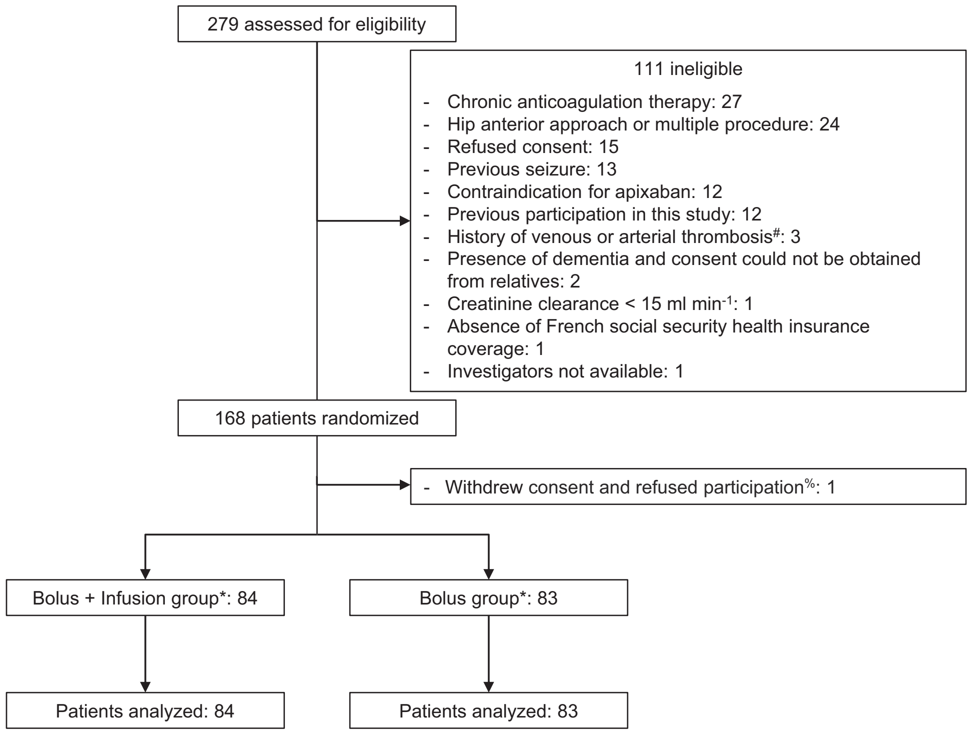


**Fig. 1.** Flow chart. #Exclusion criteria amended (for details, see "Patients" in Materials and Methods section). %French legislation precludes any reporting of data from this patient. *Patients received an unblinded intravenous bolus of 1 g of tranexamic acid followed immediately by an intravenous infusion of either 1 g of tranexamic acid (bolus-plus-infusion group) or a matching placebo (bolus group) for 8 h.

Digital Content, http://links.lww.com/ALN/B521).[5,11–14] The characteristics of the trials included are summarized in table 3. On the basis of the Cochrane Collaboration tool, one study was classified as having a high risk of bias (fig. 3).[5] In each study the total amount of tranexamic acid administered was greater in the perioperative group than in the preoperative group. In the perioperative groups, tranexamic acid administration was pursued postoperatively either as a bolus (3 or 6 h after the preoperative bolus) or as a continuous infusion (more than 8 or 18 h). For each study, the numerical group-specific summary data on perioperative blood loss and erythrocyte transfusion are presented in the Supplemental Digital Content (http://links.lww.com/ALN/B521). Compared to a single preoperative tranexamic acid bolus alone, additional perioperative administration of tranexamic acid did not reduce bleeding events. The pooled ratio of blood loss was 1.00 (95% CI, 0.94 to 1.06; $P = 0.99$; fixed-effect model) (fig. 4). There was no evidence of heterogeneity ($I^2 = 1.6\%$). The treatment effect was not modified when the analysis was limited to studies considered at low risk of bias (two studies, pooled ratio 1.01; 95% CI, 0.93 to 1.10; $P = 0.83$; fixed-effect model; $I^2 = 7.9\%$). The odds ratio for transfusion of at least 1 unit of allogeneic erythrocytes was 0.67 (95% CI: 0.26 to 1.75; $P = 0.41$; fixed-effect model; $I^2 = 0\%$), see forest plot in the Supplemental Digital Content (http://links.lww.com/ALN/B521). No funnel plot check was performed in view of the small number of studies included.

## Discussion

In this study, an additional perioperative infusion of 1 g of the antifibrinolytic agent tranexamic acid during 8 h did not reduce blood loss in patients having received a preoperative 1 g intravenous loading dose of tranexamic acid for primary hip arthroplasty. To compare our results with previous studies in hip arthroplasty,[5,11–14] we performed a meta-analysis. No difference in blood loss between patients receiving a single preoperative bolus of tranexamic acid and those additionally receiving tranexamic acid perioperatively was seen either in the individual studies included or in the overall analysis. The relatively narrow CI indicates a precise estimate of the absence of any difference between the two regimens.

In orthopedic surgery, the effect of perioperative administration of tranexamic acid in addition to a preoperative bolus has also been studied in patients undergoing knee replacement. Three studies found that additional perioperative administration of tranexamic acid reduced blood loss by 24, 25, and 33%, respectively,[15–17] whereas another study showed no such effect.[18]

In total hip arthroplasty, fibrinolytic activation begins just after the start of surgery and is maintained postoperatively for up to 18 h.[3,4] Given the 2-h half-life of tranexamic acid,[7] we designed this study to assess the necessity of maintaining therapeutic plasma concentrations of tranexamic acid with a continuous infusion pump in the intra- and postoperative period. Yet inhibition of fibrinolytic activation, mediated by increased

**Table 1.** Baseline Patient and Surgical Characteristics

| Characteristic | Bolus + Infusion Group (N = 84) | Bolus Group (N = 83) |
|---|---|---|
| Age, yr | 66 (59, 73) | 68 (57, 78) |
| Female, no. (%) | 47 (56) | 39 (47) |
| Weight, kg | 73 (63, 86) | 76 (65, 87) |
| Body mass index | 27 (24, 31) | 28 (24, 31) |
| Creatinine clearance, ml/min* | 86 (74, 110) | 88 (64, 109) |
| Ischemic heart disease, no. (%) | 7 (8) | 9 (11) |
| Atrial fibrillation, no. (%) | 6 (7) | 1 (1) |
| History of stroke or transient ischemic attack, no. (%) | 3 (4) | 4 (5) |
| History of venous thromboembolism, no. (%) | 8 (10) | 4 (5) |
| ASA score III or IV, no. (%) | 22 (26) | 29 (35) |
| Antiplatelet therapy, no. (%) | | |
| Chronic use | 20 (24) | 20 (24) |
| Perioperative use† | 18 (21) | 19 (23) |
| Nonsteroidal antiinflammatory drugs, no. (%) | | |
| Chronic use | 9 (11) | 5 (6.0) |
| Perioperative use | 46 (55) | 33 (40) |
| Interval from preanesthesia consultation to surgery [days]‡ | 23 (14, 28) | 22 (17, 32) |
| Preoperative iron supplementation, oral-intravenous, no. (%) | 13-1 (17) | 14-1 (18) |
| Preoperative erythropoietin, no. (%) | 3 (4) | 2 (2) |
| Preoperative anemia, no./N (%)§ | 7/69 (10) | 9/71 (13) |
| Iron supplementation in anemic patients, no./N (%) | 4/7 (57) | 5/9 (56) |
| Postoperative iron supplementation, oral-intravenous, no. (%) | 79-0 (94) | 72-1 (87) |
| Indication for surgery, no. (%) | | |
| Osteoarthritis | 55 (66) | 50 (60) |
| Avascular necrosis | 15 (18) | 16 (19) |
| Dysplasia | 7 (8) | 4 (5) |
| Inflammatory arthritis | 3 (4) | 7 (8) |
| Other | 4 (5) | 6 (7) |
| Type of anesthesia, no. (%)‖ | | |
| General | 83 (99) | 80 (96) |
| Spinal anesthesia | 1 (1) | 4 (5) |
| Femoral nerve or fascia iliaca block | 74 (88) | 66 (80) |
| Duration of surgery, min | 70 (59, 80) | 64 (60, 80) |
| Duration of anesthesia, min | 115 (102, 133) | 117 (104, 130) |
| Intraoperative crystalloid, ml | 600 (500, 850) | 600 (450, 900) |
| Body temperature at end of surgery, °C | 36.1 ± 0.6 | 36.2 ± 0.5 |

Continuous data are shown as the means ± SD and median ($25^{th}$, $75^{th}$ percentiles) in the case of nonnormal distribution.

*Creatinine clearance was estimated using the Cockcroft–Gault formula. †At least one dose of antiplatelet therapy between preoperative day 3 and postoperative day 5. ‡Anesthetists had exclusive responsibility for preoperative patient blood management. §Hemoglobin level was less than 12 g/dl for women and less than 13 g/dl for men; the hemoglobin count was not available for every patient at the preoperative anesthesia consultation. ‖Spinal anesthesia was converted to general anesthesia in one patient in the bolus group due to spinal block failure; epidural anesthesia was not performed.

ASA = American Society of Anesthesiologists.

inhibition of tissue plasminogen activator, can also begin during surgery, resulting in a fibrinolytic shutdown that peaks the day after surgery.[19] The timing of transition from hyperfibrinolysis to a hypofibrinolytic state has not yet been defined.[3] If this transition occurs soon after hip arthroplasty surgery, postoperative tranexamic acid administration may not be necessary. On the other hand, if the transition occurs later, our perioperative 8-h infusion of tranexamic acid may have been insufficient. This is unlikely, because a study in hip arthroplasty found no additional benefit of an 18-h postoperative tranexamic acid infusion.[18]

Postoperative fibrinolytic activity may differ according to the surgical procedure. For example, after tourniquet use in knee replacement surgery, postoperative fibrinolytic marker levels are higher than without tourniquet use and are also higher than in hip arthroplasty.[4,20] Although tranexamic acid is effective in many different surgical procedures,[1] the differences in fibrinolytic response according to the type of surgery suggest that the optimal regimen for tranexamic acid administration is probably procedure-specific. Thus, our results concerning primary hip arthroplasty should not be extrapolated to other surgical procedures, in particular knee replacement surgery.

We chose to administer a preoperative loading dose of 1 g of tranexamic acid on the basis of previous randomized trials showing that compared to placebo, a tranexamic acid dose of 10 to 15 mg/kg or 1 g significantly reduced blood loss and

**Table 2.** Primary and Secondary Endpoints

| Primary Outcome | Bolus + Infusion Group (N = 84) | Bolus Group (N = 83) | Mean Difference or Odds Ratio [95% CI] | *P* Value |
|---|---|---|---|---|
| Perioperative blood loss, ml* | 919 ± 338 | 888 ± 366 | 30 [−77; 137] | 0.58 |
| Preoperative Hb, g/dl | 14.2 ± 1.5 | 14.2 ± 1.5 | 0.0 [−0.45; 0.45] | 0.88 |
| Hb on day 5, g/dl | 11.4 ± 1.4 | 11.5 ± 1.3 | −0.13 [−0.54; 0.28] | 0.23 |
| Hb decrease on day 5, g/dl | 2.8 ± 1.0 | 2.7 ± 1.1 | 0.13 [−0.20; 0.45] | 0.44 |
| Postoperative drainage blood loss (24 h), ml | 265 (200, 390) | 300 (170, 390) | 0 [−50; 40]† | 0.89 |
| Patients receiving erythrocyte transfusion up to day 5, no. (%) | 1 (1.2%) | 1 (1.2%) | 0.99 [0.06; 16.1] | > 0.99 |
| Patients receiving erythrocyte transfusion up to week 6, no. (%) | 3 (3.6%) | 3 (3.6%) | 0.99 [0.19; 5.04] | > 0.99 |
| Symptomatic vascular events and death up to week 6, no. (%)‡ | 0 (0%) | 2 (2.4%) | n.a. | 0.25 |

Normally distributed continuous variables are shown as the means ± SD and were analyzed using Student's *t* test. In the case of nonnormal distribution, continuous data are shown as the median (25th, 75th percentiles) and were analyzed using Mann–Whitney U test. Categorical variables were analyzed using Fisher's exact test.

*Calculated blood loss based on hemoglobin (Hb) balance (using preoperative and day 5 Hb values). †Hodges–Lehmann nonparametric median between-treatment differences estimator. ‡Defined as the composite of any confirmed symptomatic deep-vein thrombosis, pulmonary embolism, stroke, myocardial infarction, and limb ischemia; two patients in the bolus group experienced a bilateral distal venous thrombosis.

n.a. = not applicable.

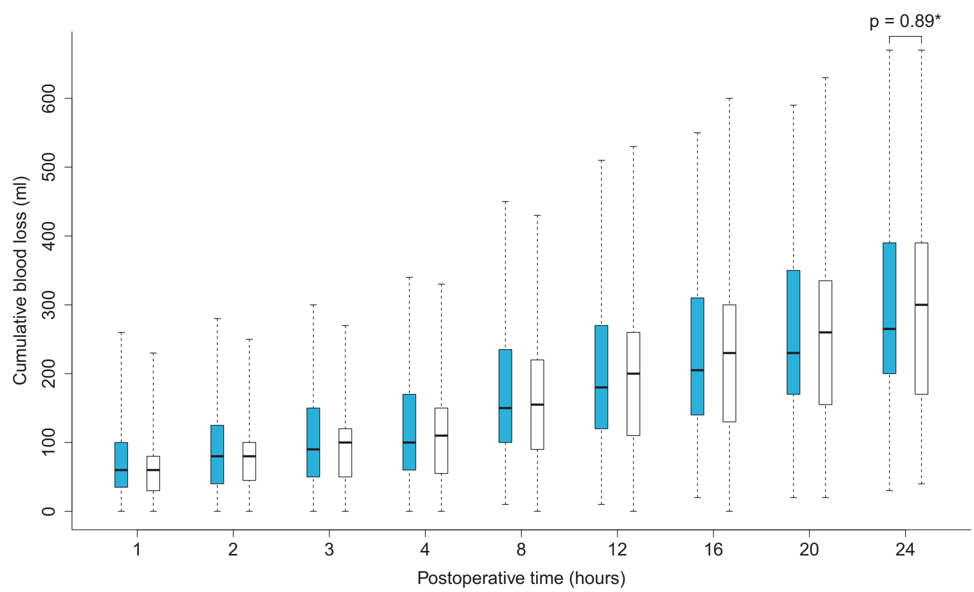


**Fig. 2.** Postoperative drainage blood. The box-and-whisker plots show minimum and maximum values, 25th and 75th percentiles, and medians (*horizontal bars*) of cumulative blood loss. *Blue boxes* indicate the bolus-plus-infusion group, and *white boxes* indicate the bolus group. *Mann–Whitney U test.

transfusion.[8] One pharmacokinetic study in three healthy volunteers reported that the minimum effective therapeutic plasma concentration of tranexamic acid ranged from 5 to 10 mg/l.[7] This study showed that a 1-g intravenous dose of tranexamic acid maintained tranexamic acid plasma concentrations above 10 mg/l for 3 h. Our simulation, based on these data and a pharmacokinetic model in cardiac surgery,[21] suggested that 1 g of tranexamic acid followed by a continuous infusion of 1 g during 8 h would maintain plasma concentrations above 10 mg/l during infusion (unpublished work). The other trials evaluating perioperative administration of tranexamic acid in hip arthroplasty used doses similar to ours.[5,11–14]

The benefit of administering higher perioperative doses is therefore unknown. Two recent trials in hip arthroplasty showed that combined intravenous tranexamic acid and intraoperative topical administration of tranexamic acid reduced blood loss by 13% compared to a single preoperative intravenous tranexamic acid dose.[22,23] Topical administration of tranexamic acid permits delivery of high concentrations of tranexamic acid to the bleeding site. These findings suggest that the effect of higher perioperative tranexamic acid plasma concentrations than those tested in our trial would be worth studying if tranexamic acid is to be administered only intravenously.

Our study is subject to several limitations. The first limitation is the unreliability of the primary outcome measurement. The formulas used to calculate blood loss do not ensure that the values obtained are sufficiently accurate for absolute

**Table 3.** Characteristics of Studies Included in the Meta-analysis

| Reference | Year | Tranexamic Acid Intravenous Dose (No. of Patients Randomized) | | Type of Anesthesia* | Type of Hip Arthroplasty* | DVT Prophylaxis | Mean Patient Age | Mean Patient Weight | Perioperative Blood Loss Measurement |
|---|---|---|---|---|---|---|---|---|---|
| | | Preoperative Group | Perioperative Group | | | | | | |
| Borisov[11] | 2011 | 1 g before surgery (N = 30) | 1 g before surgery + 1 g 3 h after (N = 30) | Spinal + GA | Uncemented; anterolateral approach | Nadroparin | 52 | 76 | Up to day 2 (Hb balance) |
| Borisov[12] | 2011 | 1 g before surgery (N = 35) | 1 g before surgery + 1 g more than 8 h after (N = 35) | Spinal + GA | Uncemented; anterolateral approach | Nadroparin | 52 | 77 | Up to day 5 (Hb balance) |
| Imai[5] | 2012 | 1 g before surgery (N = 25) | 1 g before surgery + 1 g 6 h after (N = 26) | Epidural + GA | Uncemented; anterolateral approach | Enoxaparin | 63 | 54 | Up to day 14 (Ht balance) |
| Hourlier[13] | 2014 | 30 mg/kg before surgery (N = 85) | 10 mg/kg$^{1}$ before surgery + 2 mg/kg/h$^{1}$ for 18 h starting 2 h after (N = 79) | Femoral nerve block + GA | Uncemented; anterolateral approach | Fondaparinux followed by tinzaparin or rivaroxaban | 69 | 81 | Up to day 7 (Ht balance) |
| Barrachina[14] | 2016 | 15 mg/kg before surgery (N = 35) | 10 mg/kg$^{1}$ before surgery + 10 mg/kg$^{1}$ 3 h after (N = 38) | Spinal | Uncemented; anterolateral or posterolateral approach | Enoxaparin | 66 | 73 | Up to day 2 (Ht balance) |
| Current trial | 2017 | 1 g before surgery (N = 84) | 1 g before surgery + 1 g more than 8 h (N = 84) | Femoral nerve or fascia iliaca block + GA | Uncemented; posterolateral approach | Apixaban | 66 | 76 | Up to day 5 (Hb balance) |

*Type of anesthesia and surgery most commonly performed.

DVT prophylaxis = deep venous thromboprophylaxis; GA = general anesthesia; Hb = hemoglobin; Ht = hematocrit.

measurement. Yet a recent study indicates that formulas that take into account both anthropometric and laboratory parameters, as we did, are useful for evaluating the efficacy of interventions aiming to decrease blood loss.[24] A second limitation is related to use of a surrogate endpoint as the primary outcome. As a consequence, this study lacked sufficient power to detect any difference concerning infrequent but more clinically relevant outcomes, such as erythrocyte transfusion. The 3.6% rate of allogeneic erythrocyte transfusion up to 6 weeks in this study was similar to those found in other recent trials using tranexamic acid associated with a restrictive transfusion trigger based on hemoglobin level.[5,11–13,22,23] Compared with the erythrocyte transfusion rate of 45% reported between 1990 and 2010 in hip replacement surgery,[25] these results highlight the decrease in blood transfusion rate achieved through implementation of recently recommended, cost-effective patient blood management measures.[26] This study was also underpowered to detect any differences regarding safety endpoints. The 1.2% incidence of death or symptomatic vascular adverse events (two cases of distal deep-vein thrombosis among 167 patients) during 6 weeks postsurgery was in the lower range of those observed in cohort studies in hip arthroplasty.[27,28] We did not search for asymptomatic events, such as cardiac troponin I elevation or asymptomatic deep-vein thrombosis, as a review of 129 trials, including a total of 10,488 surgical patients, did not indicate an increased risk of thromboembolic events with tranexamic acid.[1] A third limitation of this study is the generalizability of the trial findings. Most of our patients underwent general anesthesia with a femoral nerve or fascia iliaca block. As general anesthesia is associated with increased levels of plasminogen activator inhibitor-1,[29] an inhibitor of fibrinolysis, it could be suggested that the results of our study might not be applicable to centers using primarily neuraxial anesthesia. Yet our meta-analysis indicates results similar to ours in trials that used exclusively spinal anesthesia or various combinations of neuraxial and general anesthesia. Finally, it should be emphasized that morbidly obese patients, patients undergoing chronic anticoagulation therapy, and those with bleeding disorders were not included in the studies entered in our meta-analysis.

In conclusion, this study indicates that additional perioperative administration of tranexamic acid did not further reduce blood loss in patients having received tranexamic acid before primary hip replacement surgery. A single preoperative bolus of tranexamic acid associated with a restrictive transfusion trigger strategy resulted in low erythrocyte transfusion rates.

| | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Risk of bias within a study |
|---|---|---|---|---|---|---|---|
| Borisov, 2011[11] | + | ? | - | ? | + | + | ? |
| Borisov, 2011[12] | + | ? | - | ? | + | + | ? |
| Imai, 2012[5] | - | - | - | ? | + | - | - |
| Hourlier, 2014[13] | + | ? | + | + | + | + | + |
| Barrachina, 2016[14] | + | + | + | + | + | - | ? |
| Current trial | + | + | + | + | + | + | + |

**Fig. 3.** Risk of bias of selected studies according to the Cochrane Collaboration tool. A *plus sign* indicates a low risk of bias; a *minus sign* indicates a high risk of bias; and a *question mark* indicates a plausible bias that raises some doubt about the results.

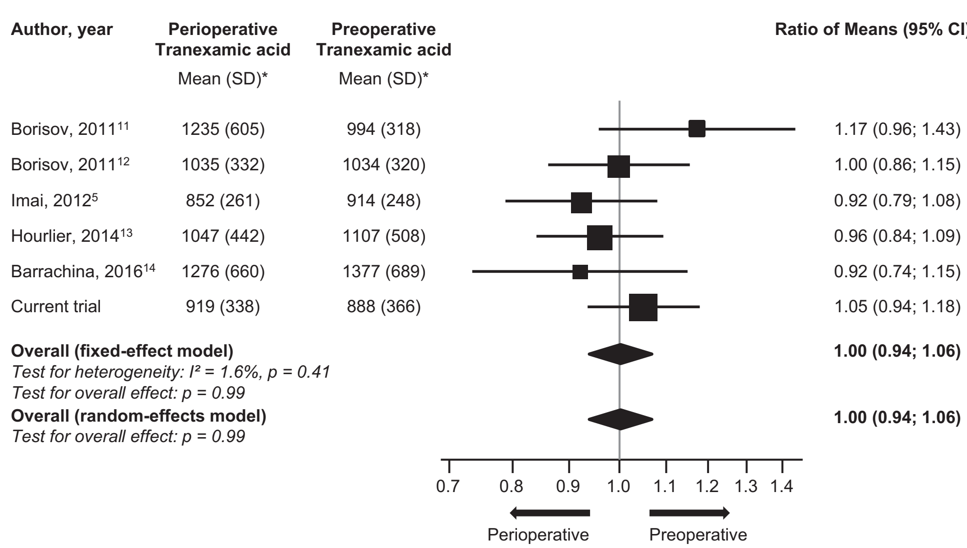


**Fig. 4.** Meta-analysis of the impact of additional perioperative tranexamic acid *versus* preoperative tranexamic acid alone on surgical blood loss. The effect estimates are back-transformed ratios of geometric means with 95% CI. *Mean perioperative blood loss (ml).

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## Competing Interests

All the authors except Dr. Borisov are employees of the funding source, which had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

## Reproducible Science

Full protocol available at: paul.zufferey@chu-st-etienne.fr. Raw data available at: paul.zufferey@chu-st-etienne.fr.

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## Appendix: Investigators of the PeriOpeRative Tranexamic acid in hip arthrOplasty (PORTO) Study

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## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

# Laughing Gas at Brunswick and Balke's 1879 World Billiards Tournament


On February 7, 1879, Jacob Schaefer, Sr. (*left*) defeated George F. Slosson (*right*) at the finals of the "Second World Championship" of three-ball carom billiards. One week before vanquishing Slosson, Schaefer had won Game 18 of that same tournament against another opponent in New York City. Few of that January game's spectators ever learned that, just before cues had been crossed, an aching tooth had been extracted from Game 18's manager. For that on-site anesthetic, pioneer dental anesthetist Gardner Q. Colton (1814 to 1898) had administered nitrous oxide. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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